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**Harmony, Creating Hope for
the Future**

Global Breast Cancer Conference 2009

**with the 7th Biennial Meeting of
the Asian Breast Cancer Society**

October 8~10, 2009

Sheraton Grande Walkerhill, Seoul, Korea

www.gbcc.kr

좋은 소식이
이어집니다

CONFIDENCE REASSURANCE TRUST

재발, 조기유방암 환자에게 있어서 가장 큰 두려움입니다.

- The ATAC trial 100개월 F/U 결과 Arimidex는 Tamoxifen대비*
 - 치료 종료 후에도 재발을 예방하는 것이 입증된 유일한 시제제입니다.
 - 원위재발과 반대측 유방암 재발을 모두 예방하는 것이 입증된 유일한 시제제입니다.
- Tamoxifen대비 Arimidex의 효과는 시간이 지나도 지속되었고(Carryover effect), Arimidex 5년 치료가 장기간의 효과를 나타냄이 확인되었습니다.
- The ATAC trial 100개월 F/U 결과 Arimidex는 폐경 후 유방암 치료의 Standard of Care임이 다시 한번 입증되었습니다.

Reference 1. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial, *Lancet Oncol* 2008; 9: 45-53



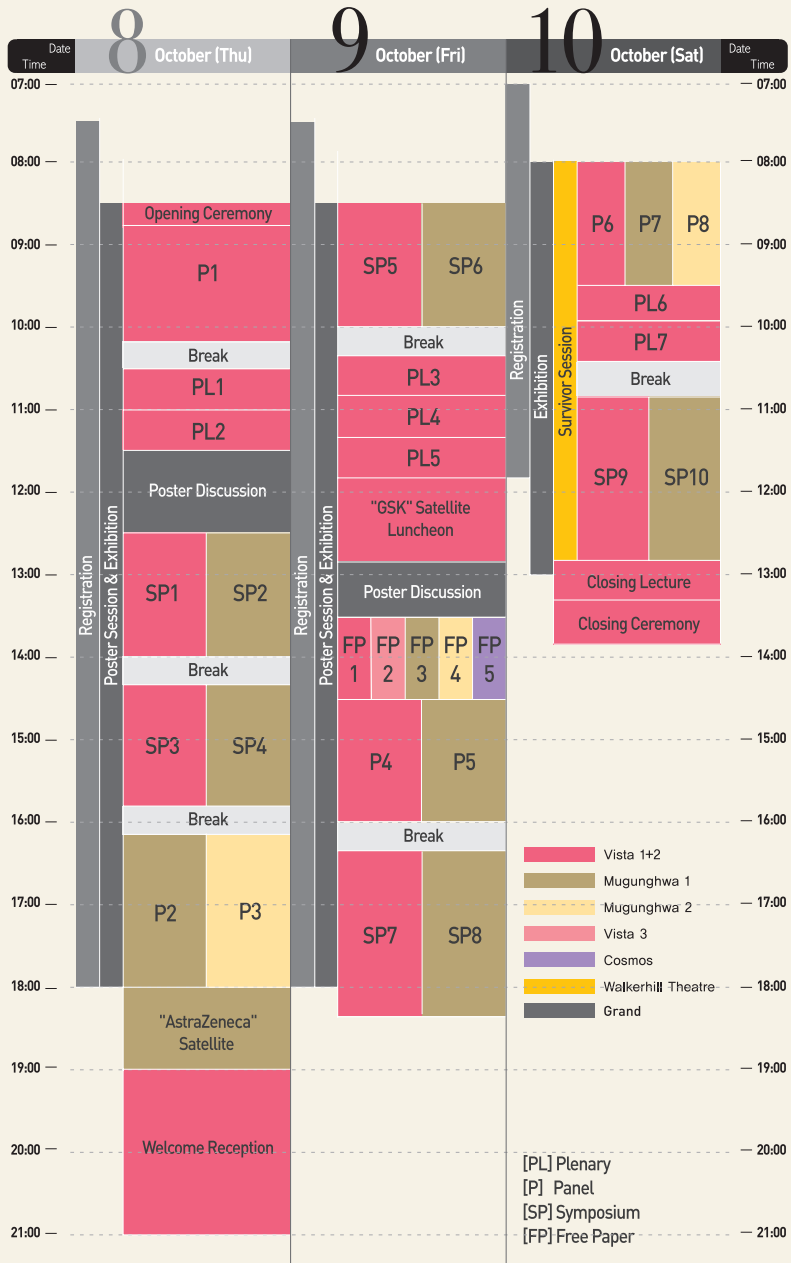
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PROGRAM AT A GLANCE



SCIENTIFIC PROGRAM

Opening Ceremony

08:30-08:40 / October 8, 2009 (Thursday)

Vista Hall I+II

Opening Speech for GBCC2009

Min-Hyuk Lee

Soon Chun Hyang Univ. Hospital, Korea

Official Speech for 7th ABCS

Nam-Sun Paik

Kunkuk Univ. Medical Center, Korea

Panel 1. Portraying Breast Cancer in Asia

08:40-10:10 / October 8, 2009 (Thursday)

Vista Hall I+II

Moderator: Shin-cheh Chen, Chang Gung Memorial Hospital, Taiwan

P1-1 Matter of Gap-Breast Cancer Disparity

17

Hee-Soon Juon¹

¹Department of Health, Behavior & Society, Johns Hopkins Bloomberg School of Public Health, United States of America

P1-2 Current Status of Breast Cancer in Korea

19

Nam-Sun Paik¹

¹Konkuk University Medical Center, Republic of Korea

P1-3 Changing Patterns and Present Status of Female Breast Cancer in China Over 30 Years

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Zhi-Ming Shao¹

¹Department of Surgery, Cancer Hospital, Fudan Univ., China

10:10-10:30 / Break

Plenary 1.

10:30-11:00 / October 8, 2009 (Thursday)

Vista Hall I+II

Moderator: Yung-Jue Bang, Seoul National Univ. Hospital, Korea

PL-1 A Promising Future Therapeutic Strategy for Breast Cancer

3

Eric P. Winer¹

¹Dana-Farber Cancer Institute, United States of America

Plenary 2.

11:00-11:30 / October 8, 2009 (Thursday)

Vista Hall I+II

Moderator: Chang-Ok Suh, Yonsei Univ. Health System, Korea

- PL-2 Evolution and Future Direction of Local Treatment for Breast Cancer** 4
Jay R. Harris¹
¹Department of Radiation Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital Harvard Medical School, United States of America

Poster Discussion with Lunch

11:30-12:30 / October 8, 2009 (Thursday)

Grand Hall

Symposium 1. Update - Breast Cancer Research Summaries after 2007

12:30-14:00 / October 8, 2009 (Thursday)

Vista Hall I+II

Moderators: Soonmyung Paik, NASBP Foundation, Inc, USA
Hy-De Lee, Gangnam Severance Hospital, Korea

- SP01-1 Preclinical** 67
Soonmyung Paik¹
¹Division of Pathology, NSABP Foundation, Inc., United States of America
- SP01-2 Research Local Therapies** 68
Barbara L. Smith¹
¹Comprehensive Breast Health Center, Massachusetts General Hospital, United States of America
- SP01-3 Updates in Systemic Therapy of Breast Cancer** 70
Jo Anne Zujewski¹
¹Clinical Investigations Branch, National Cancer Institute, United States of America

Symposium 2. Psychosocial Needs of Women with Breast Cancer

12:30-14:00 / October 8, 2009 (Thursday)

Mugunghwa I

Moderator: Eunyong Suh, Seoul National Univ., Korea

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Bok Yae Chung¹

¹Nursing, Kyungpook National Univ. College of Nursing, Republic of Korea

SP02-2 Interventions to Enhance Breast Cancer Adjustment among Patients and their Partners 75

Wendy C. Budin¹, Carol Noll Hoskins², Judith Haber², Deborah Witt Sherman³,

Greg Maislin⁴, Frances Cartwright-Alcares⁵, Mildred Ortu Kowalski⁶,

Christina Beyer McSherry⁷, Renee Fuerbach², Shilpa Shukla⁸

¹Nursing, NYU Medical Center/New York University College of Nursing, United States of America,

²College of Nursing, New York University, United States of America, ³School of Nursing,

University of Maryland, United States of America, ⁴Biomedical Statistical Consulting, Wynwood,

United States of America, ⁵NYU Clinical Cancer Center, United States of America, ⁶Novartis

Pharmaceuticals, United States of America, ⁷School of Nursing, William Patterson University,

United States of America, ⁸Department of Pathology, Yale University, United States of America

14:00-14:20 / Break

Symposium 3. Preoperative Systemic Therapy: Multidisciplinary Perspectives

14:20-15:50 / October 8, 2009 (Thursday)

Vista Hall I+II

Moderators: Hyun Cheol Chung, Yonsei Univ. Health System, Korea

Gyung Yub Gong, Asan Medical Center, Korea

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Sung Yong Kim¹

¹Soon Chun Hyang Univ. Hospital, Cheonan, Republic of Korea

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Jungsil Ro¹

¹Center for Breast Cancer, National Cancer Center, Republic of Korea

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Barbara L. Smith¹

¹Comprehensive Breast Health Center, Massachusetts General Hospital, United States of America

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Young Kyung Bae¹

¹Pathology, Yeungnam Univ., College of Medicine, Republic of Korea

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14:20-15:50 / October 8, 2009 (Thursday)

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Barbara F. Piper¹
¹Research and Practice Division, Scottsdale Healthcare/ University of Arizona, United States of America
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Andrea Barsevick¹
¹Cancer Prevention & Control, Fox Chase Cancer Center, United States of America

15:50-16:10 / Break

Panel 2. ABCS Session I: Sharing Ideas and Experiences of Clinical Trials

16:10-18:00 / October 8, 2009 (Thursday)

Mugunghwa I

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Shou-Ching Tang, Univ. of Colorado Denver Health Medical Center, USA

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Chanheun Park¹
¹Dept. of Surgery, Hallym Univ. Kangdong Sacred Heart Hospital, Republic of Korea
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¹Clinical Investigations Branch, National Cancer Institute, United States of America
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¹Chief of Division of Breast Surgery, Tung Wah Hospital Breast Centre University of Hong Kong, Hong Kong
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¹Department of Surgery, National Taiwan Univ. Hospital, Taiwan
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¹Dept. of Medicine, Samsung Medical Center, Cancer Center, Republic of Korea
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¹Medical Oncology, Tata Memorial Hospital, Mumbai, India, India
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Arlene Chan¹
¹Mount Breast Group, Mount Hospital, Australia

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16:10-18:00 / October 8, 2009 (Thursday)

Mugunghwa II

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Tadashi Ikeda, Teikyo Univ. School of Medicine, Japan

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Mugunghwa I

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08:30-10:00 / October 9, 2009 (Friday)

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¹Department of Surgery, Seoul National Univ. College of Medicine, Republic of Korea
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¹Department of Surgery, Brigham and Women's Hospital, Dana Farber Cancer Institute, Harvard Medical School, United States of America
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¹Surgery, Memorial Sloan-Kettering Cancer Center, United States of America
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Ki Chang Keum¹
¹Radiation Oncology, Yonsei Univ. College of Medicine, Republic of Korea

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Mugunghwa I

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¹College of Nursing, Korea Univ. College of Nursing, Republic of Korea
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¹Department of Adult Nursing, St. Luke's College of Nursing, Japan
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¹Breast Division, Department of Surgery, Samsung Medical Center, Comprehensive Cancer Center, Republic of Korea
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¹Department of Nursing, Samsung Medical Center, Republic of Korea
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¹College of Nursing, Korea Univ., Republic of Korea

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10:20-10:50 / October 9, 2009 (Friday)

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Moderator: Eun Sook Lee, Korea University Anam-Hospital, Korea

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V. Craig Jordan¹

¹Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, United States of America

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Graham A. Colditz¹

¹Surgery, Washington Univ. School of Medicine, United States of America

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Marc Sutterlin¹, Frederik Wenz²

¹Dept. of Obstetrics & Gynecology, University Medical Center Mannheim, University of Heidelberg, Germany, ²Dept. of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Germany

Satellite Luncheon Symposium: GSK

11:50-12:50 / October 9, 2009 (Friday)

Vista Hall I+II

Moderator: Sang Jae Lee, Choong-Ang Univ. Hospital, Korea

Optimizing Treatments for ErbB2 Driven Breast Cancer

Arlene Chan

Mount Hospital, Australia

Poster Discussion with Lunch

12:50-13:30 / October 9, 2009 (Friday)

Grand Hall

Moderators: Kyung Hae Jung, Seoul Asan Medical Center, Korea
Sung Hwan Park, Catholic Univ. of Daegu, Korea

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¹Breast and Endocrine Surgery, Aichi Medical University, Japan, ²Pathology, National Cancer Center, Japan, ³Basic Pathology, National Defense Medical College, Japan
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¹Department of Surgery, Korea University Hospital, Republic of Korea, ²KBCS, The Korean Breast Cancer Society, Republic of Korea
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¹Surgery, Korea Institute of Radiological & Medical Science, Korea Cancer Center Hospital, Republic of Korea, ²Pathology, Korea Institute of Radiological & Medical Science, Korea Cancer Center Hospital, Republic of Korea, ³Radiation Oncology, Korea Institute of Radiological & Medical Science, Korea Cancer Center Hospital, Republic of Korea, ⁴Radiology, Korea Institute of Radiological & Medical Science, Korea Cancer Center Hospital, Republic of Korea, ⁵Laboratory Medicine, Korea Institute of Radiological & Medical Science, Korea Cancer Center Hospital, Republic of Korea, ⁶Surgery, Kang-Won National University, Republic of Korea, ⁷Surgery, Konkuk University, Republic of Korea
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¹Cancer Early Detection Branch, National Cancer Control Research Institute, National Cancer Center, Republic of Korea, ²Cancer Epidemiology Branch, Division of Cancer Epidemiology and Management, Research Institute, National Cancer Center, Republic of Korea, ³Department of Breast and Endocrine Surgery, College of Medicine, Korea University, Republic of Korea, ⁴Functional Genomic Branch, Division of Convergence Technology, Research Institute, National Cancer Center, Republic of Korea, ⁵Department of Epidemiology, Graduate School of Public Health, Seoul National University, Republic of Korea, ⁶Department of Preventive Medicine, Seoul National University College of Medicine, Republic of Korea
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 Hye-Kyung Na¹, Eun-Hee Kim², Do-Hee Kim², Young-Joon Surh²
¹Department of Food and Nutrition, Sungshin Women's University, Republic of Korea, ²National Research Laboratory of Molecular Carcinogenesis and Chemoprevention, College of Pharmacy, Seoul National University, Republic of Korea

Moderators: Young-Tae Bae, Pusan National Univ. Hospital, Korea

Kweon Cheon Kim, Department of Surgery, Chosun Univ., Korea

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¹Breast Disease, Hospital of Obstetrics and Gynecology Fudan University, China, ²Shanghai Cancer Recovery Club & Shanghai Cancer Recovery School, China
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¹Dept. of Breast Cancer, Shandong Cancer Hospital & Institute, China, ²Dept. of Breast Cancer, Beijing University Cancer Hospital, China, ³Dept. of Pathology, Guangdong General Hospital, China, ⁴Dept. of Breast Cancer, Fudan University Cancer Hospital, China, ⁵Dept. of Breast Cancer, Third Military Medical University Southwest Hospital, China, ⁶Dept. of Breast Cancer, Sun Yat-sen University 2nd Affiliated Hospital, China, ⁷Dept. of Breast Cancer, Guangdong General Hospital, China
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¹Department of Surgery, Dong-A University College of Medicine, Republic of Korea, ²Department of Pathology, Dong-A University College of Medicine, Republic of Korea
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¹Department of Thoracic and Visceral Organ Surgery, Gunma University Graduate School of Medicine, Japan, ²Department of Emergency Medicine, Gunma University Graduate School of Medicine, Japan
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¹Center for Breast Cancer, Research Institute and Hospital, National Cancer Center, Republic of Korea, ²Department of Radiation Oncology, Seoul National University College of Medicine, Republic of Korea

13:30-14:30 / October 9, 2009 (Friday)

Mugunghwa I

Moderators: Keun Seok Lee, National Cancer Center, Korea
Lee Su Kim, Hallym Univ. Sacred Heart Hospital, Korea

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¹Dept of Rad Oncology, Allan Blair Cancer Center, Canada, ²Dept of Rad Oncology, London Regional Cancer Center, Canada, ³Dept of Rad Oncology, Cross Cancer Center, Canada
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¹Surgery, Gyeongsang National University Hospital, Republic of Korea, ²Surgery, Seoul National University Hospital, Republic of Korea
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¹Center for Breast Cancer, National Cancer Center, Republic of Korea, ²Cancer Biostatistics Branch, Research Institute for National Cancer Control & Evaluation, Republic of Korea
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¹Breast Clinic, Saegyaero Hospital, Republic of Korea, ²Nuclear Medicine, Busan PET Center, Republic of Korea

Moderators: Se Heon Cho, Dong-A Univ. Medical Center, Korea
Chanheun Park, Hallym Univ. Kangdong Sacred Heart Hospital, Korea

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Fiona Tsui-Fen Cheng¹
¹Department of Surgery, Division of General Surgery, Shin Kong Wu Ho-Su Memorial Hospital, Taiwan
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¹Hematology-Oncology, Samsung Medical Center, Republic of Korea, ²Surgery, Samsung Medical Center, Republic of Korea, ³Pathology, Samsung Medical Center, Republic of Korea
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¹Dep. of the Medical Informatics, Ajou University, Republic of Korea, ²Dep. of the Surgery, Ajou University, Republic of Korea, ³Dep. of the Surgery, Samsung Medical Center, Republic of Korea, ⁴Dep. of the Surgery, National Police Hospital, Republic of Korea
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¹Center for Breast Cancer, National Cancer Center, Republic of Korea, ²NHS Foundation Trust & Institute of Cancer Research, Royal Marsden Hospital, London, United Kingdom, ³Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, United States of America, ⁴Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, United States of America, ⁵US Oncology Research Inc, Sammons Cancer Center, Dallas, TX, United States of America, ⁶Dept Medical Oncology, University Hospital J. Minjoz, Besancon, France, ⁷Division of Medicine, Instituto De Enfermedades Neoplasicas, Lima, Peru, ⁸Oncology R&D, GlaxoSmithKline, Durham, NC, United States of America, ⁹Oncology R&D, GlaxoSmithKline, Collegeville, PA, United States of America, ¹⁰Oncology R&D, GSK, Collegeville, PA, United States of America
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Myungsun Yi¹, Eun Young Park¹
¹College of Nursing, Seoul Nat'l Univ, Republic of Korea

Free Paper 5

13:30-14:30 / October 9, 2009 (Friday)

Cosmos

Moderator: Jeonghee Kang, Chonbuk National Univ., Korea

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Insook Lee¹, Won-Hee Lee²
¹Department of Nursing, Che-ju Halla College, Republic of Korea, ²Department of Clinical Nursing, Yonsei University College of Nursing, Republic of Korea
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¹Department of Nursing, National Taipei College of Nursing, Taiwan, ²Department of Health Care Management, National Taipei College of Nursing, Taiwan, ³Institute of Population Health Sciences, National Health Research Institutes, Taiwan, ⁴Department of Oncology, National Taiwan University Hospital, Taiwan
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¹Family Health Science, College of Nursing, Yonsei University, Republic of Korea
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Hyang Sook So¹, Hae Young Kim², Eun Ko³, Young Hee Noh⁴
¹Nursing College, Chonnam National University, Republic of Korea, ²Department of Nursing, Chonnam Techno College, Republic of Korea, ³Department of Nursing, Nambu University, Republic of Korea, ⁴Department of Nursing, Dong Kang University, Republic of Korea

Panel 4. Revisiting Estrogen and ER Measurement

14:30-16:00 / October 9, 2009 (Friday)

Vista Hall I+II

Moderators: Young-Joon Surh, Seoul National Univ., Korea

V. Craig Jordan, Lombardi Comprehensive Cancer Center, Georgetown Univ. Medical Center, USA

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¹College of Pharmacy, Seoul National Univ., College of Pharmacy, Republic of Korea
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V. Craig Jordan¹
¹Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, United States of America
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Yoon-La Choi¹
¹Pathology, Samsung Medical Center, Republic of Korea

Panel 5. Targeting Biological Subtypes and Pathways

14:30-16:00 / October 9, 2009 (Friday)

Mugunghwa I

Moderators: Byeong-Woo Park, Yonsei Univ. College of Medicine, Korea
Dong Wha Lee, Soonchunhyang Univ. Hospital, Korea

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¹College of Molecular, School of Molecular and Veterinary Medicine, The University of Edinburgh, United Kingdom
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Seock-Ah Im¹
¹Dept. of Internal Medicine, Seoul National University Hospital, Republic of Korea
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¹Tumor Cell Biology, Beckman Research Institute of the City of Hope, United States of America
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¹Department of Internal Medicine, Korea Univ. Anam Hospital, Republic of Korea

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Symposium 7. Update on Endocrine Treatment

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Vista Hall I+II

Moderators: Sei-Hyun Ahn, Seoul Asan Medical Center, Korea
R. Charles Coombes, Hammersmith Hospital, UK

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¹Division of Breast Oncology, National Kyushu Cancer Center, Japan

Symposium 8. Breast Cancer Control Opportunities in Asia

16:20-18:20 / October 9, 2009 (Friday)

Mugunghwa I

- Moderators:** Mehra Golshan, Brigham and Women's Hospital, Dana Farber Cancer Institute, Harvard Medical School, USA
Kyung Hee Lee, Yeungnam Univ. Medical Center, Korea
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¹Surgical Oncology, The Avon Foundation Breast Center at Johns Hopkins, United States of America
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¹Surgery, Kyungpook National Univ. Hospital, Republic of Korea
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¹Department of Breast Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan, ²Department of Breast Oncology, Saitama Medical University International Medical Center, Japan, ³Department of Breast Surgery, Niigata Cancer Center, Japan, ⁴Department of Breast and Thyroid Surgery, Kawasaki Medical School, Japan, ⁵Department of Biostatistics, Kitasato University, Japan

Panel 6. A Team for Long-Term Care

08:00-09:30 / October 10, 2009 (Saturday)

Vista Hall I+II

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Lillie Shockney, The Avon Foundation Breast Center at Johns Hopkins, USA
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Kwang-Man Lee¹
¹Breast and Endocrine Surgery, Wonkwang Univ. Hospital, Republic of Korea
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Dukhyoung Lee¹
¹Department of Disease Policy, Ministry for Health, Welfare and Family Affairs, Republic of Korea

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¹Internal Medicine, Seoul St.Mary's Hospital, Republic of Korea
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¹Graduate School of Public Health, Yonsei Univ. Graduate School of Public Health, Republic of Korea
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¹Oncology R&D, GlaxoSmithKline, Republic of Korea

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¹Breast&Thyroid Surgery, College of Medicine, Chonbuk National Univ., Republic of Korea
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¹Division of Surgery, Chang Gung Memorial Hospital, Taiwan
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¹Department of Surgery, Seoul National Univ. Hospital, Republic of Korea

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¹College of Medicine, Seoul National University, Republic of Korea

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Monica Morrow¹

¹Surgery, Memorial Sloan-Kettering Cancer Center, United States of America

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¹Clinical Trials Centre, The University of Hong Kong, Hong Kong

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¹Surgery, Kyoto Univ., Japan

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¹Department of Medicine, Asan Medical Center, Republic of Korea

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Soonmyung Paik¹

¹Division of Pathology, NSABP Foundation, Inc., United States of America

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¹Social Work, California State University, East Bay, United States of America

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Rebekkah Schear¹
¹International Program Manager, Lance Armstrong Foundation, United States of America

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Hee-Soon Juon

Johns Hopkins Bloomberg School of Public Health, USA

Best Presentation/Poster Award

Sung-Bae Kim

Seoul Asan Medical Center, Korea

Closing Remark

Dong-Young Noh

Seoul National Univ. Hospital, Korea

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²Department of Biochemistry, Siriraj Hospital, Mahidol University, Thailand
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¹Physiological Nursing, University of California, San Francisco, United States of America,
²Markstein Cancer Center, Alta Bates Summit Medical Center, United States of America,
³Community Outresearch Program, Korean Community Health Services, United States of America
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²Radiology, Seoul St. Mary's Hospital, Catholic University of Korea, Republic of Korea,
³Pathology, Seoul St. Mary's Hospital, Catholic University of Korea, Republic of Korea,
⁴Radiation Oncology, Seoul St. Mary's Hospital, Catholic University of Korea, Republic of Korea,
⁵Medical Oncology, Seoul St. Mary's Hospital, Catholic University of Korea, Republic of Korea,
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GBCC 2009

Plenary Lecture

A Promising Future Therapeutic Strategy for Breast Cancer

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Evolution and Future Direction of Local Treatment for Breast Cancer

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The Early Breast Cancer Trialists' Cooperative Group (EBCTCG) has clearly demonstrated that reducing local recurrence (LR) either by the use of better surgery or by the use of radiation therapy (RT) after either breast-conserving surgery (CS) or after mastectomy in node-positive patients not only reduces local recurrence (LR), but also improves long-term survival [1]. The EBCTCG specifically found that the absolute reduction in the 5-year rate of LR was proportional to the absolute reduction in 15-year breast cancer mortality with a 4:1 ratio. It was previously widely believed that local treatment reduced local recurrence, but had no impact on survival. A meta-analysis from the EBCTCG has also demonstrated that CS combined with RT provides equivalent long-term survival as achieved by mastectomy. Advances in surgery over the past decade include (1)-the use of sentinel node biopsy (SNB) instead of axillary node dissection for most patients, (2) improved techniques of breast reconstruction and the use of skin-sparing mastectomy to facilitate reconstruction and (3)-the use of preoperative systemic in patients initially deemed suitable for CS+RT to convert them to be suitable for CS+RT. Advances in RT over the past decade include (1) the serendipitous findings that when RT is combined systemic therapy, LR is substantially reduced, (2)-the development of techniques that minimize cardiac irradiation and (3) the finding that accelerated whole breast irradiation (16 treatments, no boost) is appropriate in many patients aged greater than 60 who don't require a 'boost' or nodal irradiation. This evolution in the local treatment of breast cancer has resulted in very low rates of LR in patients with early-stage breast cancer while at the same time providing improved quality of life.

The future of local treatment for breast cancer has many exciting directions. There is preliminary evidence that the use of preoperative systemic can decrease the need for ALND, but this needs to be more clearly established. There is also preliminary evidence that accelerated partial breast irradiation can substitute for conventional whole breast irradiation in some patients, but this too needs to be more clearly established. Critically important, we await the utilization of molecular-genetics in decisions regarding local treatment. Standard clinical-pathologic features have not been able to identify patients who can be treated without RT

after CS, but it is hoped that molecular-genetic markers can. We also currently have only crude indicators of which patients would benefit from RT following mastectomy, but validated molecular-genetic markers would also be extremely useful in this setting. Breast surgeons and radiation oncologists need to understand their treatments in the context of continually improving adjuvant systemic therapy. To date, improvements in adjuvant systemic therapy have only increased the importance of effective local treatment, but ultimately very effective systemic therapy will lessen the need for local treatment. One of the striking developments in the U.S. is the recent increased use of mastectomy in patients with invasive cancer and ductal carcinoma-in-situ considered suitable for CS and RT. Breast surgeons and radiation oncologists need to learn new techniques to more effectively communicate information to newly-diagnosed breast cancer patients to facilitate that the most rational and appropriate decisions are made.

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Maximizing Benefits of Endocrine Therapy

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In 1970, Sir Alexander Haddow FRS, presented the inaugural Karnofsky lecture at the American Society of Clinical Oncology [1]. He was not optimistic that tumor specific anticancer agents would be developed, and he was disheartened that there were no tests available to predict whether a treatment would be effective in a particular cancer. Haddow was a pioneer, who developed first chemical therapy for any cancer [2]. High dose estrogen treatment is effective in about 30% of metastatic breast cancers in postmenopausal women, but he declared that although tumor regressions were dramatic in about 1% of patients, the underlying mechanism of action was unknown.

Long-term adjuvant tamoxifen therapy remains a cheap, effective, life-saving treatment for patients with estrogen receptor (ER) positive breast cancer. Until recently, tamoxifen treatment might be recommended based solely upon ER status for the tumor. However, although it has been known since the 1980s that tamoxifen needs to be metabolically activated for optimal action [3], only recently has it been recognized that mutations in the CYP2D6 gene prevents metabolic activation to the important metabolite, endoxifen. Endoxifen has a high binding affinity for the estrogen ER, and patients with CYP2D6 mutations tends to have fewer hot flashes and an increased recurrence rate for breast cancer [4]. Additionally, it seems that selective serotonin re-uptake inhibitors (SSRIs), which are routinely used to reduce hot flashes in patients on tamoxifen, actually block the metabolic activation of tamoxifen to endoxifen. Thus, it appears that personalized medicine for tamoxifen may soon be commonplace with patients screened for genotyping their CYP2D6, and if they are postmenopausal and have a functional mutated enzyme, then an aromatase inhibitor could be used as an alternative.

With the rigorous evaluation of tamoxifen and the aromatase inhibitors as adjuvant endocrine therapies, it seems that we may have reached the zenith of what can be achieved with monotherapy. Laboratory research suggests that drug resistance to tamoxifen involves the activation of angiogenic mechanisms through the VEGFR2 activated mechanisms. This implies that an inhibitor of VEGFR2 may be able to improve the antihormonal activity of tamoxifen. However, high dose ther-

apy with VEGFR2 inhibitors may not be an appropriate strategy for long-term treatment. We have tested the hypothesis that a combination of tamoxifen and sub-effective doses of a VEGFR2 inhibitor, Brivanib alaninate may be superior to either drug administered alone. Laboratory studies have demonstrated that the hypothesis is correct. However, the problem to be addressed is how to evaluate efficacy of this approach prior to committing to long term adjuvant clinical studies. We suggest that the strategy for clinical testing may be found in a study of drug resistance to antihormone treatment in metastatic breast cancer.

Knowledge of the evolution of antihormonal drug resistance has revealed a vulnerability of breast cancer cells that can be exploited for clinical benefit. Physiological estrogen causes apoptosis and tumor regression in antihormone resistant breast cancer, and these laboratory observations have been effectively translated into clinical trials [5]. However, the question arises of how can this new knowledge be best deployed to aid patients with ER positive metastatic breast cancer who have failed exhaustive antihormonal therapy? We believe there are at least two approaches to address the problem based upon the prediction that short term low dose estrogen treatment will produce about 30% response rates in tumors that have become refractory to exhaustive antihormonal therapy. The question is whether we can enhance response rates by undermining survival mechanisms in the 70% of tumors that do not respond to estrogen treatment. The two approaches that seem feasible are to use a short term estrogen therapeutic treatment duration (12 weeks) and incorporate in either an agent that generally creates survival vulnerability (L-Buthionine sulfoximine) [6], or a range of new targeted inhibitors of tumor cell survival that may work with estrogen to increase the proportion of complete responses in metastatic breast cancer. Most importantly, based on laboratory evidence [7], tumors that respond to the apoptotic actions of estrogen can be maintained effectively on reintroducing antihormonal therapy.

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Lifestyle Determinants for Breast Cancer Risk Offer Potential for Prevention

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A widely held view among breast cancer researchers, advocates, and clinicians treating this disease is that prevention is difficult or impossible. Yet breast cancer incidence rates historically differed by as much as 5-fold comparing low risk to high risk countries. This difference in rates and documented changes in incidence among populations that migrate from low risk to high risk countries provides substantial evidence supporting the potential for reduction in the burden of breast cancer through prevention strategies.

Breast cancer incidence in many emerging economy countries continues to increase and prevention remains an unfulfilled promise for this the leading cancer diagnosis among women. Known causes of breast cancer include radiation, alcohol, female hormones (endogenous and exogenous), and family history as a marker of genetic risks. In addition lack of physical activity and postmenopausal obesity also cause increased incidence. A full appreciation of the causal relation between exposure and cancer and the potential for prevention requires a clear documentation of the time in the life course at which exposure is most important, understanding of how much we can change exposures, and for how long change must be sustained before risk of cancer is substantially reduced.

Age incidence curves for breast cancer from many countries show similar patterns, risk increases from menarche to menopause at approximately 8% per year then slows to 2.5% per year after menopause. Consistent with this, early menopause (resulting in a change from high to low annual increase in risk) is associated with substantial reduction in lifetime risk of breast cancer.

Radiation exposure among atomic bomb survivors clearly documents the importance of exposures in childhood and adolescence determining lifelong risk of breast cancer. Growing evidence for physical activity throughout premenopausal years and soy intake in childhood and adolescence add to the evidence for potential prevention through lifestyle changes. Further evidence on adolescent exposures and risk of proliferative breast disease adds support to the role of childhood and adolescent exposures as causes for breast cancer and offer strategies to modify risk through lifestyle changes.

Adiposity after menopause is a growing global epidemic causing higher levels of circulating estrogen, which directly drive incidence of estrogen receptor positive

breast cancer. Estrogen inhibition through use of SERMs and weight loss after menopause, clearly shows substantial reduction in breast cancer incidence. Combining 1 and offers guidance for lifestyle changes that can reduce risk of breast cancer.

Integration of lifestyle factors into models of breast cancer incidence allows us to classify level of risk and show a more than 6-fold difference in risk between the top and bottom 10% of any age stratum of women. We propose the use of risk stratification such as from the Colditz and Rosner model to tailor prevention strategies to women according to their level of risk. We estimate that more than half of breast cancer could be prevented if we act on what we already know to guide the use of prevention strategies. For women carrying BRCA1/2 genes, oophorectomy halves risk for breast cancer. For women in the highest 10 to 20 percent of risk, SERMs significantly reduce risk by half or more. For women after menopause, weight loss and increase in physical activity will reduce risk by 30 to 50%. Long-term strategies must address childhood and adolescent physical activity and diet to protect the next generation of women.

Intraoperative Radiotherapy with Low Energy X-rays for Breast Cancer

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The standard postoperative radiotherapy after breast-conserving surgery (BCS) is percutaneous irradiation of the entire breast to a total dose of 50 Gy, usually followed by a tumor bed boost. Due to the increased detection of small breast cancers by mammographic screening, it is necessary to consider modifications of the existing therapeutic practice. In this context, intraoperative radiotherapy (IORT) for breast cancer using either electrons or low-energy X-rays is of increasing interest.

The Intrabeam system (Carl Zeiss, Oberkochen/Germany) is an innovative mobile device for IORT that includes a miniature radiation source generating isotropic low energy X-ray beam energies to 50 kV maximum. Using a spherical applicator, a single high radiation dose of 20 Gy is administered to the tumor bed in the operating room immediately after wide tumor resection without the need for further surgical preparations. There are only minimal shielding requirements for personnel in the operating room.

Preliminary data suggest that IORT given as a tumor bed boost with the Intrabeam system after breast-conserving surgery could be a reliable alternative to conventional postoperative fractionated boost radiation by accurate dose delivery without geographical miss and by enabling smaller treatment volumes, complete skin-sparing and reducing postoperative radiation time by 7-10 days. The first five years of experience of our institution in 154 breast cancer patients treated between 2002 and 2007 using low energy X-rays (20 Gy) followed by 46-50 Gy external beam radiotherapy (EBRT) of the whole breast with a median follow up of 34 months shows a low local recurrence rate of 1.5% in 5 years and low toxicity rates (grade III fibroses of the tumor bed in 5% of the patients after 3 years). Early initiation of EBRT (<5-6 weeks after IORT) seems to be associated with a higher risk of long-term toxicity such as fibrosis II-III°.

Preliminary data suggest, that targeted intraoperative radiotherapy delivered to the tumor bed alters the cytokines and growth factors expression patterns in the

surgical wound and abrogates their stimulatory effect on cancer cell growth and motility. This postulated novel mechanism of action of radiotherapy might partly be able to explain the very low recurrence rates found in the large pilot studies with this technique so far and open new avenues for perioperative therapies.

Since the majority of local recurrences are close to the former tumor bed, the question arises whether tumor bed irradiation alone might be a therapeutic alternative to total breast irradiation for a selected group of patients with early stage invasive breast cancer. TARGIT is an international randomised clinical trial designed to test the hypothesis that the strategy of delivering a single dose of targeted IORT in patients eligible for breast conserving therapy (with the addition of whole breast radiotherapy in those patients at high risk of recurrence elsewhere in the breast, e.g. lobular carcinomas and extensive intraductal component) is equivalent to a conventional course of postoperative EBRT. The TARGIT trial will reach its accrual goal by the end of 2009.

In addition, breast conserving surgery with IORT is a valuable alternative to mastectomy with good local control and tolerability for patients with local breast cancer relapse after breast-conserving therapy with EBRT for the primary tumor.

In our institution, we use IORT with the Intrabeam system for all three clinical settings since 2002. Patients with primary breast cancer receive IORT after BCS either as a tumour-bed boost followed by 46 Gy EBRT or within the scope of the international TARGIT trial as accelerated partial breast irradiation (PBI) only, if they fulfill the inclusion criteria for the study. The presentation will focus on the feasibility and surgical aspects of IORT with Intrabeam and will summarize our experience with its effectiveness such as local control and its side effects.

In the follow up of patients treated with IORT, it is important to know that IORT is associated with a high incidence of large oil cysts, which arise from likewise large partially organized wound cavities. On ultrasound pronounced partial organization with polypoid inner wall thickening is a frequent finding in those cavities.

In summary, IORT with the Intrabeam system is a easily feasible and safe method to deliver a single high radiation dose to breast cancer patients. The treatment is well tolerated and shows a good cosmetic outcome as it does not cause greater damage than the expected late reaction in normal tissue. The existing data with regard to its effectiveness are promising.

Upsurge of Breast Cancer in Young Asian Women: Trend and its Determinants

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Breast cancer is the most common cancer in many Asian countries. Although the incidence rate remains low, it is increasing at a more rapid rate than in western countries due to changes in lifestyle and diet. Epidemiologic studies showed that inherent and acquired risk factors for breast cancer are common for Asian and Western women. However, the relative exposure to those factors, i.e., lifetime exposure to hormones, high fat diet, obesity, and hormone receptors expression, may vary by ethnicity. The level of serum estradiol among Korean women was much lower than that of Western women, and even lower than Japanese women. A similar pattern of high and low penetrance genes has been observed through molecular epidemiologic studies in Asian and Western women, although the frequency may vary. Particularly noteworthy is that the mean age at onset of breast cancer is younger than in the West, and unlike the West, the age-specific incidence decreases after the age of 50 years. Differences in age-specific incidence curve of breast cancer between Asian and Western women seem to be a real difference in occurrence of premenopausal breast cancer patients. Another reason might be due to the marked increase in breast cancer screening experience especially in middle-aged women in a country like Korea. Breast cancer is usually presented and diagnosed at a later stage of development in Asian women, except in Korea and Japan, because there is no population-based breast cancer screening program in the majority of Asian countries. Based on this evidence, it can be speculated that the age curve of breast cancer currently observed in Asian countries may follow that of the Western women in the future according to the exposure level of hormone, risk factors, and the receptor status.

The Clinical Dilemma of Ductal Carcinoma in Situ (DCIS)

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Current management strategies for ductal carcinoma in situ (DCIS) range from mastectomy to excision plus radiation therapy (RT), to excision alone. This diverse spectrum of therapies reflects our inability to predict which DCIS will progress to invasive cancer, or even which DCIS will recur when treated conservatively with excision alone, making the selection of the appropriate therapeutic approach for the individual patient with DCIS a major dilemma. It is generally accepted that mastectomy is indicated when the size of the DCIS precludes complete excision with an acceptable cosmetic outcome, and that treatment with mastectomy results in local control and long-term survival in more than 95% of DCIS patients. The need for adding RT following excision to maintain local control in patients with DCIS is controversial, in part due to retrospective, single-institution studies of highly selected DCIS patients treated with excision alone which reported very low rates of local recurrence. Subsequently, 4 prospective randomized trials have shown an approximately 50% reduction in local recurrence when RT is added to excision, and subset analyses failed to identify a group of patients who, based on favorable clinical-pathologic features, derived no benefit from RT. Critics of the randomized trials feel that inadequate attention was paid to defining the completeness of the excision carried out in those studies. To many, the randomized trials demonstrated that with routine tissue processing and minimal negative margins, RT was beneficial in decreasing local recurrence, but did not answer the question of whether a wider excision could eliminate the need for RT. This hypothesis was tested in a prospective, single-arm study performed by the Intergroup. Eligibility was restricted to those with high-grade DCIS between 3 mm and 10 mm in size, and to those with low- or intermediate-grade DCIS between 3 mm and 25 mm in size. Margins of at least 3 mm were required, and a post-excision mammogram was obtained for all participants. At a median follow-up of 6.7 years, the 5-year rate of local recurrence was 15.3% (95% CI: 8.2-22.5%) for the patients with high-grade DCIS, and 6.1% (95% CI: 4.1-8.2%) for the patients with low/intermediate-grade DCIS. The annual hazard rate for ipsilateral breast events is fairly constant over the first 10 years after treatment in low/intermediate-grade DCIS, so one could anticipate the 10-year rate to be about 12%. In addition, patients in this trial had more favorable characteristics than required for eligibility, suggesting that these results may not be generalizable to the majority of those with DCIS. In the

low/intermediate grade group, there was no difference in the 5-year rate of local recurrence based on margins greater or less than 10 mm (6.7% and 5.6%, respectively). The challenge for the future is to identify markers which reliably predict behavior since even in the hands of experienced clinicians using defined protocols for surgery, mammographic evaluation, and tissue processing, DCIS patients selected for treatment with excision alone using conventional clinical-pathologic features have a significant short-term risk of local recurrence.



GBCC 2009

Panel

Matter of Gap-Breast Cancer Disparity

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Breast cancer is the most prevalent cancer in the world. An estimated 1 million women worldwide are newly diagnosed with breast cancer annually. Previously a malady that mostly afflicted white, affluent women in the industrial hubs of North America and Western Europe, breast cancer is everywhere. Asia, Africa, Eastern Europe, and Latin America have all seen their caseloads spike. By 2020, 70% of all breast cancer cases worldwide will be in developing countries. The purpose of this session is to address the breast cancer disparity among Asian women. In addition, hereditary differences of breast cancer in Asian women will be addressed.

Data on breast cancer mortality, incidence, and survival rates will be summarized by using most recent data available from the World Health Organization Statistical Information System (WHOSIS) and International Agency for Research on Cancer (IARC). For differences of germline mutations in BRCA1 and BRCA2 of Asian women with breast cancer, systematic review and meta-analysis was conducted with 46 papers from PubMed and EMBASE for English publication since 1990.

The incidence of breast cancer in Asian countries was lower than that in Western countries. Differences in breast cancer incidence rates in Asian countries exist. Morbidity and mortality related to breast cancer has strikingly increased in Asia. For a woman battling breast cancer in high-income countries, new diagnosis and treatment options come along all the time. However, these new developments are not available for women battling breast cancer in low- and middle-income countries. In the U.S., the five-year breast cancer survival rate is 83 percent. By contrast, Europe's rate is 69 percent and China's survival rate is 61 percent. While the risk factors for the disease may cross borders freely, the cultural understanding it takes to treat it does not. Americans' attitude regarding breast cancer is vastly different from those in other parts of the globe, where breast cancer is still a misunderstood disease.

Random effect meta-analysis results showed a pooled prevalence of 10% for BRCA1 mutation and 8% for BRCA2 mutation. For breast cancer women with family history, prevalence for BRCA1 and BRCA2 mutations are 13% and 9%.

For early-onset breast cancer women, the prevalence for BRCA1 and BRCA2 mutations are 6% and 3%.

We need to reduce breast cancer disparities in Asia by increasing breast cancer awareness among Asian women in consideration of cultural differences of breast cancer such as the myths of breast cancer. We also need to work on progress in the prevention, early detection, and treatment of breast cancer. One of the efforts is organizing a multidisciplinary breast cancer conference in Asia to collaborate efforts among researchers, health professionals, and policy makers.

Current Status of Breast Cancer in Korea

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Since 1988 year, cancer has become the most common cause of death in Korea. In terms of incidence, still gastric cancer is the most common cancer in male, but since 2001 year breast cancer became the most common cancer in female. There are several reasons, 1) Westernized food patterns; high fat and high calorie diet, 2) lower birth rate, 3) shorter period of breast feeding, 4) longer exposure to estrogen; early menarche with late menopause, hormone replacement therapy and use of oral contraceptives, 5) late first-delivery, 6) smoking, 6) higher BMI (low physical activity), 7) higher in educational level, etc.

In 2002 year about one million cases of new breast cancer were estimated all over the world. But in Korea 9,668 cases were newly registered in 2004, 11,275 cases in 2006 and 14,000 cases in 2008, among them in situ carcinoma was 8.5% in 2004, but in 2006 13.6%. The level of breast cancer incidence in Korea is considered being low comparing to world-wide incidence. Annual average increase of breast cancer all over the world is about 1%, but that is about 10% in Korea, and the frequency of breast cancer in Korea shows dramatically increasing tendency. The most common age group of breast cancer is the fifth decade, but late 30's age group shows increasing tendency. The proportion of premenopausal patient in Korean breast cancer group is higher than that of western. The percentage of early stage cancer is rapidly increasing. So in Korea the frequency of conserving surgery has gradually increased to 44.8 & in 2006.

Five-year & ten-year survival rate for invasive breast cancer diagnosed during 1993-2002 were 80.3% and 70.1%. And five years observed survival rate of 1st and 2nd 5 years was 77.6% and 82.6%. Five-year survival rate is increased to five percentage. So five-year survival rate was similar to Japan and USA. This improved five-year survival rates may be due to an increase in early detection through early screening and development of treatment modality including surgical procedure, postoperative chemotherapeutic agents, radiation technique, hormone and target therapy.

Changing Patterns and Present Status of Female Breast Cancer in China Over 30 Years

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Breast cancer is one of the most common malignant tumors among women worldwide. Compared with western countries; Asia, Black and Hispanic women still have lower incidence rates. However, breast cancer is increasing in developing countries, with rates rising dramatically in recent years. In the most recent two decades, socioeconomic development, accelerating urbanization, prolonging lifetime expectancy and the aging of the Shanghai population has greatly contributed to the increase in the incidence and mortality of chronic diseases such as heart diseases, diabetes and cancers. As a metropolis with rapid social and economic development over the past three decades, Shanghai has a breast cancer incidence that surpasses all other cancer registries in China. In this study, epidemiological features from 1975 to 2004 and clinical features from 1990 to 2007 were analyzed to reveal the changing patterns of breast cancer in urban Shanghai, in the order to provide etiologic clues and direction for prevention programs in other areas with similar rapid development.

In order to estimate the regular changing patterns of female breast cancer in urban Shanghai, population-based incidence data from 1975 to 2004 were studied. Population-based data were provided by Shanghai Cancer Registry which was started in 1963. In addition, one-hospital-based clinical records were consecutively selected from the database established by Department of Surgery of Shanghai Cancer Hospital, which had collected information of more than 13,000 patients. In all, 7443 female breast cancer patients treated surgically between Jan-1990 and Jul-2007 were reviewed, retrospectively.

We observed that breast cancer incidence increased dramatically over the past 30 years and documented a peak incidence represented by the middle-age group (45-59 yrs), which emerged in the last 20 years. The incidence peak moved from the 40-44 year group in the previous two decades to the 50-54 year group in the most recent decade. Median age at diagnosis was earlier in Shanghai than in the western countries and about 56% patients were premenopausal women. However, median age at diagnosis increased from 47.5-yr in 1990 to 50-yr in 2007. Considerably higher exposure to reproductive risk factors and relatively fewer hormone-dependent cases were observed. Of all the 3,116 cases from 2002 to 2007, pro-

portion of hormone-dependent breast cancer was relatively lower among Chinese female with ER+ 49.2%, PR+ 46.1%. The proportion of asymptomatic cases detected by screening gradually increased, as well as that of early-stage cases (from 78.6% in 1990 to 93.3% in 2007) and carcinoma in situ (14.7% in 2007). Analysis of surgical treatment patterns suggested a trend of less-invasive options.

Rapid socioeconomic growth and birth-control policies have revealed some unique risk factors, which pushed the pattern of breast cancer in Shanghai towards that of the western countries. Age of peak incidence as well as median age at diagnosis increase with time, which suggests that increased incidence trending along with increasing age will be observed in the future. The middle-age group born after 1950s would be involved in current birth-control policies and they are also the cohorts related to the incidence boom. Thus specific screening protocols should be refined for the Chinese population, considering not only increasing age but also birth cohorts. Improvements in breast cancer detection provide patients with more opportunities for less invasive treatment options.

Introduction of KBCSG

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Challenges in Breast Cancer Clinical Trials

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Clinical trials in breast cancer have been evolving over the past several decades.

The development of effective therapies has resulted in an improvement in disease free and overall survival. However, as the prognosis of patients with early stage breast cancer has improved and each advance adds incrementally to prior therapies, we are conducting very large trials to demonstrate increasingly smaller gains in patient survival. This is associated both with overtreatment of patients, as not all patients eligible for a clinical trial will derive benefit from that trial, as well as under treatment, as women still recur in spite of receipt of the best available therapies. Molecular profiling techniques and improved diagnostics offer the opportunity for the selection of appropriate therapies by patient selection and tailoring therapy to the particular tumor types, tumor microenvironment, or host characteristics. Currently a multi-parameter assay is used in North America to help clinicians assess the potential chemotherapy benefit in patients with lymph node negative and hormone receptor positive breast cancer. This assay, in addition to selected clinical and pathologic characteristics, may also be used to select those node negative women at highest risk for distant recurrence for participation in clinical trials. Another novel paradigm is the conduct of pre-operative trials in early stage breast cancer that either precede, or are conducted concurrently with, larger randomized studies for the adjuvant treatment of breast cancer that have disease free survival or overall survival as a primary endpoint. These trials allow us to study the molecular mechanisms of therapeutic response and develop hypotheses that can be validated in the larger studies. Ongoing trials in North America include trials testing trastuzumab +/- lapatinib in the treatment of early stage breast cancer, the role of the angiogenesis inhibitor, bevacizumab and platinum in triple negative breast cancer, and the mechanisms and activity of 3 aromatase inhibitors in the pre-operative treatment of hormone receptor positive breast cancer. Molecular profiling techniques are being explored in the context of these trials. These molecular studies should help expand our knowledge of mechanisms of drug sensitivity and resistance, as well as assist us in tailoring therapy for an individual's tumor type. Increasingly, it is being recognized that additional information regarding therapeutic response can be obtained by molecular markers as well as an objective response to therapy.

Advances in the development of targeted therapeutic and improvements in the

prognosis of patients with metastatic breast cancer have influenced the conduct of early phase clinical trials in breast cancer. Targeted agents often have improved anti-tumor efficacy when combined with more traditional chemotherapeutic agents. Since traditional chemotherapy agents have activity in the disease being studied, it has become increasingly apparent that the most useful data will be obtained from randomized phase 2 clinical trials. The treatment of breast cancer has become more complex, underscoring the need for more creative randomized phase 2 clinical trial designs.

Advances in breast cancer therapeutics have also underscored the need for additional collaboration, so that research efforts can be focused on smaller, less well-studied presentations of breast cancer. Examples of international collaboration include the world-wide ALTTO trial (Adjuvant lapatinib and trastuzumab optimization study), randomized clinical trials in breast cancer assessing the role of aromatase inhibitors in the treatment of hormone receptor positive pre-menopausal breast cancer, and the role of systemic therapy as an adjunct to local therapy in the treatment of chest wall recurrence after mastectomy.

Changing paradigms in breast cancer therapy requires increased international coordination and collaboration in development of novel clinical trial methodology. Harmonization of trial nomenclature and endpoints will facilitate sharing of clinical trial data. Future challenges include the need for development of improved therapy for metastatic breast cancer, uncommon presentations of this disease, survivorship issues and prevention.

Hong Kong

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Sharing Ideas and Experiences of Clinical Trials in Taiwan

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Having been actively participating in global clinical trials, Taiwan is known for its good quality and high recruitment rate in conducting trials. As breast cancers in Taiwan have some different features from those in western countries, investigators in Taiwan also try to initiate studies to meet the need of Taiwanese women. Hopefully, the results from Taiwan's local trial can shed light on breast cancers in other regions.

Although the incidence of breast cancer in Taiwanese women is considered to be among the lowest in the world, breast cancer has become the most common cancers in women in Taiwan. As more than 50 percent of breast cancers develop in premenopausal patients and the incidence of women aged 40 to 49 years is close to that of women in Caucasians, breast cancer screening for women in this age group is needed. Although it is well documented that mass screening using mammography lowers the mortality of breast cancer among women older than 50 years of age, women aged 40 to 49 years do not appear to benefit to the same extent, which may be due to the lower sensitivity of mammography in young women. Addition of other screening modality, such as breast ultrasound, may be helpful. We launched a multi-center randomized trial in Taiwan to investigate whether breast ultrasound and mammography can be an ideal combination for breast cancer screening among women aged 40 to 49. Women randomized to one study arm received mammography screening for the first and third year, and ultrasound screening in the second and fourth year. Women randomized to the other study arm received ultrasound screening for the first and third year, and mammography screening in the second and fourth year. No image examination was done for control group. We aimed to evaluate the performance of mammography and ultrasound, separately, in detecting breast cancer, and the efficacy of combined ultrasound and mammography screening.

As large breast cancers are still frequently seen in Taiwan, neoadjuvant chemotherapy is a common practice in Taiwan. We designed a multi-center randomized phase III trial to compare the pathological complete response (pCR) rates after neoadjuvant chemotherapy with tailored chemotherapeutic regimens or standard

chemotherapy for tumor larger than 3 cm. Recent evidences have showed that the expression of several proteins in the tumor samples such as tau, topoisomerase II alpha (topo II), and ERCC1 can predict the tumor response to taxanes, anthracyclines, and platinum, respectively. We hypothesized that select chemotherapeutic agent according the expressions of drug sensitivity predictive biomarkers from patient's tumor sample may improve the efficacy of breast cancer treatment. In this randomized phase III trial, TE (docetaxel/epirubicin) will be given in control arm since it is a highly active regimen for breast cancer. In the Tailored chemotherapy arm, 7 different combination chemotherapy regimens that containing 2 drugs among taxotere, epirubicin, cisplatin, vinorelbine, and 5FU, will be given according to the expressions of tumor biomarkers.

Lapatinib, an oral inhibitor of EGFR and HER2, have been shown to be an effective treatment in HER2/neu overexpressing metastatic breast cancer patient. In pre-clinical studies, the highest synergism between anti-Her2 treatment (trastuzumab) and cytotoxics was seen with vinorelbine. We are interested in lapatinib plus oral vinorelbine as first line treatment in Her2+ metastatic breast cancer. We believe this convenience treatment offer a good response rate but better life quality compared to the combination of capecitabine and lapatinib. This is a phase I/II clinical trial. In phase I part, the primary objective is to determine the recommended dose of the combination of lapatinib with oral vinorelbine in patients with Her2+ metastatic breast cancer. In phase II part, the primary objective is progression free survival of the combination of lapatinib with oral vinorelbine as first line chemotherapy in patients with Her2+ metastatic breast cancer. The secondary objectives are safety profile and response rate.

Acupuncture is a traditional Chinese treatment and has demonstrated benefit for postoperative and chemotherapy-induced nausea and vomiting. We have conducted a randomized trial to evaluate auricular acupuncture for the prevention of chemotherapy-induced nausea and vomiting. The main eligibility criteria is cancer patient receiving chemotherapy with acute emetogenicity of level 3, 4 or 5. Antiemetic medications were allowed in the trial. Visual analog scale, FLIE score of emesis-and nausea-specific quality-of life questionnaire and WHO QOL-brief questionnaire were used to evaluate the efficacy of auricular acupuncture. The primary endpoint is FLIE score change between 1st and 2nd C/T.

Clinical Trials in Korea

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Over the last decade, many innovative drugs have been developed as a result of tremendous advances in the understanding of the molecular biology of breast cancer. The introduction of these new agents into clinical practice has significantly improved disease control and some survival benefits in patients with breast cancer, mainly through the conduct of large, prospective, randomized, multicenter clinical trials and translational research.

There are 2 breast cancer study groups in Korea, KBCSG (Korea Breast Cancer Study Group) and Breast Cancer Subcommittee of KCSG (Korea Breast Cancer Study Group), both of which are not-for-profit clinical trial cooperative groups which have designed and conducted clinical trials that have changed the standard of treatment in breast cancer. The ultimate goals of our study groups are to improve the standard of breast cancer care and establish more effective therapeutic strategies in Korea.

We are actively participating in many important international adjuvant clinical trials such as ALTTO, BETH, BEATRICE studies as well as clinical trials in neoadjuvant and metastatic settings such as NEO-ALTTO, Neosphere, and AVADO studies. We are conducting many nationwide investigator-initiated, multicenter trials as well.

Clinical trials conducted in Korea will be presented in detail.

Sharing Ideas and Experiences of Clinical Trials: India

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The tradition of rigorously conducted clinical trials is of relatively recent vintage in many Asian countries including India. A number of federal agencies have issued guidelines regarding the ethical conduct of clinical trials in India [1-3]. India has been a low incidence region for breast cancer until recently; however breast cancer has increased in incidence in urban areas where it has become the leading cancer in women [4]. The demographic distribution of the Indian population is such that it is a bottom heavy (predominantly young) pyramid. Therefore the median age of patients in most series is between 45-50 years of age. There are unique issues in caring for and researching breast cancer in young and very young patients, including those of psycho-social rehabilitation, fertility and long-term treatment related toxicity. The fraction of patients with hormone receptor positivity is lower (50-60%) and those with triple negative phenotype is higher (20-30%). The latter group presents opportunity for clinical and translational research in an aggressive subtype of breast cancer that has until recently been considered devoid of targets. It would also be interesting to correlate the triple negative phenotype with the intrinsic basal subtype by expression profiling studies. A recently started randomized study from our centre aims to evaluate the inhibition of insulin-like growth factor receptor signaling in triple negative disease in the neoadjuvant setting. Another recently proposed study from our centre aims to correlate the traditional population risk factors for the development of breast cancer with specific subtypes, including the triple negative one. The fraction of patients who present in locally advanced and metastatic stages ranges from 25-50% in various regions of India. These patients present the opportunity to research therapeutic strategies and agents at a later time point in the natural history of the disease, including in the neoadjuvant setting. In metastatic disease chemotherapy is often stopped after a few cycles beyond best response; this is contrary to the North American practice of continuation until disease progression. There is opportunity to research this in the setting of a controlled trial.

Most patients in India have no or limited access to health insurance and have therefore limited ability to receive expensive treatments like targeted therapies. There is emphasis on evaluation of low cost interventions that might impact the outcomes in a cost-effective manner. Three examples from our centre are pertinent in this regard. One randomized study (to be reported soon) evaluates the role of

artificial induction of pregestogenic environment at the time of primary surgery for operable breast cancer. Another randomized study is evaluating the role of estrogenic priming as part of adjuvant chemotherapy. A third non-randomized study has evaluated the accuracy of limited axillary nodal sampling compared to formal sentinel lymph node technology. These studies have the potential to guide clinical practice in India and similar countries.

Systematic access to clinical trial funding is difficult in India especially for studies that evaluate drug therapy. Another challenge is to conduct translational studies that need partnership with like-minded basic scientists and laboratory support. Good epidemiological data is already available from the National Cancer Registry Programme and is likely to further accrue from a number of ongoing cohort studies at our centre and others that employ techniques of molecular epidemiology. An increasing number of industry sponsored trials have successfully accrued patients and good quality data from India. Dedicated multidisciplinary breast cancer teams, like the one at our centre, are needed to further improve the quality of care and research nationwide.

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Breast Cancer Clinical Trials: Experience in a Single Australian Institution

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Overview and Japanese Guidelines to Diagnose/Treat Breast Cancer Patients

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The aim of the guideline is to change the clinical practice to more sophisticated and standardized one. There are two types of guidelines namely evidence based one and consensus based one. The example of consensus based guideline is St Gallen consensus. ASCO clinical practice guidelines are examples of evidence based guideline. NCCN guidelines are evidence based as well as consensus based. It is interesting to see who or what organization leads to make a guideline. For example, St Gallen consensus seems to be in a position to use endocrine therapy as much as possible. It is mandatory to clear the conflict of interest of all members involved to make guideline in order to keep justice. The guidelines should be user friendly and it is better to make a book for the patients to understand guidelines. The guidelines should be revised periodically because many evidences are rapidly generated nowadays. Finally, to check the guideline itself and to test the behavioral changes in clinical practice after using guidelines are very important. I will talk about Japanese guidelines in order to explain these issues.

The first guideline for breast cancer treatment was published in 1998 in Japan. It was a guideline for post-operative radiation in concordance with operation methods. After that, the guidelines that cover almost all the field of breast cancer diagnosis and treatment were published in 2003, which program was led by the ministry of health and welfare. This process was succeeded by the Japanese Breast Cancer Society (JBCS). JBCS published guidelines for medical treatment of breast cancer in 2004 followed by surgical treatment, radiological treatment, epidemiology/prevention, and screening/diagnosis in 2005. Since then, all guidelines have been revised every three years. Besides these guidelines, there is a book for the patients to understand and use guidelines. It covers not only clinical questions appeared in the guidelines itself, but also many other questions which breast cancer patients usually have. Over hundred doctors belonging to JBCS have been involved to achieve this project. These guidelines are basically evidence-based, and the references used as well as structured summaries of them are listed at the end of each recommendation. For example, there are 61 clinical questions in the guideline for medical treatment of breast cancer. Each clinical question is followed by the recommendation statement, comments, and references. Recommendation statement

is graded as A: strongly recommended, B: recommended, C: not recommended, D: strongly not recommended according to the evidence levels of the references.

Several issues have been emerged along with the use of guidelines. For example, 1) the questionnaire revealed that the most utilized guideline among Japanese physicians is St Gallen's consensus (59%), followed by the JBCS guidelines (39%), and then NCCN guidelines. 2) There are time lags among the times when evidence first appeared at the meeting, paper, and the timing to recognize as Grade 1a evidence, timing of approval of government insurance. The timing to adopt new evidence into evidence based guideline is rather late compared to the consensus based guideline. For example, significant improvement of disease free interval by using trastuzumab was first reported at ASCO 2005, although use of trastuzumab in the adjuvant setting has been recommended as grade A since 2007 in the guideline, and it has been approved by government insurance since 2008. 3) The evidences came from Japan is rather small compared to those came from western countries. So the Japanese guidelines are mostly based on the evidences originally came from western countries without any reconfirmation of the evidences. 4) The meaning of the recommendation grade C is not clear. There are two types of the meaning of grade C: one is promising but not enough evidences, the other is not recommendable because of inadequate evidences despite long clinical practice.

Guidelines should be used widely but also it should be recognized that it is not a bible at all situations. It may be very interesting and helpful to compare guidelines in each country to improve them.

Practice Guidelines for Breast Cancer-Philippine Society of Oncology

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The management of Breast Cancer differs in some parts of the world. This is due to ethnic differences, but more importantly, the high cost of health care delivery, especially with new developments in Biomarkers and Targeted therapy.

A committee was created by the society to review the current practice in the management of Breast Cancer. The objective was to create guidelines relevant to Filipino cancer patients, taking into account its limited resources.

These guidelines were included in the “Handbook of Oncology” edited and published by the Philippine Society of Medical Oncology, available to all practicing oncologist in the country.

These guidelines is now widely used as a standard reference by oncologists in the Philippines.

China

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There are many options for the treatment of breast cancer. Because there is a whole armamentarium of options, evidence-based guidelines have been developed to aid the health practitioner in deciding the best treatment for the individual. Treatment should be individualized taking into account not only the age and general health of the person, but also the characteristics of the cancer. Breast cancer is a heterogenous disease, hence no two women have exactly the same pathological scenario.

In Malaysia, the development and coordination of clinical practice guidelines were taken over by the Health Technology Assessment (HTA) Unit of the Ministry of Health in April 2001. The objective of this unit is to improve the quality of care of patients by reducing variation in practice through the development and implementation of evidence based CPG's.

There are 4 committees responsible for the development of CPG's, (1) the HTA and CPG Council (which is chaired by the Director General of Health) (2) the CPG Technical Advisory Committee (TAC), (3) the CPG Review Committee and (4) the CPG Development Committee. The CPG Development committee consists of members who will do the work of developing the clinical questions, reviewing the literature, drawing up evidence tables, and drafting the guidelines for presentation to the Review committee and then on to the TAC and the CPG Council, before it is finally approved. Although the members of the development committee are from the Ministry of Health and universities, the members of the review committee are made up of representatives from the professional bodies, such as the Malaysian Oncological Society, the Academy of Medicine, the private sector and senior consultants from the Ministry of Health.

The first CPG for the Management of Breast Cancer was produced in Jan 2002. Currently it is in the process of being updated, and at present the development committee is in the process of producing the evidence tables. One important aspect of the development is that it is multidisciplinary consisting of public health, family medicine, pathology, radiology, psychologist, breast surgery, oncology, palliative care, clinical geneticist and a breast cancer survivor/advocate. Another important

aspect is the non-involvement of any pharmaceutical company in the development process, and each member of the development team is expected to declare any competing interests at the first meeting. At the first meeting, a decision was also made that the end point used for oncology trials will be overall survival and not disease-free survival. This would have important implications in the adjuvant aromatase inhibitor trials which only show significant disease-free survival and not overall survival.

Many clinical practice guidelines are available in the developed countries, such as the NCCN Guidelines and the NICE guidelines. Would it not be less work to adopt these guidelines rather than develop our own? However these guidelines are developed for countries with a different resource level. For example, in the NICE guidelines, the cost effectiveness of any new treatment is evaluated, and above a certain QALY (Quality Adjusted Life Year), a new treatment is not deemed cost-effective and may not be recommended. Each country will have a different QALY based on its resource level. Hence it is important for each country to develop its own clinical practice guidelines.

The clinical practice guidelines in Malaysia cover several areas:

1. Risk factors for developing breast cancer
2. Screening
3. Assessment/Diagnosis
4. Referral to surgical/breast clinic
5. Treatment-surgery, radiotherapy, chemotherapy, hormone therapy, targeted therapy, complementary and alternative therapy
6. Psychosocial support
7. Palliative Care
8. Follow-up
9. Familial breast cancer

Once the recommendations have been approved, a patient version of the guidelines will be developed. Dissemination and implementation of the CPG is monitored by the CPG Technical Advisory Committee (TAC) which will identify and recommend need for any revision.

Clinical Practice Guideline of Breast Cancer in Asia: Thailand's Experiences and Perspective

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Clinical practice guidelines of cancer management, including breast cancer, have gained increasing importance and acceptance in clinical practice, as well as in health policy formulation and reimbursement globally and nationally. Issues in clinical practice guideline development, implementation, and utilization occurred and varied greatly from country to country. The scope of breast cancer guidelines in clinical practice in Thailand ranges from broadly based on expert consensus to focused and highly evidence-based in individual therapeutic issue. Nevertheless, the translation of definitive clinical research results into practice guidelines is often not rapid and requires multidisciplinary consensus. Reasons for gradual development and dissemination, as well as limited implementation of clinical practice guideline of breast cancer in Thailand, are multiple and complex. Improving the timely distribution, implementation, and utilization of clinical practice guideline in breast cancer requires a comprehensive and committed partnership between national authorities, professional societies or organizations, and clinicians. The ultimate goal of all efforts is to maximize the impact of breast cancer guidelines on clinical practice, treatment outcome, and the quality of breast cancer care. Various international clinical practice guidelines of breast cancer have been reviewed and considered as valuable resources and prototypes for national clinical guideline development. Nevertheless, a number of limitations of the international clinical practice guidelines of breast cancer also have been pointed out, especially their limitation and difficulty in implementation to daily practice in several countries including Thailand. Efforts of initiatives in partnership with committed professional societies or organizations to improve the timely development, distribution, and implementation of clinical practice guidelines of breast cancer in Thailand have been undertaken and will be reviewed.

Practice Guideline of Breast Cancer in Korea

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After the introduction of evidence-based medicine (EBM) numerous guidelines in medicine have been made on the basis of that. Many practice guidelines for breast cancer have also been made and revised every year according to new emerging evidences. In Korea, the first practice guideline of breast cancer was made in 2002 by Korean Breast Cancer Society (KBCS) under the influence of guidelines of Western countries. That was a pocket-sized booklet with contents of concise summaries about breast cancer management. In 2006, the guideline was revised and published as the 2nd edition of that with reinforcement of new evidences in the management of breast cancer.

In 2008, a newly revised guideline was born as the 3rd edition of practice guideline of KBCS, which was a work of multidisciplinary experts as well as evidence-based medicine. Guideline team was composed of many experts in various fields for management of breast cancer, such as surgical oncology, medical oncology, radiational oncology, pathology, radiology, nuclear medicine, plastic surgery, rehabilitation medicine, etc. Definitions of level of evidence and grade of recommendation were made and evidence was reviewed and evaluated according to the definition. For the issues of weak or insufficient evidence, consensus meetings was held and the results were applied on the guidelines.

The experiences and processes of making and revising a practice guideline in Korea will be presented.

4-Hydroxyestradiol Induces Anchorage-Independent Growth of Human Mammary Epithelial Cells Through Activation of NF- κ B Signaling: Potential Role of Reactive Oxygen Species

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Estrogen is metabolized by cytochrome P450 1B1 to 4-hydroxyestradiol (4-OHE2) a putative carcinogenic metabolite of estrogen. This catechol estrogen metabolite is oxidized further to produce a reactive quinone via semiquinone. Redox-cycling between 4-OHE2 and its quinoid generates reactive oxygen species (ROS). ROS not only can cause oxidative DNA damage but also stimulate abnormal cell proliferation.

In the present study, we examined 4-OHE2 induced anchorage-independent colony formation in human mammary epithelial cells (MCF-10A) and underlying molecular mechanisms.

MCF-10A cells treated with 4-OHE2 exhibited increased accumulation of intracellular ROS. The antioxidant N-acetyl-L-cysteine (NAC) inhibited the neoplastic transformation induced by 4-OHE2. ROS overproduced by 4-OHE2 increased the nuclear translocation of NF- κ B and its DNA binding through induction of I κ B kinase- α (IKK α) and IKK β activities. The inhibition of the IKK activities using Bay 11-7082 significantly reduced the anchorage-independent growth induced by 4-OHE2. The 4-OHE2-induced activation of ERK and Akt resulted in enhanced IKK activities and phosphorylation of I κ B α , thereby inducing NF- κ B activation as well as the anchorage-independent growth of MCF-10A cells. In conclusion, ROS concomitantly overproduced during redox cycling of 4-OHE2 caused neoplastic transformation of MCF-10A cells by stimulating the cell proliferation. The ROS-induced neoplastic transformation of MCF-10A cells was associated with activation of IKK-NF- κ B signaling which, in turn, was mediated via the upstream kinases, including Akt and ERK.

Taken together, the above findings suggest that the catechol estrogen 4-OHE2 can promote breast epithelial cell proliferation by activating the IKK signaling.

Understanding the Complexity of Estrogen Action

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The scientific strategy of targeting the tumor estrogen receptor (ER) with long term adjuvant tamoxifen therapy substantially increased patient survivorship [1]. However, the challenge for the future is to decipher the molecular mechanism of estrogen action, so that new strategies can be developed to subvert antihormonal drug resistance. Estrogen increases cell replication through molecular events mediated by the ER. In contrast, antiestrogens, that block estrogen action at the ER, cause a G1 blockade of the cell cycle, but do not kill the cells because cell surface signaling through growth factor receptors is enhanced. It is this survival mechanism that is key to understanding antihormonal drug resistance.

Antihormonal drug resistance evolves through at least two Phases [2]. During Phase I, tamoxifen resistant ER positive breast cancer cells grow in response to either tamoxifen or physiological estrogen treatment. However, the continued treatment of micro-metastatic breast cancer for up to five years results in tamoxifen stimulated Phase II tamoxifen resistance, where physiological estrogen now acts as an apoptotic trigger. Similarly, long term estrogen deprivation results in ER positive breast cancer cells that grow spontaneously, but estrogen causes rapid apoptosis [3]. At the molecular level, it is now estrogen that causes a G1 blockade, and there is a rapid decrease in cyclin levels with enhanced production of pre-apoptotic markers. Nevertheless, not all long term estrogen deprived ER positive breast cancer cells respond rapidly to estrogen treatment with apoptosis. The question to be addressed is why?

It is now becoming clear that estrogen mediated events through the estrogen receptor are modulated by other significant estrogen regulated pathways. GPR30 is a unique G-protein thought to be resident in the endoplasmic reticulum. Much work has been completed and published on the role of GPR30 in the early phosphorylation of the ER. However, GPR30 activation can also modulate intracellular calcium levels. A GPR30 specific ligand, referred to as G1, does not interact with the ER, but mobilizes calcium very rapidly, and blocks the actions of estrogen that cause estrogen stimulated growth in MCF-7 cells. We have used cells that are refractory to the apoptotic actions of estrogen to determine the biological activ-

ity of G1. We have found that G1, in contrast to estrogen, will cause rapid apoptosis in antihormone resistant breast cancer. GPR30 may represent a new target for drug development in the treatment of breast cancer.

Overall, research during the last 30 years to exploit the ER as a target in breast cancer has been invaluable for advancing women's health. Adjuvant tamoxifen therapy has dramatically improved survivorship in ER positive breast cancer patients, and tamoxifen is the pioneer medicine for the prevention of breast cancer [4]. The related compound, raloxifene, is the first selective receptor estrogen modulator (SERM) to be used for the prevention of osteoporosis, which reduces the risk of breast cancer at the same time. Raloxifene is also approved for the prevention of breast cancer in high risk postmenopausal women [5]. As a result of these clinical successes, there is now a whole range of new SERMs being developed for multiple diseases in women [6]. However, it is through the study of models for the anti-hormonal resistance of breast cancer that a new biology of estrogen action has been discovered. Not only does the description of the mechanism of estrogen induced apoptosis explain why high dose estrogen therapy was effective as a treatment for breast cancer before tamoxifen, but is also enhanced opportunities to use this knowledge for the treatment of breast cancer in women [7].

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Measurement of ER Expression

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Novel Markers of Anthracycline Sensitivity: A Potential Role for Chr17 CEP in Selecting Patients for Anthracycline Therapy

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Anthracyclines provide significant clinical benefit over and above non-anthracycline polychemotherapy (CMF). However, these are toxic agents with both short and long term sequelae. Evidence from randomised clinical trials suggests only a sub-population of breast cancer patients benefit from anthracyclines. Therefore researchers have sought evidence of biological markers which may select patient sub-groups with enhance benefit from anthracyclines. Previous candidate markers include the HER2 and TOP2A oncogenes which have, in a number of studies, been suggested as predictive markers of anthracycline response. However current evidence for HER2/TOP2A as predictive biomarkers of anthracycline response is conflicting, possibly due to the small size of the majority of studies, and these markers do not explain the potential for benefit in HER2/TOP2A negative breast cancers. An interim meta-analysis [1] suggested only a weak, statistically significant, association between TOP2A and anthracycline benefit. We have shown duplication of chromosome 17 alpha satellite (CEP17) predicts sensitivity to anthracyclines independently in three trials (BR9601, NEAT and MA.5, [2]). This data suggests that CEP17 is a predictive biomarker for anthracycline benefit in three trials for which previous biomarker data is conflicting. Combined analysis of adjuvant trials demonstrated a highly significant treatment by marker effect for CEP17 duplication as a predictor of benefit from anthracyclines for both RFS in both univariate and multivariate regression analyses. HER2 and TOP2A did not show any significant interactions either in this analysis or in meta-analyses. Further analysis is warranted to explore the underlying mechanisms for this effect. CEP17 is readily assessed by FISH analysis of HER2 status and may represent a clinically useful biomarker and pragmatic for selection of patients likely to benefit from anthracycline containing chemotherapies.

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Targeting Biological Subtypes and Pathways

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The importance of angiogenesis in tumor growth and development is well known. Overexpression of vascular endothelial growth factor (VEGF), the key mediator of angiogenesis, is associated with poor prognosis in cancer. As a result, several therapeutic agents that inhibit the actions of VEGF or its receptors are currently in development for use in advanced solid tumors including breast cancer. There are many clinical trials using anti-VEGF agents in breast cancer (Table 1). The results from these trials will be presented, with a focus on the efficacy and safety of the anti-VEGF agent.

The anti-VEGF monoclonal antibody, bevacizumab, is the only approved antiangiogenic agent for breast cancer and currently available in the clinic. Phase III trial evaluated weekly paclitaxel with or without bevacizumab (10 mg/kg every 2 weeks) in patients with previously untreated locally recurrent or MBC. Median PFS was approximately doubled, from 5.8 months for patients receiving paclitaxel alone to 11.4 months for patients receiving paclitaxel plus bevacizumab ($P < 0.0001$). In addition, the overall response rate was more than doubled, increasing from 23.4% for paclitaxel alone to 48.0% for paclitaxel plus bevacizumab ($P < 0.0001$). At 1 year, survival in the combination arm was significantly better than in the paclitaxel alone arm (81.4% versus 74.0%; $P = 0.017$). Bevacizumab combinations with other agents were also tested in AVADO and RIBBON-1 trial. Based on preclinical evidence suggesting that the VEGF pathway is interlinked with both the epidermal growth factor receptor (EGFR) and HER-2 pathways, a phase I/II trial of bevacizumab in combination with trastuzumab in MBC has produced promising preliminary data. Activity in preclinical models and evidence that tumor dependence on VEGF is highest early in disease suggest that anti-VEGF agents may provide their greatest benefit in patients with early disease, when tumors are small and/or there is minimal residual disease post-operatively. Trials to investigate the effectiveness and safety of bevacizumab as adjuvant (BEATRICE, E5103, BETH) and neoadjuvant (NSABP B40) therapy for breast cancer are ongoing or planned.

Adverse events related or possibly related to bevacizumab are hypertension, proteinuria, haemorrhage, arterial and venous thromboembolic events, wound-healing complications, gastrointestinal perforations and congestive heart failure (CHF).

Despite the rapid development of anti-VEGF therapy in clinical practice and in

contrast to the consolidated evidence with imatinib and trastuzumab that demonstrated a direct correlation between the presence of target and drug activity, it is very difficult, at present, to identify validated and useful biomarkers to monitor the efficacy of these compounds and to appropriately select patients most likely to benefit from such treatments. However, emerging data suggest that this is not presently feasible for antiangiogenic drugs. Although tumoral and/or circulating VEGF levels have been associated with poor prognosis, to date, there is no validated evidence suggesting their role as potential predictive biomarkers of response to anti-VEGF therapy. Recently, many studies have documented promising results with the evaluation of circulating endothelial cells and/or progenitors, and the use of several imaging techniques, such as dynamic contrast-enhanced MRI, PET, dynamic CT scan and functional ultrasound. These preliminary data need a validation in larger prospective trials.

Table 1. Anti-VEGF therapeutic agents currently in development for breast cancer

Mechanism of Action	Drug	Molecular target(s)	Stage of clinical development
Anti-VEGF antibody	Bevacizumab	VEGF ligand	Approved
Tyrosine kinase inhibitor	Sorafenib (BAY 43-9006)	Raf-1, Flt-3, c-Kit VEGF receptors-2 and -3, PDGFR-	Phase II
	Sunitinib (SU11248)	VEGF receptors-1, -2 and -3, Flt-3, PDGFR-, c-Kit .PDGFR-	Phase II/III
	Vatalanib (PTK/ZK)	VEGF, c-Kit, c-Fms (.receptors-1, -2 and -3, PDGFR-	Phase II
	Vandetanib (ZD6474)	VEGF receptors-2 and -3, EGFR	Phase II
	Motesanib (AMG-706)	VEGF receptors-1, -2 and -3, PDGFR, c-Kit	Phase II
	Pazopanib	VEGF , and c-Kit receptors-1 and -2, PDGFR-	Phase II
	Axitinib	VEGF receptors-1, -2 and -3, PDGFR, c-kit	Phase II

Aromatase Inhibitors and Aromatase Expression Modulators

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Estrogen plays an essential role in hormone-dependent breast cancer development by binding to the estrogen receptor (ER) and inducing the expression of peptide growth factors that are responsible for the proliferation of cancer cells. Aromatase is an enzyme that converts androgens to estrogens and is primarily expressed in adipose tissue in postmenopausal women. It has been found that abnormal expression of aromatase in breast cancer cells and/or surrounding adipose stromal cells have a significant influence on tumor development and growth. Recent clinical trials demonstrated aromatase inhibitors (AIs) to be more effective in the treatment of hormone-responsive breast cancer than tamoxifen, the previous standard therapy for hormone-dependent breast cancer, in postmenopausal women, and to more significantly prevent contralateral cancers. Currently, three AIs are used to treat hormone-dependent breast cancer: exemestane (EXE), letrozole (LET) and anastrozole (ANA). EXE is a steroidal inhibitor and an analogue of the androgen substrate. It is also a mechanism-based inhibitor in that aromatase converts it into an active derivative, leading to irreversible inactivation of the enzyme. Furthermore, irreversible binding of EXE triggers proteome-mediated degradation of aromatase protein in cells. LET and ANA are not androgen analogues and are referred to as nonsteroidal inhibitors. These AIs have a triazole functional group which interacts with the heme prosthetic group of aromatase and act as competitive inhibitors with respect to androgen substrates.

AIs are highly potent and specific drugs, such that minimal levels of estrogen remain in patients after AI treatment, leading to side effects from estrogen deficiency, such as vasomotor symptoms, musculoskeletal-related adverse effects, bone loss and disruption of lipid profiles. Previous investigations from this and other laboratories have found that expression of aromatase in breast cancer tissue is driven by promoters different from those used in non-cancer tissues. Therefore, the potential for selective suppression of aromatase expression/estrogen biosynthesis in breast cancer tissues through the down-regulation of breast tumor-specific promoters would be a novel approach to reduce side effects associated with whole-body suppression of estrogen biosynthesis achievable with AIs. Our recent research has found that the DAC inhibitor panobinostat (PAN) is a potent inhibitor

of aromatase expression (IC₅₀=15 nM). Our results also indicate that PAN selectively suppresses the promoters I.3/II of the human aromatase gene. PAN is the first drug identified to selectively suppress these breast cancer-specific aromatase promoters and, not other promoters used to drive aromatase expression in non-cancerous tissues. Cell culture experiments were performed to show the synergistic interaction of PAN+LET in suppressing the proliferation of hormone-responsive breast cancer cells. While experiments are being performed to clearly define the molecular mechanisms involved, the results demonstrating synergistic interactions between PAN and LET in modifying breast cancer cell proliferation may hold potential value for future clinical evaluation of these agents in combination.

Management of TKI Related Cutaneous Toxicity and Diarrhea

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Novel targeted therapies have recently demonstrated efficacy against several tumor types including breast cancer. Among the tyrosine kinase inhibitors that are commercially available as yet, the agents that target EGFR, erlotinib, gefitinib, lapatinib, and CI-1033 have been tested in breast cancer. And, other multi-TKIs, including sunitinib, which target VEGFR, PDGFR, FLT3, are in clinical development. Although they share the same mechanism of action, namely competitive ATP inhibition at the catalytic binding site of tyrosine kinase, they differ from each other in the spectrum of targeted kinases, their pharmacokinetics as well as substance-specific adverse effects. The toxicities usually present as a mild-to-moderate reaction, and may evolve into a painful condition that limits daily functions and quality of life. Since the low grade but persistent toxicities can lead to delay, dose reduction, or discontinuation of drug, it is important to aware and manage the adverse effects appropriately.

Lapatinib, an oral TKI inhibiting ErbB-1 and ErbB-2 receptors, has been approved for the treatment of ErbB-2 overexpressing breast cancer. The most common specific toxicities with this agent are rash and diarrhea.

Diarrhea occurred in 55% of lapatinib treated patients and 24% of patients not receiving lapatinib in the clinical trials in metastatic breast cancer. In the studies with combination therapy, all grade diarrheas occurred in 51% of patients with lapatinib monotherapy and 65% with lapatinib and capecitabine. Combined with paclitaxel, 48% of patients experienced any grade of diarrhea. Most of the diarrhea with lapatinib is grade 1/2, and grade 3 (<10%)/4 ($\leq 1\%$) events is rare. The first diarrhea occurs within 6 days of treatment initiation, with a median duration of 5 days. Most diarrhea resolves with conventional approaches, with 85% of patients requiring dose adjustment or interruption and only 2% discontinuing therapy due to diarrhea. Severe diarrhea does not occur with lapatinib-containing regimen when proactive monitoring and appropriate intervention were employed.

With variations from drug to drug, EGFR tyrosine kinase inhibitors display the broadest spectrum of adverse effects on skin and hair, including folliculitis, paronychia, facial hair growth, facial erythema, and varying forms of frontal alopecia in

more than 50% of patients. Dermatologic disorders are also frequently reported adverse events with lapatinib treatment. In the patients receiving lapatinib monotherapy, more than 50% experienced grade 1 or 2 skin reactions, but no grade 4 was reported. Rash was the most common dermatologic events, typically occurs early within 1-14 days, and did not require any intervention, dose reduction, interruption, or discontinuation. However, the patients receiving sunitinib experience significant grade of hand-foot skin reaction (HFSR). Although there is no randomized study on prevention or palliation of HFSR, expert opinion advocates protective measures, therapeutic skin care, systemic analgesics for pain, and TKI dose modification.

In conclusion, the toxicities of new targeted drugs should be recognized and properly addressed early in patient treatment since most of the drug-related toxicities are manageable with supportive care, then can obviate a need for long interruptions, dose reductions, or permanent discontinuation of the treatment.

A Team for Long-Term Care: Healthcare Provider's Perspective

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Breast cancer is a chronic and long-term illness requiring long-term care and follow-up. More people are surviving breast cancer and living longer lives as a result of early detection and advanced treatment technologies. The overall 10-year survival rate of Korean breast cancer patients treated between 1993-1998 is 76.6%. Studies have confirmed that cancer treatment is optimally administered by a multidisciplinary healthcare team comprised of physicians and a variety of non-physician professionals, such as oncologic nurses, psychologists, physical therapists, dietitians, and spiritual carer.

And nowadays, growing attention is being focused on cancer survivors and the experience of living through and beyond their illness and its treatment, because there are a large and increasing numbers of survivors, and more and more of these individuals are surviving longer after treatment. After the cancer treatment, there is a decline in physical side effects, such as nausea, vomiting, and hair loss. However breast cancer survivors often experience many physical and psychosocial adjustments after treatment ends. Physiologic effects that can persist include menopausal symptoms, weight gain, sexual issues, and fertility issues in young women. Psychosocial adjustment may be marked by anxiety, grief, loss, depression, and uncertainty about future. Social adjustment and concerns about relationships with spouse or family members and friends, sexual issues, employment and insurance concerns are very real in the after-treatment period. And concern about cancer recurrence never fully goes away. In this period, not only a long-term follow-up plan but also a survivorship program are needed.

Close cooperation between clinicians, psychologists, psychiatrists, social workers, and oncologic nurses is crucial to achieve maximum quality of life of cancer survivors. Coordination of care is also important for the overall quality of care. And breast cancer survivors or self-help groups play an important role in psychological support for cancer survivors through collaboration with healthcare providers. A survivorship program and guideline for psychosocial support are needed.

Health-Promoting Lifestyle of Korean Breast Cancer Survivors

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As the numbers of breast cancer survivors and their length of survival expand, long-term health issues specific to cancer survival and health promotion became a great health concern. Breast cancer survivors often experience changes in appetite, sleeping patterns, or exercise by stressors such as a diagnosis and treatment of cancer. They also have higher risks of having secondary cancer and other diseases than the general population. As a matter of fact, the most important issue that breast cancer survivors face is the recurrence of cancer. Thus many breast cancer survivors strive to minimize physical dysfunction and promote their lifestyle by changing lifestyles for better prognosis and survival. Yet many of them could not comply with health-promoting behaviors. The purpose of this presentation is to provide determinant factors of health-promoting lifestyle in Korean breast cancer survivors.

A Total of 282 breast cancer survivors participated in the study during 2007. The regression model using health-promoting lifestyle as the dependent variable and knowledge, health locus of control, depression, and social support as independent variables was utilized to identify which variables influence, and how much they explain health-promoting lifestyle.

Multiple regression analysis revealed that 34.1% ($F=23.30$, $p=0.0001$) of the variance in health-promoting lifestyle were explained by the variables of knowledge, internal locus of control, depression, and perceived social support. The variable that affects the most to health-promoting lifestyle was social support, followed by depression and internal locus of control. No significant differences were found in health-promoting lifestyle by demographic and illness-related characteristics. It indicates that social integration as well as nurturance and assistance must be provided in the intervention of health promotion. It also suggests that oncology professionals need to design and implement interventions for health promotion based on the degree of internal health locus of control of breast cancer survivors. And depression must be assessed before implementing health-promoting interventions and/or integrated to interventions.

The results of the study support the importance of social support, depression and internal health locus of control in explaining the occurrence of health-promoting lifestyle among Korean breast cancer survivors. Thus these factors may be integrated in developing interventions to encourage adoption of health-promoting behaviors.

Government's Perspective: A Team for Long-Term Care/ National Cancer Program (of Breast Cancer)

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To introduce cancer control and prevention policies and the long-term plan of the government of Korea, and to explore long-term care of breast cancer.

Cancer (as overall cancers) has been the leading cause of death in Korea since 1983. In 2007, Korea had about 143 thousand new cases and 68 thousand deaths with 536 thousand under treatment. Five-year survival rates of cancer patients (2001 to 2005) were 43.7% for men and 62.4% for women. As is the case of the global society, cancer control has become one of the critical national agenda especially with rapid aging of the population.

National cancer program in Korea started with cancer registry in 1980. It has evolved with long-term national plans, national cancer screening programs, National Cancer Control Law, the National Cancer Center and Regional Cancer Centers.

The Korean government formulated its first 10-year national comprehensive cancer control plan in 1996. It placed emphasis on infrastructure and capacity building. The National Cancer Control Act as a legal framework was made and a dedicated governmental unit (now Division of Cancer Policy) was set up within the Health Ministry in 2001. The National Cancer Center came into being with about 10 year incubation period and 9 Regional Cancer Centers were designated and established at the existing Regional National University Hospitals within years. The National Cancer Screening Programs since 1999 continued to expand target population and target cancers.

The second 10-year plan succeeded the first plan in 2006 and its goal is practically to reduce cancer mortality through comprehensive programs. The plan is composed of 4 main programs, 3 supportive programs and a research program. 4 main programs are primary prevention, early detection, diagnosis and treatment, and palliative care. The supportive programs focus on education, capacity building, and registry. And a research program appears self-explanatory.

The government implements and supports the programs such as anti-smoking programs, cancer screening programs, financial aid programs for treatment and palliative services, public awareness programs and research and development activities with close collaboration with academic societies and NGOs. In addition to

national cancer registry, cancer surveillance system as a part of public health monitoring system will be formulated in the near future.

National cancer program of Korea has evolved with major cancers as a group. Next step must be having vertical program for each major cancer. For now, there might be specific approaches especially for (the long-term care of) breast cancer.

First, private-public partnership should be more emphasized in the area of education and training and campaigns for improving public awareness about the importance of primary prevention and early detection.

Second, breast cancer screening rate in the target population especially within the National Cancer Screening Program should be raised significantly. Enhancing customer satisfaction and sustained quality assurance of the cancer screening units are essential requirements in achieving higher screening rate.

Third, Clinical Practice Guideline for Breast Cancer was formulated in 2008 with concerted participation by the related societies. This guideline would be adopted widely and it will be complemented as necessary.

Fourth, the government has implemented measures to reduce financial burden of the cancer patients by way of expanding health insurance coverage on several steps. Now copayment of cancer care is 5 percent for both inpatient and outpatient care of the national health insurance scheme (General copayment is 20 percent for inpatient care only). In addition to this insurance policy, cancer patients with income level of lower half are eligible for financial aid program for the medical expenditure supported by shared responsibilities between the central and local government.

Fifth, rehabilitation and reconstruction of breast cancer would be highlighted.

Of course, actually not fifth. The order here is just for the convenience of presentation.

Vertical program for breast cancer is about to be explored with high considerations and concerns of the interested experts, supporters and organizations.

Use of Evidence in the Review and Assessment of Cancer Treatment and Quality Improvement

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Health policy in South Korea has rapidly been changed since the 1980s. With the introduction of national medical insurance in 1977 and the implementation of it to whole population in 1989, the access to medical service has been pretty much improved, and the facilities and manpower for the health care have been expanded. And the Ministry of health, welfare and family in Korea has continuously tried to reduce medical cost by decreasing the misuse of medicine with the introduction of the idea of “Evidence Based Medicine” when they review medical practices for reimbursement. It seems like that such an effort reached to a level of great success. Now it has become possible in Korea to get high quality of medical service with less cost comparing with that of other developed countries. The gradual increase of medical expenditure is a global phenomenon and it has been largely affected by the introduction of the new technologies and drugs. For the OECD member countries, total medical expenditure comprised 7% of GDP in 1980s which was increased up to 8.5% 20 years later. In Korea, the increase of total medical expenditure during 10 years from 1990 much exceeded the increase of GDP in same period. Cancer has been the leading cause of death in Korea and medical cost for the treatment of cancer has been enormously increased from 136 million US dollars in 1990 to 1.2 billion US dollars in 2005. Especially recent introduction of many kinds of target agents which are extremely expensive, has made it easier to treat cancer, but on the other hand, limited the chance to provide best treatment to the cancer patients. As Dr. Muir Gray said in his book “Evidence Based Health care”, the major, common problems in medical practice in many countries are, 1) the increasing cost of health care, 2) the lack of capacity in any country to pay for the totality of health services demanded by health professionals and general public, 3) marked variation in the rates of delivery of health services within a country and among countries, and 4) delayed implementation of research findings into practice. And ‘Evidence-based decision making’ is an essential element in the provision of health care for the 21st century.

Korean Government decided to launch “Severe Disease Review Committee” to improve the access of patients for the best treatment for many severe diseases and cancer was the first target of it. So ‘Cancer Review Committee’ was firstly

formed in that year and started its work by collecting current chemotherapy protocols from all the hospitals in South Korea. The committee was formed with oncology specialists from many different disciplines and many different institutes. They reviewed all the protocols collected, along with the evidence level, and decided for one by one, whether to accept for the reimbursement or not. And the result was published as “a Guideline for the reimbursement for cancer treatment”.

The guideline was not the academic guideline but at least evidence based guideline for the reimbursement. It was surprising that many medical practices which have been believed as effective ones, didn't actually have much evidence for their effectiveness. And the guideline has changed the pattern of cancer treatment in many ways.

Use evidence based medicine definitely improved the quality of clinical practice especially in cancer treatment in Korea. But there has been problems newly found during the application of evidence based medicine, which should be solved before we can widely apply it to the review and assessment of clinical practice in Korea.

Pharmacoeconomics

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In addition to safety and efficacy, which are essential components of medical interventions required to be proven to get approval by authorities, cost-effectiveness or efficiency has been an important consideration in adopting a new medical intervention or in choosing an alternative among various treatment options. Especially, increasing number of treatment options for the same purpose, increasing health care expenditure, and rising price of new and advanced medical interventions make ‘cost-effectiveness’ more important in reimbursement and pricing decisions by health care payers in most of the developed countries. Also, cost-effectiveness studies are useful to develop clinical guidelines.

Pharmacoeconomics is a discipline developed to compare costs and effectiveness of treatment alternatives, in particular pharmacologic treatments, and to evaluate whether clinical benefits of a particular treatment alternative justify extra spending required to receive that treatment. Basically, there are four types of pharmacoeconomic analysis depending on how clinical benefits of medical interventions are measured and expressed: cost-minimization analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), and cost-utility analysis (CUA).

Breast cancer is among the leading causes of cancer morbidity worldwide and accounts for a significant proportion of overall health care costs. Cost-effectiveness and cost-utility evaluations of therapy provide insight into the societal value of different treatments, assisting decision makers to prioritize resource allocation and maximize benefit in cancer control within resource constraints. A large number of cost-effectiveness studies have been conducted for breast cancer screening program and various treatment strategies. The reported incremental cost-effectiveness ratio for the same screening or treatment alternative varies from country to country. Since input parameters, including drug costs, disease costs and epidemiological characteristics vary from country to country, cost-effectiveness analysis results from one country can not be entirely applicable to other countries. Thus, local studies are necessary for their own health care settings. In order for a local study to be possible, country-specific data such as cost of treating breast cancer (i.e. lifetime per-patient costs and costs by age, disease stage [initial, continuing, and terminal]), epidemiological information (i.e., incidence, prevalence, mortality rate etc.), and health-related utility values for breast cancer are necessary elements. Also, the breast cancer specific willingness-to-pay range acceptable by each society should be developed, if possible, to aid decision making for cost-effectiveness of the breast cancer treatment options.

From Health Technology Assessment to Health Policy to Evidence Based Practice

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With limitation of health care budget, health technology assessment (HTA) and economic evaluation is essential to assist the decision-making process for the reimbursement of drugs and other health technologies. HTA is mainly conducted based on clinical efficiency from the randomized clinical trials (RCT) and analysis for cost-effectiveness. The primary endpoint for the RCT in oncology using progression free survival (PFS) in order to bring the drug to the patients earlier and one for HTA with overall survival (OS) to see outcome such as QALY conflicts when the trial has early termination with outstanding results from PFS with interim analysis. For oncology drugs, standard technology to evaluate cost-effectiveness would not be suitable, since the disease is fatal and rare. In this setting, equity, equality, solidarity, precedent and priority should be in consideration for reimbursement in addition to usual evaluation on clinical efficiency and cost-effectiveness. Involvement of more stakeholders, publicity with transparency and challenges to decision made are needed for health policy.

Evidence based medicine (EBM) cannot be completely reflected to evidence based practice due to health policy based on various factors. More commitment to practice from EBM can generate more evidence in real life through observational studies and registries to revisit the relevance on decision for reimbursement if it can be given conditionally. Evidence based practice is from EBM through health policy, but would only be fair when other value is well respected such as access right to medicine of the patients via broader scope of stakeholders' decision with transparency.

Circulating Tumor Cells in Breast Cancer: Detection, Clinical Relevance and Future Prospects

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Despite advances in early detection and improvements in the treatment of breast cancer, mortality remains relatively high and is invariably associated with the development of metastases. Determining prognostic and predictive factors of response to treatment and early diagnosis of metastatic disease are growing areas of interest in breast cancer research, and the study of circulating tumor cells (CTCs) in the peripheral blood is a promising instrument in this field [1].

Highly sensitive and specific immunocytochemical and molecular assays allow detection of “occult” metastatic tumor cells at the single cell level in the peripheral blood and bone marrow (BM) before the occurrence of incurable overt metastases. However, because of the high variability of results in disseminated tumor cells (DTCs)/CTCs detection, standardization of current technologies is urgently required [2].

Recent studies have shown that CTCs can be detected in the different stages of progression and metastasis can occur early in the development of the tumor [3]. The clinical relevance of CTCs measurements is still under investigation. While CTCs might serve both as a prognostic and predictive marker for early assessment of therapeutic response in patients with metastatic breast cancer [4], the impact of CTCs in early stage breast cancer without overt metastasis need to be demonstrated in prospective multicenter studies [5]. And studies for the potential to replace or supplement BM examination are still ongoing [6]. Moreover, some investigators have focused on determining the feasibility of performing the genotypic characterization of CTCs and correlate it with the expression of similar genes in primary or metastatic lesions [7]. Further clinical trials will reveal whether the assessment and monitoring of therapeutic targets (e.g., HER2 or VEGF) on CTCs might contribute to improving targeted and more individualized therapies. These molecular characterization of CTCs will provide new insights into the biology of metastasis and, therefore, help to improve treatment strategies.

We will focus on the detection, clinical relevance, and future prospects of CTCs, since this seems to be the most crucial step in breast cancer progression.

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Designing Clinical Trials Using Biomarkers to Guide Treatment Decision

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Biomarkers are developed for many purposes, including diagnosis, screening, classification, prediction and prognosis. Markers can be a single trait or a grouping (signature) of traits. Prognostic markers has been defined as differing risk of specific outcome in the absence of systemic therapy or outcome differentiation despite empiric systemic therapy. A predictive marker is a marker can predict the differential efficacy. To achieve successfully the personalized therapy for cancer, identification and verification of predictive biomarkers is the most essential. There are four designs for predictive biomarker studies, (1) marker by treatment interaction design, separate test, (2) test of interaction, (3) marker-based strategy design and (4) modified marker-based design the TAILORx and MINDACT trials are the examples of the hybrid designs.

The biomarker for clinical trial development will through the following major tests before it's adopted for routine clinical use. First, the biomarker must be robust and reproducible; second, clinical value and clinical decision but be proven for patient benefit; third, clinical accepted the biomarker and be convinced the need, and finally the cost-effectiveness been evaluated.

DNA microarray analysis to define subgroups of breast cancer patients based on unique profiles of gene expression that have distinct clinical outcomes. Other work has made use of gene-expression profiles to develop genomic signatures of cell-signaling pathways that can then serve as guides for directing the use of targeted therapeutic agents, also been developed to predict the sensitivity to a variety of standard-of-care cytotoxic chemotherapeutic drugs.

There are numberour successful biomarkers on breast cancer through different methodologies such as hormonal therapy and ER. Targeted therapy from Anti-HER-2/neu and angiogenesis, proliferation and uPA/PAI-1 and Ki67, molecular pathway through PI3KCA and CTC.

The ethnic differences in breast carcinogenesis exist among Asian and western population. So, the pharmacoethnicity might be described as ethnic diversity in drug response or toxicity. These include strong environmental influences on bioavailability and metabolism, which can be ethnically divergent; local practice preferences of treating health care providers; ethnic-specific drug-drug interactions ethnic variation in a drug's targets; and genetic polymorphisms in drug-related genes.

Cancer Stem Cell

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It has been known that cancers originate from a single cell by aberrant proliferation, but cancer cells display heterogeneous phenotypes. Recently, the tumor-initiating cells (TICs) or cancer stem cells hypothesis is developed to explain this biologic heterogeneity of cancer. The TICs model posits that a defined subset of cancer cells has the exclusive ability to form a tumor, which is similar to self-renewing ability of normal stem cells. These TICs are responsible for initiating and maintaining the growth of the tumor and furthermore, may be highly resistant to radiation and chemotherapy. Consequently, their relapse after remission is likely due to failure to eradicate TICs, which, despite bulk tumor shrinkage, can subsequently reproduce the entire malignant phenotype. Therefore, there is a need for the effective targeting of these cell populations.

The purification and characterization of cancer mammary stem cell could be extremely helpful for developing a new drug to target multidrug-resistant breast cancer and breast tissue engineering. Since 2002, we have investigated breast cancer stem cell. Our aims of this study were (1) to characterize the human breast cancer stem cells, (2) to investigate the differentiation mechanism and check the plasticity of mammary somatic stem cells, and (3) to find out some novel genes and proteins that are related to the maintenance of stemness and differentiation. At 2004, we conducted mammosphere culture system in collaboration with Prof. Gabriel Dontu & Prof. Max S. Wicha at University of Michigan. After coring out the human breast cancer tissue, single epithelial cells were isolated. Clonal propagation ability was tested in 96-well cultures and the degree of anoikis was measured in the mammosphere culture condition. We found that mammosphere formation resulted from clonal propagation of a single mammary epithelial cell. Despite the remarkable anoikis, approximately 0.1% of initial cells survived for more than 10 weeks forming mammospheres. Under confocal microscopy, vimentin and fibronectin, nestin as well as Wnt-1 and CK5/6 are expressed in long-term cultured cells in the mammosphere culture system. Moreover we could obtain four mammospheres to be maintained more than 18 months, which are named as SBCC-1, SBCC-2, SBCC-3, NDY-1.

Especially, we have first isolated self-renewing sarcospheres (refer to NDY-1)

from sarcomatous carcinoma of breast (95% <mostly composed of sarcoma) specimen by using anchorage-independent culture method. We have sorted a subpopulation of CD49d+/high cells from NDY-1 spheres, which displayed tumor initiating and in vivo self-renewing properties by serial transplantation in NOD/SCID mice. In addition, the CD49d+/high derived tumor cells resemble the original spheres xenograft tumor and have doxorubicin resistance compared with CD49d-/low population. This study is the first identification of TICs in the sarcoma. Therefore these observations may provide a valuable target for the design of therapeutic strategies for sarcoma.



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Preclinical

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Research Local Therapies

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Local therapy research has led to dramatic changes in surgical and radiation options for breast cancer treatment over the last two decades. Needle biopsy techniques have replaced open surgical biopsy for diagnosis of most breast cancers, breast conserving surgery is a viable alternative to mastectomy for many patients and sentinel node biopsy rather than axillary dissection is the standard of care for patients with clinically negative axillary nodes.

Progress continues toward more precise and less invasive local treatment for breast cancer. Future innovations in breast surgery will reduce re-excision rates through improved pre-operative imaging and improved methods for assessment of lumpectomy margins. Research is now aimed at development of technologies for real time identification of tumor at margins of a lumpectomy specimen or in cavity walls in the breast to allow excision of positive margins during the initial lumpectomy procedure. Ramen spectroscopy, optical coherence tomography and radiofrequency spectroscopy have been used in pilot studies for margin assessment of breast specimens.

Technical innovations will continue to improve cosmetic results of lumpectomy and mastectomy procedures. While the primary goal of breast conserving surgery is effective local control, achievement of a pleasing cosmetic result is an important secondary goal. Many breast surgeons now incorporate a variety of plastic surgery techniques into breast cancer resections, in an approach being termed “oncoplastic” surgery. Local advancement flaps, concurrent mastopexy or reduction mammoplasty, creative incision placement and other procedures may be incorporated into excision of the breast tumor and closure of the resulting defect. These oncoplastic techniques allow extensive resections that may extend eligibility for breast conservation and improve overall cosmetic outcome.

For patients who require mastectomy for risk reduction or for treatment of a breast cancer not involving the nipple, nipple sparing mastectomy may now be considered. In nipple sparing mastectomy all skin, including the nipple and areola, is left in place, with the mastectomy performed through an incision that is closed primarily. For many patients, the cosmetic result possible with this approach is superior to that achieved with skin sparing mastectomy and nipple reconstruction.

Increased use of nipple sparing mastectomy is likely if early results that suggest excellent local control are confirmed, and if ongoing efforts to identify eligible patients pre-operatively prove successful. Techniques for oncoplastic surgery and nipple sparing mastectomy will be reviewed.

There is interest in development of non-surgical methods for ablation of breast tumors. RF ablation, cryoablation and laser ablation are the most promising approaches for breast tumor ablation as they produce a circumferentially expanding kill zone around a probe placed within a mass under image guidance. Limitations and potential uses of these approaches will be reviewed. Significant problems to be resolved before widespread application of RF ablation include: current inability to precisely determine tumor size (and ablation target) on pre-treatment imaging, inability to assess completeness of tumor cell killing without surgery, inability to assess margins, uncertainty as to whether ablation procedure scarring will hamper detection of local recurrence and uncertainty as to long term cosmetic outcome.

Advanced breast imaging technologies are likely to enhance both diagnosis and management of breast cancers. Breast tomosynthesis and functional imaging techniques such as MRI, PET and breast-specific gamma imaging are in various stages of development and application. It is hoped that these approaches will enable earlier detection of breast tumors and provide increased sensitivity and specificity for screening. In addition, it is hoped that future imaging technologies will provide a more accurate definition of tumor geometry to permit more precise lumpectomies with fewer positive margins, and potentially provide specific enough information to accurately guide non-surgical ablation techniques and for non-surgical staging of the axilla. These approaches may also be useful for early and ongoing assessment of tumor response to neoadjuvant systemic therapy.

Shorter and more targeted forms of radiation, including partial breast irradiation, and Canadian fractionation have been studied. These newer approaches may help reduce the side effects of radiation in breast-conserving surgery, reduce the time and costs required for treatment, and increase access to breast conservation. In particular, partial breast irradiation techniques show the potential to reduce cardiac and lung toxicities by reducing the amount of non-target normal tissues included in the treatment field.

With these changes in treatment options, both surgeons' and radiation oncologists' roles in guiding a patient from initial diagnosis through complex multidisciplinary care will continue to evolve. Research aimed at developing better tools to aid both physician and patient decision-making will continue to be important. This talk will review some of the progress to date in these local therapy areas and high-light ongoing areas of investigation.

Updates in Systemic Therapy of Breast Cancer

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The last decade has brought about a major change in the way we understand breast cancer. It is now recognized that breast cancer includes a spectrum of diseases, rather than a single uniform entity. The purpose of this update is to review recent major advances in the systemic treatment of breast cancer.

Clinical trials results from clinical trials in unselected patients with early stage breast cancer as well as clinical trials in early stage or advanced breast cancer in the 3 major subtypes of breast cancer that can be readily identified in the clinic are reviewed. These include trials in hormone receptor positive (Estrogen Receptor and/or Progesterone Receptor); “triple negative” (Estrogen receptor negative, progesterone receptor negative, and HER-2 negative); and HER-2 positive.

The Breast International Group trial (BIG-1-98) had previously reported that in post-menopausal women with early stage hormone receptor positive breast cancer therapy 5 years of therapy with the aromatase inhibitor, letrozole, was therapy with tamoxifen. In this randomized, phase 3 women were randomized to receive 5 years of tamoxifen monotherapy, 5 years of letrozole monotherapy, or 2 years of treatment with one agent followed by 3 years of treatment with the other. In 2009 results from the sequential therapy arms were published. At a median follow-up of 71 months, disease-free survival was not significantly improved with either sequential treatment as compared with letrozole alone. In pre-menopausal breast cancer the ABCSG-12 (Austrian Breast Cancer Study Group) trial randomized 1,803 pre-menopausal women in a 2 × 2 factorial design to ovarian function suppression with letrozole plus goserelin versus tamoxifen and a second randomization to the bisphosphonate, zoledronic acid, versus not. There was no difference in outcome with the 2 hormonal therapies; however, those who took zoledronic acid had a 36 percent reduction in cancer recurrences and metastases, compared with women who did not get this drug. Additional studies are ongoing.

In metastatic triple negative breast cancer a randomized phase 2 study was reported at the 2009 ASCO plenary session that showed patients treated with the investigational poly ADP-ribose polymerase-1 (PARP-1) inhibitor BSI-201 in combination with standard gemcitabine and carboplatin chemotherapy had significantly better outcomes than women who received standard chemotherapy alone.

PARP-1, a ubiquitous nuclear enzyme with roles in DNA base excision repair, is upregulated in the majority of triple-negative breast cancers. By inhibiting PARP-1, BSI-201 potentiates the effects of chemotherapy-induced DNA damage. Complete or partial response was observed in 48% of patients who received BSI-201 (57 women) versus 16% who received standard chemotherapy (59 women). Median progression-free survival was 6.9 months with BSI-201 versus 3.3 months without the investigational drug ($p < 0.0001$). A phase III trial with BSI-201 in metastatic triple-negative breast cancer is ongoing. Anti-tumor activity of the PARP inhibitor olaparib as a single agent has also been reported in patients with BRCA1 positive metastatic breast cancer.

The results of NSABP B-30, a large randomized phase 3 trial in unselected women with early stage breast cancer evaluating different schedules and combinations of adjuvant therapy containing doxorubicin, docetaxel and cyclophosphamide in women with operable, node-positive breast cancer has been reported. In this study 5,351 patients were randomized to standard chemotherapy with doxorubicin and cyclophosphamide followed by docetaxel; doxorubicin and docetaxel $\times 4$ cycles, or doxorubicin, cyclophosphamide and docetaxel $\times 4$ cycles. In this study, the longer duration of therapy with AC followed by docetaxel appears to be trending better in terms of outcome. Interestingly, women who became amenorrheic for at least 6 months has a 25% lower risk of recurrence than those who did not. Ongoing prospective randomized clinical trials are addressing additional questions regarding the dose and schedule of standard adjuvant chemotherapy regimens as well as ovarian function suppression versus tamoxifen in pre-menopausal women.

In HER-2 positive early stage breast cancer, two large prospective international trials are ongoing. The ALTTO (Adjuvant Lapatinib and Trastuzumab Treatment Optimization) is evaluating the role of chemotherapy plus trastuzumab and lapatinib alone, in combination, and in sequence in patients with early stage HER-2 positive breast cancer. The BETH trial (Bevacizumab with Trastuzumab Adjuvant Therapy in HER2+ Breast Cancer) is designed to determine the value of adding bevacizumab to chemotherapy plus trastuzumab in patients with resected node-positive or high risk node-negative, HER2-positive breast cancer.

Results of clinical trials are contributing to our understanding of this disease. Future trials in breast cancer will need to address the role of both targeted therapy and the traditional chemotherapy regimens in the major subtypes of breast cancer.

A Life Transformed: Living with Breast Cancer

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Is breast cancer patients' life transformed by breast cancer? The women who diagnosis breast cancer never think they may have breast cancer in their life. What the life is when women feel some strange mumps in their breast one day or when they receive the paper from the health insurance company to check their breast again because of something was in. They become nervous. They think what this is!! Probably, breast cancer? Breast cancer patients usually said they can not remember what they ask to doctor, what the doctor said to them except they have breast cancer. They call their family or friends. Breast cancer patients and their family collect all information about breast cancer. They call some doctors who they can touch. They decide the hospital and doctor who can treat them. But they do not know hospital environment and process of treatment. They just know they should accept the present situation! After operation, breast cancer patients think they may survive!! But they do not know the periods, types, effects, and side effects of treatment. They do not know how much the treatment pick on them. They should follow the doctor's prescription even it really hurt them day by day. They do not find the other strategy to overcome this difficult situation. They can not stand up to go to the rest room in their house because they are submerged under the chemotherapy. At the same time they recognize their changed body from the surgery, radiation, and chemotherapy. Some of them lose all the hair. Some of them lose the shiny skin. They could not love with their partner well because of their transformed breast, dry vaginal, abundant stress and fear. During this process, they think what the life is. They also suppose they can die when they find the tumor in other place of the body. They suffered from the cancer recurrence all the time. They could not escape from the recurrence of breast cancer. They could not enjoy foods any more. They always concern about which food is good or bad to eradicate the breast cancer! Someone said to them meat will be very harmful to the breast cancer. From they hear that information, they can not eat and enjoy meats comfortably. Many breast cancer patients lost their enjoyable life since they have the breast cancer. After breast cancer diagnosis, some of breast cancer patient recognize the role and responsibility in family. They recognize their family can survive well without them. At this time, breast cancer patient consider their life carefully. What is important to me? What the life is to me. How do I have to live with breast cancer? They hope to try rebuilding their life.

Is Breast cancer a critical event? It is increasing health professionals concern about the suffering of breast cancer patients. It is supposed the patients who diagnosed breast cancer have the most unbearable experience. Health professionals think breast cancer patients are in difficulties and suffered. Many of them think; yea! they are in difficulties!! But they have to accept the situation! It is a process of treatment!!! But health professionals have to think and understand what the breast cancer patients feel and think!! It is not enough! Health professionals should understand what breast cancer patients dream every night! What breast cancer patients want to know, cope, and escape after they receive cancer diagnosis?

What breast cancer patients need to overcome breast cancer? Breast cancer patients suffer from physio-psycho-social functional problems after cancer diagnosis. Distress continues to disrupt and spoil the daily life. Chung and Xu (2008) suggested breast cancer patients need the physical and cosmetic, informational, psychosocial, and cognitive-behavioral rehabilitation in her rehabilitation model. Physical and cosmetic rehabilitation relies on managing treatment-related symptoms, regaining physical function and improving functional health outcomes. Informational rehabilitation given to breast cancer patients is important to the adjustment to this chronic condition. Psychosocial rehabilitation consists of psychological and social approaches to solving the psychosocial discomfort of breast cancer patients. Interview, recreation, counseling, and self management are common used strategies. Rehabilitation programs composed of psychology-based education, exercise, and peer support group activity promote the recovery of the affected shoulder joint ROM, alleviate physical symptoms, and improve psycho-social adjustment and the quality of life. Cognitive-behavioral rehabilitation is the problem solving activities that are focused on discovering and challenging automatic negative thoughts, activity planning, and discovering by breast cancer patients themselves. A combination of physical and psychological techniques such as education, relaxation, exercise training, and goal setting was adapted with a positive outcome.

Conclusions: To support the breast cancer patients is not only a scientific challenge, but also a clinical and ethical imperative. Health professionals should understand the imminence situation of breast cancer patients. Education and training of healthcare professionals regarding breast cancer patients is equally important for an effective support to facilitate physical and cosmetic, informational, psycho-social, cognitive behavioral rehabilitation.

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Interventions to Enhance Breast Cancer Adjustment among Patients and their Partners

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Background: Although various forms of psychoeducation and counseling interventions have been examined among patients with a variety of diagnoses, the unique contribution of phase-specific psychoeducation and telephone counseling to the ongoing process of adjustment has not been explored among patients with breast cancer and their partners.

Purpose: To conduct a randomized controlled clinical trial of phase-specific, evidence-based psychoeducation and telephone counseling interventions to enhance emotional, physical, and social adjustment in patients with breast cancer and their partners.

Methods: A purposive sample of 249 patient-partner dyads were assigned randomly to one of four groups: (a) control group receiving disease management (DM), (b) standardized psychoeducation via video (SE), (c) telephone counseling (TC), or (d) standardized education plus telephone counseling (SE+TC). Data were collected at baseline, the diagnostic, post-surgery, adjuvant therapy, and ongoing recovery phases. Outcome variables included measures of: 1) emotional adjustment, 2) physical adjustment, and 3) social adjustment.

Results: Patients showed poorer adjustment over time in the DM group relative to those receiving interventions on selected measures of emotional adjustment. All patients showed improvement over time in overall health and adjustment in social and vocational environments. Partners in all groups exhibited improvement over time for measures of adjustment in the social environment, but no changes in psy-

chological well-being or overall health. Partners in the TC group had poorer scores on physical symptoms compared to the SE+TC group, and contrary to expectation partners in the TC group had poorer vocational scores compared to the DM group.

Conclusions: Emotional, physical, and social adjustment outcomes in both patients and partners varied with phase of illness. Congruent with the stress and coping and crisis intervention models (Lazarus & Folkman, 1984; Aguilera, 1998), the findings substantiate that chronic health problems such as breast cancer, extend over time and that education and counseling interventions are more effective for patients than no interventions at all. Although there were no treatment group effects for partners or treatment group effects for overall perceived health or social adjustment outcomes for patients, our study did show that patients who received the study interventions had less side effect distress, less side effect severity, and higher levels of psychological well-being than patients who received only standard care (DM) at ongoing recovery. This study warrants replication with other populations including more socio-economically diverse groups with adequate representation of minority and underserved women and their partners in order to increase the external validity. Although there was improvement over time for both patients and partners from post-surgery to ongoing recovery, higher than normal levels of adjustment problems were still evident at the final data collection time period in this study. Survivorship issues as well as late effects of treatment often continue well beyond the time when treatment is completed. Clearly more long-term follow-up is needed to address survivorship and recovery issues. Future research is warranted to explore needs and test interventions aimed at enhancing long-term adjustment of patients and partners during the ongoing recovery phase of breast cancer. Findings from this study provide preliminary support for the value of phase-specific standardized psychoeducation by video and telephone counseling interventions to enhance selected adjustment outcomes for patients with breast cancer and their partners.

Preoperative Endocrine Therapy in Estrogen Receptor Positive Breast Cancer

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Endocrine treatment for breast cancer has been used since the last century, as it was shown that oophorectomy caused regression of advanced breast cancer [1]. Later endocrine therapies including adrenalectomy and hypophysectomy, and the use of estrogens, were developed. In the 1970s, tamoxifen became the standard treatment for hormone receptor (HR)-positive breast tumor and has been used for more than two decades [2,3]. Nowadays, it is known that endocrine treatment may reduce the annual breast death rate by 31% in estrogen receptor (ER)-positive tumors [4].

Neoadjuvant therapy, also called primary, induction, or preoperative therapy, is increasingly used in the treatment of breast cancer. Neoadjuvant endocrine therapy is not as commonly used as preoperative chemotherapy and has been less widely studied. Nevertheless its origins go back more than 50 years. In 1957 Kennedy et al. [5] reported on 27 postmenopausal women whose large and sometimes locally advanced breast cancers were treated with hormone therapy prior to surgery, mainly using estrogen, which was novel at the time, they described tumor softening and shrinking, with some tumors becoming “more difficult or impossible to palpate”.

Since then there have been occasional reports of premenopausal women treated with preoperative oophorectomy or leuprorelin and responses have been described [6,7], but the data are insufficient to allow meaningful conclusions, and neoadjuvant chemotherapy is much more widely used for younger women.

There are both clinical and research-directed reasons to use neoadjuvant endocrine therapy in women with hormone receptor-positive breast cancer. Clinically this approach might be considered as an alternative to surgery, particularly in women unfit for this procedure through age or medical infirmity. This approach has short-term attractions but also important limitations, as described below. The main clinical indication is to down-stage large breast cancers, so that mastectomy might be avoided or to achieve operability in previously inoperable cancers [8].

Recently, an international expert panel has updated the indication for the neoadjuvant systemic treatment of operable breast cancer [9]. Although it was already widely accepted that neoadjuvant treatment was the standard treatment for locally advanced breast cancer, they also considered that it should be a standard option for

primary operable disease. This is because of the main clinical advantages of neoadjuvant therapy, which has been demonstrated to reduce tumor size, thereby allowing the resection of previously inoperable tumors, or to enhance the chances for carrying out breast-conserving surgery (BCS) in large operable tumors initially destined for mastectomy, without compromising survival rates [10].

Other than surgical improvements, neoadjuvant therapy offers additional advantages. Although adjuvant therapy requires much larger patient numbers and longer follow-up periods to ascertain its effectiveness, tumor responses following neoadjuvant therapy can be directly evaluated. It therefore permits the prediction of subsequent sensitivity to a given agent in the adjuvant setting, or an early change of therapy in the case of resistance [11]. It also provides insights into the molecular mechanisms of breast cancer and corresponding interactions with different anticancer compounds, as well as the opportunity to search for molecular biomarkers that might be of value in predicting outcome. As a result, information obtained from neoadjuvant therapy is expanding our knowledge ultimately to ensure the appropriate choice of therapy for each patient.

Administration of endocrine therapies preoperatively has proven effectiveness in HR-positive postmenopausal ever, still present concerning their use in the this setting such as how select the patients who will benefit most from these therapies, the optimal duration or treatment, the best method to evaluate the treatment response achieved, the existence of predictive factors for this response or the superiority of certain endocrine agents over others.

In parallel to its clinical role, a key research aim for neoadjuvant endocrine therapy is to develop short-term surrogate molecular end points that might predict for long-term outcome in adjuvant trials. Such trials are large, expensive to run, and take years to achieve their outcome. For example the adjuvant ATAC (anastrozole, tamoxifen alone or in combination) trial, which started in 1996, involved 9,366 patients and reported its first results 6 years later [12], while the similarly designed Breast International Group (BIG) 1-98 compared adjuvant letrozole with tamoxifen, involving over 8,000 patients, ran to a similar timetable [13]. The option of rapid preoperative alternative involving a relatively small number of patients could improve significantly the rate at which novel therapies in early breast cancer could be investigated. A further research aim would be develop predictive short-term end points for long-term outcome in the individual patient and to allow individualized adjuvant therapy rather than the current blind approach based on probabilities derived from adjuvant trials' data. A key factor underlying this type of research is the anatomic accessibility of the breast, allowing serial biopsies to investigate molecular changes during treatment and providing research opportunities that are unrivaled elsewhere in cancer medicine.

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Preoperative Therapy in HER2 + Patients

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Patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer has had a poor prognosis [1]. However, the disease course of HER2-positive breast cancer has been greatly modified by the introduction of anti-HER2 targeted agents [2,3]. Currently, trastuzumab plus chemotherapy is the standard of care for HER2-positive disease in the adjuvant and metastatic settings.

The pCR rate is a primary predictor of long-term outcome with preoperative chemotherapy and is used as a surrogate endpoint of survival in clinical trials [4]. The pCR rates of 14-16% have been reported with anthracycline-based regimens and of 26-34% with the addition of a taxane [5-7].

The recently reported results of phase III Neo-Adjuvant Herceptin (NOAH) trial demonstrated that trastuzumab in combination with an anthracycline significantly improved the pCR rate (38% vs. 20%, $P=0.003$) of the breast and axillary LNs as well as the 3-year event free survival (70.1% vs. 53.3%, $P=0.007$) compared with treatment without trastuzumab in patients with HER2-positive locally-advanced breast cancer. The preoperative regimen consisted of 3 cycles of doxorubicin and paclitaxel every 3 weeks, then 4 cycles of paclitaxel every 3 weeks followed by 3 cycles of cyclophosphamide, methotrexate, and 5-fluorouracil on days 1 and 8 every 28 days concomitantly with or without trastuzumab. The most common serious adverse event was febrile neutropenia, which developed in 8% vs. 4% of patients without trastuzumab [8,9].

The major risk with trastuzumab is cardiac dysfunction, which is observed in 27% of patients receiving trastuzumab concomitantly with a doxorubicin-based regimen, and in 1.7% to 4.1% of patients receiving adjuvant trastuzumab, either alone or in combination with a taxane [2,3]. To ameliorate the cardiac dysfunction and other toxicities including myelodysplasia [10-13], non-anthracycline-based (neo-) adjuvant regimens were developed and showed superior to or at least comparable outcomes compared with anthracyclines [14-16].

One of such non-anthracycline based regimens is paclitaxel and gemcitabine combination. Paclitaxel (P) and gemcitabine (G) has a different mechanism of action and there is a sequence-dependent synergism [17]. This regimen demonstrated a survival benefit in metastatic breast cancer patients with tolerable toxicity profiles in a phase III study that compared this combination with paclitaxel alone [18]. Preoperative PG combination therapy for stage II/III breast cancer

was evaluated in a phase II study at the National Cancer Center (NCC), Korea, where the clinical response rate was 80% (95% CI, 64% to 89%) with an 18% pathologic complete response (pCR) rate in the breast and 11% pCR in the breast and lymph nodes. Specifically, the pCR rate was 22% in the breast in the HER2-positive subset of patients [19].

Based on the synergy and favorable toxicity profiles in previous studies, a phase II multicenter study of preoperative paclitaxel, gemcitabine, and trastuzumab combination therapy in HER2-positive stage II/III breast cancer was carried out at 5- major hospitals in Korea [20]. The primary objective of the study was to evaluate the pCR rate after preoperative administration of paclitaxel, gemcitabine, and trastuzumab for HER2-positive, stage II/III breast cancer. Secondary objectives included the evaluation of clinical response rate, safety profiles, and breast conservation rate after primary systemic therapy.

Potentially operable breast cancer patients with axillary lymph node (LN) involvement, with adequate organ function, and good performance status were eligible. No prior hormonal or chemotherapy, radiation, or surgery was allowed. Patients received weekly trastuzumab in combination with paclitaxel 80 mg/m² and gemcitabine 1,200 mg/m² on days 1 and 8 of every 21-day cycle for 6 cycles. Postoperatively, patients completed trastuzumab for one year and hormone therapy for 5 years if indicated. All patients received postoperative radiation therapy.

Total 53 patients were enrolled between April 2007 and February 2008. Median age was 43 (range 26-61) years, median primary tumor size was 5.3 (range, 2.0 to >12) cm with 43.4% T3/T4; 28.0% N3; 45.0% with multiple tumors; and 45.3% with positive hormone receptors. The pCR rate was 58.5 % in both tumor and LNs, 69.8% in the breast alone, and 73.6% in the axillary LNs. Grade 3/4 adverse events (AE) were neutropenia (32%), febrile neutropenia (0.6%), and transient elevation of AST/ALT (1.6%) during a total of 318 cycles. All patients maintained normal left ventricular ejection fraction.

In conclusion, this is the first data showing that a non-anthracycline-based anti-HER2 targeted therapy can produce a remarkable pCR rate that is comparable to those of anthracycline-based regimens. Moreover, the PGH combination is safer than other trastuzumab-containing neoadjuvant chemotherapy combinations reported, including those containing docetaxel and anthracycline, with negligible cases of neutropenic fever and cardiotoxicity. Therefore, the PGH regimen could be recommended in patients who are not medically suitable candidates for anthracycline-based therapies as well. Nonanthracycline-based PGH may be an alternative regimen to treat HER2-positive, potentially operable breast cancer.

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Surgical Issues in Preoperative Therapy

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Surgery, radiation and systemic therapy are all essential components of successful treatment of locally advanced breast cancers with neoadjuvant therapy, and collaborative integration and sequencing of therapeutic modalities is essential.

Neoadjuvant systemic therapy is used with increasing frequency to shrink breast and axillary tumor masses prior to definitive surgery. It can convert inoperable cancers to operable, allow lumpectomy instead of mastectomy, and even allow smaller, more cosmetic lumpectomies. Although it may provide many advantages, the neoadjuvant approach can also create a number of surgical challenges.

When the NSABP-B18, EORTC 10902 and ECTO trials compared neoadjuvant chemotherapy versus initial surgery, there was no survival advantage with the neoadjuvant approach, but most women receiving pre-operative chemotherapy showed shrinkage of primary tumors and palpable nodes, and more lumpectomies were possible in the pre-operative chemotherapy group. Local recurrence rates were not statistically significantly higher in patients who received neoadjuvant therapy, although local failures were slightly higher overall, particularly in patients whose tumors showed patchy residual disease rather than a single tumor mass.

Surgical considerations-If breast conservation is considered, breast imaging studies should be performed before and after treatment to document the extent of disease. MRI may be particularly useful in defining the extent of tumor. Marking clips should be placed in the tumor prior to therapy to guide lumpectomy as some tumors will become clinically and mammographically undetectable after neoadjuvant chemotherapy. Lumpectomy after neoadjuvant systemic therapy may be performed with excision to clear margins rather than excision of the initial tumor volume. Multiple localizing wires may prove helpful in guiding lumpectomy for large or eccentric-shaped lesions, and have been shown to reduce re-excision rates. Oncoplastic surgical techniques may allow resection of large tissue volumes while still preserving a good cosmetic outcome.

Patients with multifocal cancers, extensive skin involvement or inflammatory

breast cancer should not be considered for breast conservation after neoadjuvant therapy if they are being treated with curative intent. Modified radical mastectomy or simple mastectomy with sentinel node biopsy is performed when mastectomy is required in patients with locally advanced breast cancer. Radical and extended radical mastectomy procedures have been abandoned as they increase morbidity without improving survival. However, a portion of the pectoralis muscle may be resected during simple or modified radical mastectomy to obtain clear margins when tumor directly involves muscle.

For patients requiring mastectomy after neoadjuvant chemotherapy, delayed breast reconstruction is the preferred approach, although immediate reconstruction may be considered in selected patients. Since most patients with locally advanced cancers will receive post mastectomy radiation, reconstruction decisions must include consideration of radiation effects. The breast surgeon and plastic surgeon should discuss systemic therapy and radiation issues with medical oncology and radiation oncology colleagues prior to any definitive surgical procedures.

Intra-operative placement of radio-opaque marking clips at the apex of the axillary dissection, at sites of muscle resection, at close margins and at other key locations will facilitate radiation planning for locally advanced breast cancers.

Axillary staging-Although axillary dissection remains standard for patients with inflammatory cancer and bulky axillary disease at initial presentation, there is increasing use of sentinel node biopsy for node negative patients and for those with palpable mobile nodes that resolve with neoadjuvant therapy.

Sentinel node biopsy may be performed before or after neoadjuvant systemic therapy with timing based on individual patient and treatment factors. In clinically node negative patients, a sentinel node biopsy prior to neoadjuvant chemotherapy allows accurate and early nodal staging, and provides information useful in selecting systemic therapy and radiation fields. Rates of sentinel node identification may be higher before pre-operative chemotherapy, and false negative rates may be lower. Sentinel node biopsy after pre-operative therapy allows axillary staging to be performed at the time of definitive surgery, without the need for a separate surgical procedure. In addition, a significant number of clinically node positive patients may become node negative following chemotherapy, and sentinel node biopsy following chemotherapy may allow such patients to avoid complete axillary dissection. For those who consider the axillary node status following pre-operative chemotherapy to be a key indicator of prognosis, sentinel node biopsy after pre-operative therapy is favored.

Pathological Issues in Preoperative Therapy

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Preoperative (neoadjuvant) therapy has been used to improve the prognosis of patients with locally advanced and inflammatory breast cancers. Recently it has become common in operable breast cancer to increase breast conservation rates by surgical downstaging among women who might have required a mastectomy. It also allows identification of in vivo tumor sensitivity to different agents, such as various cytotoxic drugs, endocrine therapy and molecular targeted therapy. In preoperative therapy, pre-treatment pathologic assessment by obtaining adequate tissue is important. Core needle biopsy (CNB) of primary tumor is preferred to fine needle aspiration because of the ability to assess tumor grade and to perform full immunohistochemical evaluation of the tumor for prognostic and predictive markers (hormone receptors and HER2). Fine needle aspiration can be used to confirm axillary lymph node status. Pathologic features known as associated with complete response to preoperative chemotherapy are smaller tumor size, presence of tumor necrosis, ductal type, high histologic grade, HER2 overexpression, ER negativity and high proliferation index. During the course of preoperative therapy, CNB is useful for monitoring therapeutic effect of the primary tumor. After surgery, the therapeutic effect of preoperative therapy has been evaluated both clinically and pathologically, although clinical assessments do not necessarily correlate with pathological response. Clinical response can be recorded by the International Union Against Cancer (UICC) and TNM classification systems. UICC criteria are based on a clinical assessment of tumor dimension and are subclassified as complete response (CR, absence of remaining tumor) or partial response (PR, $\geq 50\%$ reduction in the product of the two largest perpendicular measurement of tumor), progressive disease (PD, $>25\%$ increase in tumor size) and stable disease (SD). Pathological grading systems are based on histological findings in the surgical specimen and the achievement of a pathologic complete response (pCR) has been considered as the primary endpoint of preoperative therapy. The definition of pCR has varied across clinical trials. NSABP B-18 and B-27 that were the largest scale studies on preoperative therapy defined pCR as no invasive cancer in the breast. The presence of residual ductal carcinoma in situ maybe negligible in terms of long-term survival, but it could be an important risk factor for local recurrence after breast conserving surgery. Because of recent studies reporting that the presence of any amount of nodal disease after preoperative therapy is

associated with poorer prognosis, the preferred definition of pCR in recent days is “the absence of residual invasive cancer within both the breast and lymph nodes”. Therefore it is necessary for all investigators to make a consensus on pCR and use the same terminology in describing pathologic response. Patients who achieved a pCR showed significantly superior DFS and OS compared with patients who did not in most of clinical studies. For the interpretation of pCR in post-therapy specimens, the pathologist must sample widely to confirm that there is indeed no pathologically detectable disease. Full clinical information regarding the tumor site (placement of a marker at the time of initial biopsy is recommended), pretherapy size, post-therapy estimated size is necessary for handling the specimen. Several pathological grading methods have been suggested to assess the degree of response (below pCR) to preoperative therapy in both the primary breast carcinoma and the lymph nodes at the time of surgical resection. These postoperative pathological grading systems need to be validated for patients treated with preoperative therapy to evaluate whether they determine prognosis of the patients after preoperative therapy.

State of the Science on Cancer-Related Fatigue (CRF): Measurement & Management: Where is the Evidence, Where are the Gaps?

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The primary purpose of this presentation is to review what is known about Cancer-Related Fatigue (CRF). The significance of the CRF problem, its frequency, and impact will be discussed from the perspective of adult cancer patients. Incidence, prevalence, and patterns over time associated with CRF within the context of specific forms of therapy, their combinations, and by site and stage of malignancy, and disease trajectory (i.e., pre diagnosis, during treatment, post treatment cessation, and end of life/palliative care), will be identified. Definitions for CRF will be presented and various “case” definitions will be reviewed and emphasized. The need to develop specific CRF phenotype(s) across the illness and treatment trajectory will be suggested, as will the background and current international planning processes being made to develop and submit a case definition for CRF for inclusion in the future World Health Organization’s International Classification of Diseases, Version 11 (WHO ICD-11).

What is known about various proposed underlying mechanisms for CRF will be reviewed, including specific genetic polymorphisms or gene variants that are beginning to emerge in select populations of cancer patients. Existing CRF evidence-based guidelines put forth by the National Comprehensive Cancer Network (NCCN) in the United States (www.nccn.org) will be reviewed from the standpoint of having these guidelines serve as a beginning framework to implement, translate, and evaluate these recommendations into practice settings. Patient-, Provider-, and Systems-Related Barriers and limitations of these guidelines will be identified. Results from one of the first studies to implement and translate these guidelines into practice: “The Pain and Fatigue ‘Passport to Comfort’ Barriers Study” will be presented (National Cancer Institute [NCI] R-01 CA115323).

Methods to assess, screen, and measure CRF in practice and research will be identified. Implications for patient workup will be presented with a focus and emphasis on the “Gang of 7” or the 7 most common and treatable contributing factors to CRF (i.e., pain, emotional distress [anxiety and depression], anemia, sleep disturbance, nutrition, activity level and comorbidities). CRF management strategies will be reviewed as they relate to the “Gang of 7”. The need to always tailor treat-

ment to what may be the underlying cause(s) of CRF in a given patient situation and the patient's current medical status will be emphasized. The paper also will emphasize using concurrent multimodal (i.e., combination) strategies and referrals to supportive care multi-disciplinary teams whenever available such as physical therapy, occupational therapy, social service, psychology, dietary and chaplaincy. Pharmacologic, non-pharmacologic, and complementary alternative therapies will be reviewed.

As each section of this paper is discussed and reviewed, emphasis will be placed on identifying and discussing "where is the evidence", "what is the strength of the evidence", and "where are the gaps in the evidence". It is hoped that by using this approach consistently throughout the paper, that participants will be provided with specific directions and implications internationally for CRF practice and research. This hopefully will speed knowledge development and its application in practice settings given the international platform afforded us at this Global Breast Cancer Conference, so that we may ultimately improve the care delivered to all patients experiencing CRF.

State of the Science on the Symptom Cluster

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Individuals with cancer often complain about a confusing array of symptoms before, during, and after therapy. These can be disease-related or early or late effects of treatment. Scientific literature is accumulating about the clustering of multiple symptoms. However, it is unclear whether the concept of a “symptom cluster” is merely a buzzword for consideration of multiple discrete symptoms or the description of a distinct phenomenon with integrated facets.

This presentation examines the state of the science with regard to the symptom cluster including both clinical presentation and biological mechanisms that may underlie it. The presentation also considers implications for research and practice.

A symptom cluster has been defined as a stable group of two or more concurrent symptoms that are related to one another through common variance, a common impact on outcomes, and/or a common mechanism/etiology. A body of research points to some combination of the four most common and distressing symptoms—fatigue, insomnia, pain, and depression—as candidates for symptom clustering. Insomnia has been linked causally to fatigue. Both fatigue and insomnia are criteria for the diagnosis of depression. And all three symptoms have been linked to pain. There is also evidence that depression is a mediator between insomnia and fatigue. The evidence is convincing that fatigue, pain, and insomnia incrementally impact patient outcomes. As more of these symptoms are present, symptom burden increases and functional status deteriorates.

Most of the research has found common variance between and among these symptoms. However, only recently have investigators begun to uncover biological mechanisms and genetic determinants that could account for multiple symptoms. Gene polymorphisms have been identified in the regulator (promoter) regions of genes that encode proinflammatory cytokines; these polymorphisms could differentially influence susceptibility to cancer-related symptoms. Because cancer-related symptoms are complex, they are likely to be influenced by the cumulative effect of several gene polymorphisms. Also cytokine genes are pleiotropic in that the activity of one gene can have more than one effect. So genes that control one cancer-related symptom (such as depression or pain) could also influence fatigue.

Based on these premises, it is possible that a combination of gene polymorphisms in the cytokine pathway could influence all four of the symptoms in the proposed cluster.

With regard to practice implications, it has been shown that fatigue, insomnia, and pain have incremental detrimental effects on patient outcomes making these symptoms a high priority for assessment and management. Standardized approaches to symptom management, cross-over treatments, and a few pharmacological therapies show promise in alleviating clustered symptoms.

More research is needed to identify concurrent, related groups of symptoms that negatively impact patient outcomes. Research on the common etiology of symptoms in a cluster could identify targets for drug intervention. Collaborations between laboratory and behavioral scientists have the greatest promise to further understanding of the clinical and biological aspects of a symptom cluster.

Sentinel Node Biopsy in Breast Cancer: Evidences and Controversial Issues

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During the last decade, the sentinel node biopsy (SNB) has largely replaced the traditional axillary lymph node dissection (ALND) and is now a standard surgical technique for nodal staging in patients with early-stage breast cancer. After the pioneering works and numerous following observational studies, oncologic society has rapidly accepted the concept of SNB even before the publication of the first randomized prospective study. Moreover, SNB carries significantly less morbidities such as sensory deficit or arm swelling compared to standard ALND, which makes it an attractive choice for patients and treating surgeons as well. Nowadays, approximately 80% to 90% of patients with early stage breast cancer are candidates for SNB, and approximately two-thirds of those patients will have negative nodes and could avoid the complications of complete axillary lymph node dissection. The ASCO guideline on SNB (J Clin Oncol. 2005) recommended that the technique is acceptable for T1 or T2 or multicentric tumors, or for women who are older or obese, and for men with the disease. The situations for which SNB is not recommended include the presence of clinically palpable lymph nodes, T3 or T4 tumors, inflammatory breast cancer, prior axillary or breast surgery, prior radiation therapy, and pregnant women.

There are three important controversial issues about SNB. The first is the role of SNB for ductal carcinoma in situ (DCIS). SNB is recommended for patients with DCIS when a mastectomy is indicated. Performing SNB in patients with large or high-grade DCIS can eliminate the need for a second operation on the axilla if invasive cancer is found. Another question concerns immunohisto-chemical (IHC) analysis of the sentinel node, which is debated because the clinical significance of micrometastases is unknown. Routine use of IHC and routine ALND when IHC detects micrometastasis in the sentinel node are questionable with current evidence. De Boer, et al., in their very recent report, showed that isolated tumor cells or micrometastases in regional lymph nodes were associated with a reduced 5-year rate of disease-free survival in early-stage breast cancer. The third question was the optimum timing of SNB in relation to neoadjuvant therapy. Some surgeons wait until after preoperative chemotherapy to perform SNB, but some advocate to do SNB before starting neoadjuvant chemotherapy with different rationale.

Another important issue is predicting risk of additional metastatic lymph node when sentinel node is positive. Several groups including Memorial Sloan-Kettering Cancer Center developed nomograms to help predict a patient's risk for additional disease in the axillary lymph nodes. Our group also devised scoring system with variables: ultrasonographic finding of axilla, tumor size, lymphovascular invasion, and number of metastatic and nonmetastatic sentinel lymph nodes. We published the superiority of our scoring system compared to other nomograms for selecting patients who can avoid ALND (Ann Surg Oncol 2008).

While reports of several randomized clinical trials about SNB have been published, most of the studies have focused on quality-of-life issues and complications. We have to wait for 10 to 15-year survival data although most clinicians are expecting optimistic result.

Breast Cancer Surgery and Stage IV Breast Cancer

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In the United States, 6% of women with newly diagnosed breast cancer present with stage IV disease. The treatment of stage IV breast cancer has traditionally been palliative with surgical resection reserved for symptomatic wound complications. This practice is based on prior studies, which have shown stage IV breast cancer to be an incurable disease and one best treated with systemic therapy.

Aggressive local therapy has been found to improve survival in metastatic tumors of colorectal, renal cell, gastric and ovarian origin, prompting multiple institutions and groups to analyze the impact of definitive breast surgery on long-term survival in women presenting with stage IV breast cancer.

Several recent retrospective reviews comparing surgery versus no local therapy in women presenting with stage IV breast cancer with an intact primary tumor all show a survival advantage for the surgical cohort. These recent studies have challenged the traditional paradigm of reserving primary tumor resection for palliative purposes, by documenting improved clinical outcomes in women who underwent resection of their primary tumor. Khan et al. reviewed data from the National Cancer Data Base of the American College of Surgeons on 16,023 patients treated for stage IV breast cancer between 1990 and 1993. 9,162, or 57.2%, of these patients underwent partial or total mastectomy. Superior 3-year survival was seen in women who underwent surgical resection of their primary tumor to negative margins compared to those not undergoing breast operation (35% vs. 26%). Rapiti et al. analyzed 300 metastatic breast cancer patients enrolled in the Geneva Cancer Registry between 1977 and 1996 and reported a 40% reduction in mortality with complete excision of primary. Investigators from The University of Texas M.D. Anderson Cancer Center studied 224 patients treated for stage IV breast cancer between 1997 and 2002, and found a statistically significant improvement in metastatic progression-free survival and a trend towards better overall survival in patients who underwent resection of their primary tumor. A review of nine, Surveillance, Epidemiology, and End Results (SEER) registries between 1988 and 2003 found longer median survival after primary tumor resection for women who present with stage IV disease.

Collectively, these retrospective findings suggest that definitive breast surgery might improve survival for women presenting with stage IV breast cancer and an

intact primary tumor. However, these reports have not defined which clinical or tumor characteristics, in particular, might identify patients likely to benefit from surgery, nor how optimally to integrate surgery and systemic therapy. More critically, these studies have not had the methodological tools needed to adjust fully for clinical selection bias in the judicious selection of patients with favorable long term prognosis who might warrant breast surgery, nor have they been able to adjust for stage migration bias in distinguishing those patients found to have stage IV breast cancer before, or after, primary breast surgery.

We sought to evaluate the survival effect of primary tumor resection in women presenting with stage IV breast cancer by examining the records of patients recently treated at our institutions, specifically looking at the role of estrogen receptor and Her2neu overexpression status and the use of adjuvant chemotherapy, endocrine therapy, targeted therapy and radiation. We also sought to ascertain how the timing of staging and surgery affected overall survival.

We utilized the Clinical Research Information System (CRIS); a relational clinical database into which information on patients treated at the Dana Farber Cancer Institute (DFCI), Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH) is prospectively entered. After institutional review board approval was granted, we retrospectively reviewed the individual medical records along with the CRIS database information of patients presenting with metastatic breast cancer between January 1, 1998 and December 31, 2005.

Between 1998 and 2005, 147 women with stage IV breast carcinoma and an intact primary tumor met study criteria. Of these patients 61 (41%) underwent primary tumor resection (surgery group=S) while 86 (59%) were treated non-operatively (non-surgery group=NS). In the surgery group, 6 (10%) women underwent lumpectomy alone, 15 (25%) women received lumpectomy and axillary lymph node evaluation, and 40 (65%) women underwent mastectomy with or without lymph node evaluation. Demographic and tumor characteristics are compared in the two groups.

On univariate analysis, compared to the NS group, patients in the surgery group were more likely to have fewer sites of metastasis. They also more often received radiation to their primary tumor site. No difference between groups was found for T stage, frequency of liver, lung or bone metastasis, hormone receptor status, Her2neu overexpression, histologic subtype, use of chemotherapy, endocrine therapy or trastuzumab, and receipt of radiation treatment to sites of metastasis.

The median overall survival unadjusted was 3.52 years for S versus 2.36 years for NS ($p=0.093$). After adjusting for age, number of sites of metastasis, use of

chemotherapy, trastuzumab and endocrine therapy, and ER and Her2neu status, survival was significantly superior in the surgery group (HR: 0.47 $p=0.003$ mean 4.13 years versus 2.36 years). ER and Her2neu status were positive predictors of survival (HR: 0.191 and 0.285 $p<0.0001$) while conversely, CNS and liver metastases were adverse predictors (HR: 2.05 and 1.59 $p=0.015$ and $p=0.059$).

It occurred to us that management strategies might differ between patients who underwent surgery for presumed operable breast cancer, who were then found to have stage IV cancer by staging studies done in the perioperative period, and those who were known to have stage IV breast cancer prior to consideration of definitive breast surgery. In the S group, 25 patients underwent surgery after being diagnosed with stage IV disease while 36 patients had surgery before the diagnosis of metastatic disease on subsequent staging evaluation. Median survival among those diagnosed with stage IV breast cancer postoperatively was 4.05 years compared to 2.4 years for those diagnosed with stage IV disease before surgery ($p=0.18$). In fact, survival for women diagnosed with stage IV breast cancer prior to surgery was very similar to survival among no surgery group (2.4 vs. 2.36 years, $p=NS$).

This retrospective review of our prospectively maintained database demonstrates an association between survival and therapeutic breast surgery in women presenting with stage IV breast cancer and an intact primary tumor. As in previous studies, a surprisingly large number of women who present with metastatic breast cancer and an intact primary tumor underwent definitive local therapy. Consistent with the other studies, surgery was performed in patients with fewer sites of metastatic disease. Our clinical experience suggests that women who underwent surgery frequently did so to address wound healing concerns or palliative locally extensive tumor, had more modest disease burdens, and had had good responses to initial systemic therapy. These latter clinical factors may contribute to the observed improved survival in cohorts who undergo surgery for metastatic disease.

Unlike all of the other studies, we were able to distinguish between cases where surgery was done before or after diagnosis of stage IV disease. In our cohort, the apparent survival benefit for the surgery group could be explained by the inclusion of a patients initially thought to have localized disease, and only subsequently found to have stage IV breast cancer following metastatic work-up in the perioperative period. Among women known to have metastatic cancer and an intact primary tumor, survival was comparable either with or without definitive breast surgery.

Margins in Breast-Conserving Surgery

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Breast-conserving surgery (BCS) is a well-established method of treating breast cancer supported by prospective randomized trials. Over time, rates of local recurrence have declined steadily, and are now less than 8% at 10 years of follow-up. In spite of extensive clinical experience with BCS, confusion persists as to what constitutes an adequate tumor-free margin of resection to maximize both local control and cosmetic outcome. This confusion is evident in surveys of both surgeons and radiation oncologists. Morrow et al. performed a population-based study of BCS and found that margin reexcision was required in 22% of cases. A survey of the surgeons treating these patients indicated that there was no consensus on the width of the negative margin which would preclude reexcision. In response to the scenario of a 60-year-old woman with a 0.8 cm grade III infiltrating ductal carcinoma who was both hormone receptor negative and HER-2 negative, 11% of surgeons endorsed a margin of tumor not touching ink, 42% endorsed a margin of greater than 1-2 mm, 28% endorsed a margin of 5 mm or more, and 19% endorsed a margin of greater than 1 cm as precluding the need for reexcision. Similar variation was noted in a survey of North American and European radiation oncologists. A lack of consensus regarding the definition of a negative margin has the potential to result in unnecessary reexcisions or mastectomies, as well as increased costs to the health care system.

Margin assessment is a sampling technique, and multiple factors related to pathologic processing can influence both margin positivity and the distance from tumor to the margin. When evaluating the adequacy of a surgical resection, it is important to be aware that a negative margin does not guarantee the absence of residual tumor in the breast. Holland et al. demonstrated that only 39% of clinically unicentric cancers had tumor confined to the site of the cancer when a detailed pathology evaluation was performed. It is clear that positive margins, defined as tumor touching an inked surface, result in higher rates of ipsilateral breast tumor recurrence (IBTR) than negative margins, and this difference persists through 20 years of follow-up. In 9 studies of 5,138 patients with a mean follow-up of 91 months, the crude rate of IBTR was 15.8% for those with positive margins, and 5.6% for those with free margins, defined as tumor not touching ink. It is much less clear whether close margins (variously defined as tumor cells within 1-3 mm of the ink) increase IBTR

compared to more widely clear margins. All of these studies are retrospective, and other factors known to influence IBTR rates—such as variation in the use of systemic therapy—are not well controlled. The prospective, randomized trials which established the suitability of BCT as a management option do not provide any useful information in this regard since only the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06 trial used a microscopic margin definition, and the definition employed was tumor not touching ink.

In 2009, it is overly simplistic to consider margin status as the sole determinant of IBTR. Local recurrence rates after mastectomy and radiotherapy are similar to those currently seen after BCT. The observation that even the widely clear margins obtained with a mastectomy do not completely prevent local failure indicates that some local recurrence is a manifestation of aggressive biology rather than a high residual tumor burden in the remaining breast tissue. Although it has long been recognized that systemic endocrine therapy and chemotherapy reduce the risk of IBTR, targeted therapy appears to be particularly effective in this regard. Nguyen et al. reported a 0.8% 5-year IBTR rate for hormone receptor positive, HER-2 negative patients treated with tamoxifen compared to 8.4% for hormone receptor negative, HER-2 positive patients and 7.1% for hormone receptor negative, HER-2 negative patients receiving chemotherapy. While it is possible that these differences are simply a reflection of tumor biology, the observation that the combination of trastuzumab and chemotherapy results in an approximately 50% reduction in local regional recurrence compared to treatment with chemotherapy alone suggests that effective targeted therapy is a critical element in local control.

It is clear that adoption of a standard definition of a negative margin, not routinely requiring reexcision, is needed. Based on a review of the literature, a definition of tumor not touching ink appears reasonable for invasive cancer. It is important that margins be considered in the context of the multiple factors known to influence local control, and that clinicians are aware that small differences in margin width may be a reflection of differences in pathologic processing. Decisions regarding the need for reexcision for “close” margins should be individualized based on extent of tumor near the margin, histology/molecular subtype, age, and which margin is close.

Partial Versus Whole Breast Radiation

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For several decades, whole-breast irradiation (WBI) at 50~50.4 Gy at 1.8~2.0 Gy per fraction has been used to reduce the risk of ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery for early breast cancer. Multiple randomized clinical trials and meta-analyses have demonstrated the effectiveness and safety of WBI. Over the past several years, there has been growing interest in the use of partial-breast irradiation (PBI) as an alternative to WBI. Although the concept of PBI is relatively new, there are many modalities for its delivery. Most have been adapted from radiation techniques used to deliver a boost to the tumor bed following whole breast irradiation. These delivery systems include interstitial brachytherapy, the MammoSite balloon catheter system, external beam radiation and intraoperative radiation. In this report, we review treatment outcome of PBI and suggest the clinical implication of PBI compared with WBI.

We conducted a systemic review for published articles describing studies on comparing PBI and WBI; retrospective studies, randomized clinical trials, a meta-analysis, eligible patient criteria for PBI, and ongoing clinical trials.

There were several reports comparing clinical outcome of PBI with WBI in the retrospective manners. Those studies revealed equivalent locoregional and distant metastasis in the two groups. William Beaumont Hospital reported the cumulative incidence of IBTR at 10 years was 5% in 199 early-stage breast cancer patients treated with PBI. On matched-pair analysis, the rate of IBTR was not statistically significantly different between PBI and WBI patient groups. Valachis A et al. analyzed three randomized trials with pooled total of 1,140 patients (Abstract CRA532, the 2009 ASCO Annual Meeting). No statistically significant differences were observed between PBI and WBI arms associated with death, distant metastasis, or supraclavicular recurrences. However, PBI was statistically significantly associated with an increased risk of both local and regional disease recurrences compared with WBI. Recently, ASTRO released guidance for patients and physicians regarding the use of PBI, based on current published evidence complemented by expert opinion (Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 987-1001, 2009). The Task Force classified three patient groups: (1) a “suitable” group, for whom APBI outside of a clinical trial is acceptable, (2) a “cautionary”

group, for whom caution and concern should be applied when considering APBI outside of a clinical trial, and (3) an “unsuitable”s group, for whom APBI outside of a clinical trial is not generally considered warranted. ASTRO concluded that APBI is unlikely to replace WBI for all or even most patients treated with breast-conserving surgery, but the consensus statement will require frequent updates and modifications to account for ongoing research findings because of rapidly evolving knowledge of PBI. Large randomized phase III trials on accelerated partial breast irradiation are running at the present time in North America (NSABP/RTOG), Canada (COG/RAPID), Europe (GEC-ESTRO, IMPORT-LOW), Milan and UK (Targit). The broad inclusion of the current NSABP B-39/RTOG 0413 trial criteria allow entry of patients with stage 0-II breast cancer, with tumors measuring less than or equal to 3 cm and zero to three positive lymph nodes. The PBI techniques utilized is at the discretion of the treating physician and includes interstitial brachytherapy, MammoSite and EBRT. It will take many years for phase III trials with broad inclusion criteria to provide conclusions with adequate follow-up.

Current evidences suggest that PBI should be cautiously done in selected early stage breast cancer patients outside of a clinical trial. Data from large, randomized trials mature, we will learn whether PBI provides comparable local control to WBI and for which patients this treatment may be considered the standard of care.

Comparative Analysis of Clinical Management between U.S. and Korea

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Although the role of Advanced Practice Nurses (clinical nurse specialists and nurse practitioners) in the U.S. have evolved over nearly 100 years, within the last 20 the most dramatic changes occurred; changes which I have witnessed and experienced. There are several major factors that have helped shape this evolution. These factors include 1) changes of health policies, such as the Diagnosis-related group (DRGs) system in the 80s and Clinton's healthcare reform in the 90s, 2) shortage of health workforce, 3) empirical evidence and documents of APNs' effectiveness, 4) continuing efforts by nursing education fields and professional communities to develop APNs' roles and functions, 5) changes in the health practice paradigm from territorial or individual to intra- and inter-professional collaboration to maximize health outcomes.

With support from these factors, APNs' role has developed and is evolving continuously. They perform health history taking and physical and psycho-social examinations, initiate diagnostic tests, analyze collected information with clinical reasoning skills, identify problems and prioritize, and make plans based on individualized expected outcomes. In addition to setting imminent short term plans, APNs also establish long term plans to maximize functional abilities, prevent or minimize disabilities, and promote health maintenance. APNs' role in Oncology fields is even more critical. According to the Scope and Standards for Hospice and Palliative Nursing Practice (2002), APNs are in ideal positions to assess, diagnose, and treat pain and other symptoms because of their proximity to patients. Actually, APNs are in the center of communication channels to provide efficient, patient centered, and evidence based practices across various clinical settings to manage any stage of illness, living and dying.

Compared to the roles of U.S. APNs in managing cancer patients, the roles of Korean APNs are limited. This is because the background of APN development is different from that of the U.S. Furthermore, Korea did not have external driving forces for the APNs' development. APNs in small private hospitals or University level medical centers may work as a physician assistant and are responsible for task-oriented functions only. However, APNs' roles in large private hospitals in Korea, such as Ahsan and Samsung, are quite promising in envisioning the APN's future. They are continuously expanding and creating roles involving teaching or

symptom management and coordination for multidisciplinary collaboration. They manage out-patients' chemotherapy, coordinate bone marrow transplants, and develop patient teaching materials, intravenous-line management, and symptom or case management.

I believe APNs in Korea are going to continuously evolve to fit to clinical practice cultures and health care system. The successful APN system shown by private hospitals supports my future projection and envision for APNs. The demand for advanced practice nursing will increase to meet the needs of the clients. Without APNs' knowledge, clinical experiences, and leadership, delivered care cannot be efficient or effective. APNs will provide genetic counseling, identify and modify an individual's risk factors, participate in disease prevention and perform screening tests for early detection, and make decisions based on individual preferences and quality of life.

Society is changing rapidly, and so is medical management. Medical technologies are changing every day, and someday, there may be a decrease in cancer patients due to early intervention and genetic counseling. We are also experiencing a paradigm shift towards a management of illnesses where quality of life and personal preference is valued over traditional text book based treatments. We should diligently and continuously assess this paradigm change in order to come up with a plan to meet cancer clients' needs. How do you envision the future of the APNs' role in Korea?

Advanced Practice Nursing in Japan

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The objective of this report was to explain of the issues of Advanced practice nursing in Japan.

The report was informed by multiple data sources including Certified Nurse Specialist program curricula documents from any relevant university in Japan, interviews with academic conveners of these programs and interviews with certified nurse specialists.

In Japan, the estimated number of cancer deaths in 2005 was 325,000 persons which accounted for one-third of the total number of deaths. Give the rapid aging of the population in Japan, the prevalence cancer as well as cancer mortality will continue to rise in coming years. As the mortality from cancer increase through to 2020, cancer will come to represent half of all mortality in Japan. Cancer is the most popular disease. In the needs of the times, cancer treatment in Japan has developed remarkably due to significant advances in science and technology and increasingly more sophisticated medical treatment. The state of cancer nursing practice is also constantly adapting in response to progress in medical care and changes in awareness by people, thus undergoing continual dynamic change in order to meet modern day needs. In particular, as a result of the passing of the Basic Law on Cancer Countermeasures in 2006, we believe that the role of advanced oncology nurse practitioner will further expand hereon in.

In 1994, the Japanese Nursing Association launched a system of Certified Nurse specialist which is an area of advanced nursing practice. Persons qualified to apply were nurses who had graduated from a Master's course at a university of nursing, who had obtained credits in the required specialist subject areas, and who had 5 years or more practical experience of working as a nurse in the specialist areas concerned. Persons would be required to sit a written and an oral examination and, if successful, would be awarded a Certificate of Accreditation issued by the Japanese Nursing Association. With a view to being able to judge that the education that the certified nurse specialist applicants have received corresponds appropriately to education in the defined specialist areas, discussions were held between the Japanese Association for Nursing Programs in University (JANPU) and the Japanese Nursing Association (JNA), as a result of which the two bodies agreed

on a summary contract concerning the operation by JANPU of criteria for the specified education and a system of accreditation. Moreover, JANPU drew up a list of discussion points concerning the certified nurse specialist curriculum, established a committee for the accreditation of such a curriculum, and carried out its work of accreditation by means of evaluating the contents of the Master's course curriculum submitted by each university in terms of the target points identified in the certified nurse specialist curriculum. In the 2008 academic year, a curriculum for the certified nurse specialist focused on oncology was introduced in 18 programs in the Master's course of university graduate schools. Certified Nurse Specialist has in-depth knowledge and skills in a specific area of specialization for efficiently providing a high level of nursing care to individuals, families and groups that face complex and difficult nursing issues. They play a demonstrated role in excellent practice, consultation, coordination, ethical coordination, education, and research activities. As of this year, 128 Certified Oncology Nurse Specialists are working all over Japan.

Medical status surrounding the Certified Nurse Specialist in Japan has been changing. A notification by the chief of Health, Policy Bureau of the Ministry of Health, Labour, and Welfare, "Promotion of role-sharing among doctors, medical professionals, and administrative staffs" (as of December 28, 2007) was submitted. This notification clearly stated "adjustment of dosage within doctor's advanced directive" and "performance of intravenous injections", and so on as nurse's role. It is required to prepare new regime where highly educated Certified Nurse Specialists can exercise their professional abilities autonomously, enhance their functional roles to expand their discretionary limits, and perform their new roles in the diagnosis and treatment. JANPU recommends complete transition to new curriculum by the earliest possible time, within five years, or by 2013. Supplying 38 credits for the Certified Nurse Specialist curriculum which are advanced of pathophysiology, pharmacology, physical assessment, will be conducted in the Master's course of university graduate schools.

For rapidly changing medical reforms, it is a responsibility of nursing colleges to cultivate urgently the next generation of certified nurse specialists, who will participate in the diagnosis and treatment.

Building a Physician/Nurse Collaboration in the Management of Cancer Patients-Physician's Experience

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While nurse practitioners and/or physician assistants has been established as one of the job types of cancer patient care in North America, physicians and surgeons are dominantly providing medical care in Eastern Asian Countries such as South Korea, Japan and China. One of the reasons may be based on the history that the gendered role of nursing and the sex of nurses were almost exclusively female; in contrast, the gendered role of the medical practitioners was male. Despite of the increasing importance of multidisciplinary care, the traditional gender role seems to be conservative in Eastern Asian Countries. The gender ratio of the currently identifiable general surgeons in South Korea is 93.9% vs. 6.1% (3,995 males vs. 261 female), and the female nurses are dominating male nurses in number. In the history of National license examination for Regular Nurses organized by South Korean Government, it was the first time that the more than 5% of the successful appliers were males in 2009, and almost 3/4 of Korean male nurses got the Regular Nurse licenses in recent 5 years. As a result, in a treatment/care providing team including physician/surgeon staff, residents, interns and nurses, collaboration and communication between members can be influenced by the professional hierarchy as well as the gender.

Although it is important to get a better communication between the care-providers, it is not always easy to establish a reliable relationship between a physician and a nurse. Moreover, in the care for the breast cancer patients most of whom are women, a preference for the gender of a patient for the physician and/or the nurse may play a role. Besides the achievement of proper collaboration as a team, communication with physicians itself can be a factor for job satisfaction for nurses.

In South Korea, because of the high work intensity of surgeons and relatively underestimated medical charge for the surgery, the number of residents in surgical training has been decreased. It is one of the reasons for the vicious cycle to increase the workload for the surgeons. Recently, physician assistants were introduced in big-sized hospitals. If the vagueness of the jobs of residents or physician assistants happens, the feeling of invasion (or at least the feeling of being invaded) from both sides may occur to harm the collaboration as a team.

Although the role of nurses has not been so much specialized in South Korea as

in North America, multidisciplinary team approach including a nurse may be helpful for the treatment as well as the care of breast cancer patients. The understanding of professional hierarchy and the gender preference, the communications between the care-providers seems to be important factors in building good physician-nurse collaboration in the management of the breast cancer patients.

Building a Physician/Nurse Collaboration in the Management of Cancer Patients-APN's Experience

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Cancer care is complex and cancer patients have various needs throughout their cancer journey. The collaboration between health care professionals, especially physician and nurse is essential to provide a patient-centered care to meet the patient needs. Oncology advanced practice nurse (OAPN) as an expert in cancer care play a key role in collaboration with physician. The collaborative physician-OAPN relationship improves care quality and patient satisfaction and enhances continuity and consistency of care. Additional benefits for physician and OAPN include increased sharing of responsibility and expertise, personal satisfaction, and enhanced mutual trust and ability to meet patient needs, and expansion of professional horizons. Therefore it is imperative for physician and OAPN to build a collaborative relationship to provide optimal patient care. The OAPN's practice in Korea began in the mid-1990s and the collaborative practice between physician and OAPN is increasing in particular care such as symptom management, patient and family education, genetic counseling. But some obstacles restrict performing effective collaborative relationship. The obstacles to collaboration of physician-OAPN include professional and organizational barrier, regulatory and sociocultural issue. The effective strategies including personal and organizational efforts are necessary to overcome obstacles and facilitate collaborative physician-OAPN relationship in cancer patient management.

Discussion: Future APN's Role Development

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Current Approach in the Adjuvant Hormonal Therapy of Early Breast Cancer

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Hormonal therapy in breast cancer represents one of the earliest molecular therapy or targeted therapy in cancer treatment. Adjuvant therapy with hormonal agents in early breast cancer (EBC) reduces the recurrence rate and mortality irrespective of nodal status. Until recently, five years of Tamoxifen (TAM) therapy was the standard of care in the hormonal management of estrogen receptor (ER) and or progesterone receptor (PR) positive EBC. Of the hormonal agents, Aromatase Inhibitors (AI's) have emerged as an important option in the treatment of EBC. Data from recent randomized clinical trials (RCT) now challenge TAM for five years as the gold standard in the hormonal treatment of ER/PR positive EBC, either alone or after chemotherapy. The main issues of the paradigm shift are: whether 5 years of adjuvant therapy is adequate (duration), if TAM treatment should be followed by AI's (switching), and if AI's may replace TAM (replacement). The latest data from ASCO and San Antonio Breast Cancer Conference (SABCC) and St. Galen Meeting as well as major oncology journals will be discussed, especially the up-front strategy with AI's which seems to out-perform the sequencing strategy, especially in the high-risk population. Importantly, the use of bisphosphonates to maintain bone health in patients receiving AI's will be presented, including their possible impact on survival. Despite these promising early data, many questions remain to be explored, such as the long term toxicity of AI's in adjuvant setting, the optimal duration of the adjuvant hormonal therapy, sequencing of TAM with AI's, the use of AI's in premenopausal and Her-2 positive women and the choice of best AI's, all of which are the subject of ongoing clinical trials. Ongoing clinical trials to address these questions will be presented. New molecular prognostic markers and the utility of the newly approved Oncotype DX test will be reviewed. Finally, targeted therapy to increase the sensitivity and overcome the resistance to hormonal therapy in early breast cancer will be addressed.

In conclusion, the current randomized clinical trial data challenge the use of TAM for five years as the standard therapy in adjuvant hormonal therapy for EBC. AI's have been shown to be effective in the adjuvant treatment of EBC and now preferred agents in the adjuvant setting, although the duration of therapy and proper sequencing with TAM remain to be determined. The optimal treatment for post-

menopausal women with receptor positive EBC should include AI's either upfront or following TAM, as per current ASCO guideline. The use of AI's in premenopausal women in combination with ovarian suppression is the subject of ongoing clinical trial. Molecular predictive markers will help to identify patients with increased risk of relapse in order to offer them tailored targeted hormonal therapy in the adjuvant setting.

Endocrine Therapy for Postmenopausal Women

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We have been engaged in synthesis of new agents to optimise endocrine treatment since current agents are limited by the development of resistance. After studying the mechanism of estrogen synthesis *in vivo*, it became apparent that often resistance can occur through the expression of estrone sulphatase. One possible strategy would therefore be to inhibit the formation of estrone from storage form of the enzyme estrone sulphatase which can bypass aromatase inhibitor action. The result was the synthesis of estrone sulphatase inhibitor, Coumate 667. Trials of Coumate-667 are ongoing in Europe at the present time.

In an attempt to discover other molecular targets involved in resistance in endocrine therapy, we have carried out gene expression arrays and proteomic studies. These have disclosed key enzymes such as CDK7 and LRH-1 both of which appear to be important in mediating resistance to endocrine therapy.

Studies are ongoing to determine whether inhibition of these targets have a role in reversing resistance in patients.

Using Predictive Markers for Endocrine Therapy

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Endocrine therapy is a safe and effective method in the management of hormone receptor positive breast cancer. Unfortunately, sooner or later, tumor cells develop resistance to endocrine therapy. Therefore, predictive markers for endocrine therapy are important to assess early endocrine responsiveness of breast cancer. Additionally knowledge of molecular mechanisms for patient who acquired endocrine resistance is essential to predict later endocrine responsiveness of breast cancer.

Predictive markers for endocrine responsiveness according to ER (ER α & ER β), PR (PR-A & PR-B) and HER-2 status were reviewed by literature. The comparison between before and after specimen of neoadjuvant endocrine therapy was conducted by immunohistochemistry in some patients.

The most important predictive factor for endocrine therapy is ER. Allred score and expression of ER α & ER β ratio are revised as a predictive factor for precise endocrine responsiveness in breast cancer patients. Isoform ratio of PR-A and PR-B was also a newly interested factor for endocrine responsiveness. Loss of PR predicts relative resistance to tamoxifen and in some tumors may be a surrogate marker for increased signaling through the growth factor receptor tyrosine kinase pathway. It may help clinicians decide between initial use of an aromatase inhibitor and tamoxifen in the individual patient. HER2 overexpression results in increased membrane-initiated steroid signaling ER activity, a pathway in which tamoxifen acts as agonist. Therefore, HER2-positive tumors may show resistance to tamoxifen and may be more sensitive to aromatase inhibitors, at least in an initial phase. Ki-67 expression (index of <10%) have slow proliferation rates to be predictive for response to endocrine therapy, but others new potential predictive markers included VEGF, VEGF receptor (VEGFR), p53, tissue inhibitor metalloproteinase-3 (TIMP3), cyclin D1, p-21-activated kinase 1 (PAK1), urokinase-type plasminogen activator (uPA) and plasminogen activator inhibitors (PAI-I) are controversial.

Several markers such as ER (ER α & ER β), PR (PR-A & PR-B) and HER-2 status will help to predict the most appropriate endocrine therapy for each breast cancer patient. Recently, the molecular characterization of the complex signaling networks operating in endocrine resistant cells, e.g. EGFR, HER2, MAPK, AKT, mTOR, is ongoing to be evaluated in order to assess endocrine responsiveness and overcome or delay the onset of resistance to endocrine therapy in breast cancer.

Treatment Strategy Based on Intrinsic Subtypes for the Patients with Recurrent Breast Cancer

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The prognosis of patients with recurrent breast cancer has been improved with new drugs in Western countries (Giordano SH, Cancer 2000 and Andre F, J Clin Oncol 2004). Recently, intrinsic subtypes are important for the treatment strategy. In Japan, aromatase inhibitors and trastuzumab were approved in 2001. The purpose of this study is to evaluate the effect of these drugs on prognosis of the patients with recurrent breast cancer.

Four hundred twenty nine patients with recurrent breast cancer were divided into two groups. The recurrence was diagnosed between 1992 and 2000 in Group A (181 pts), and after 2001 in Group B (248 pts). The overall survival rates of these two groups were compared according to the intrinsic subtypes. Additionally, the clinico-pathological characteristics were evaluated in cases in which recurrence was found beyond ten years after surgical resection of the primary breast cancer.

The median overall survival (OS) of Group B was 4.2 years, which was significantly better than 2.0 years of Group A ($p < 0.001$). In cases with Luminal A disease, the median OS of Group A and B were 4.5 and 3.0 yrs, respectively ($p = 0.004$). Those in Luminal B of these groups were 3.4 and 5.0 yrs, respectively ($p = 0.17$). The median OS of cases with HER2 type in Group B was extremely improved to 5.5 yrs, while those of Group A were only 1.6 yrs ($p = 0.01$). In cases with triple negative tumors, in which only chemotherapy are indicated, the median OS of Group A and B were 1.0 and 2.1 yrs, respectively ($p = 0.05$). Multivariate analysis showed that the individual prognostic factors were the first recurrent organs with hazard ratio of 2.29, disease free interval of 1.40, hormone receptor status of 1.98, HER2 status of 1.39, and the time of diagnosis of recurrence of 1.59. Additionally, the clinico-pathological characteristics were evaluated in cases in which recurrence was found beyond ten years after surgical resection of the primary breast cancer. Nineteen patients among 429 had late recurrence after ten years of surgery. All of these cases had hormone receptor positive disease with high Allred score, while HER2 positive tumors were only two of nineteen. The recurrent tumors have responded well to the endocrine therapy, and the five year survival rates after

recurrence of these 19 cases were 73 percent.

Tailor made therapy based on the intrinsic subtypes is promising the better prognosis of the patients with recurrent breast cancer. On going clinical studies with new targeting drugs may contribute to improve treatment results. On the other hands, the prognosis of cases with triple negative tumors is still unsatisfied, and treatment strategy should be conducted including the primary systemic therapy.

Diet and Breast Cancer Risk among Premenopausal Women

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The association between diet and breast cancer risk has been a topic of debate for many years. However, most epidemiologic studies of diet and breast cancer have assessed diet in midlife or later. Also, limited studies evaluated breast cancer by hormone receptor status. Breast tumors differ clinically and biologically by hormone receptor status and may also differ etiologically by menopausal status. In a large prospective follow-up study of initially premenopausal women in the United States, we have evaluated a wide spectrum of dietary factors in relation to breast cancer risk and found that several, especially intakes of animal fat, high-fat dairy foods, and red meat, were associated with an elevated risk of breast cancer. The association was often stronger among breast cancer cases with positive hormone receptor status. Potential components in red meat that may be responsible for the positive association include heterocyclic amines created during cooking of meat, exogenous hormone residue, and heme iron. The incidence of breast cancer in Asian countries has increased dramatically, especially among premenopausal women, in recent years. The intake of animal-based food has also increased in those countries. The implication of our findings on breast cancer risk in Asian premenopausal women and relevant prevention strategies will be discussed.

Comprehensively Measuring your Quality of Care Delivered to Patients in your Breast Center

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To learn specific quality measurements and how they can be applied on measuring quality of care, efficiency, effectiveness and clinical outcomes for a breast care/breast cancer patient population learn how to benchmark against yourself and other breast centers with a similar clinical profile and patient population learn how to take the results of your quality measurements and improve patient care.

Lecture and examples of measurements and how they have been applied nationally through the national consortium of breast centers quality initiative program.

More than 240 breast centers are participating in the quality measurement initiative, each making incremental improvements in their care and delivery process.

You cannot effectively manage what you do not measure. By measuring clinical performance breast centers can improve the care they provide for their patients making the diagnosis and treatment of breast cancer the least physically and emotionally traumatic a center can achieve on behalf of their patients.

The Balance between Oncologic Safety and Cosmetic Result in Asian Breast Cancer Patients

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Oncoplastic surgery, combined oncologic extirpation of the tumor with plastic surgical reconstruction of breast shape and symmetry, is increasingly being used for breast-conserving surgery (BCS). However, the size of breast is very important factor to apply oncoplastic surgery for the Asian women. Many experts of oncoplastic surgery have recommended applying skin sparing mastectomy with immediate reconstruction using autologous or implant materials for the small and medium sized breast.

In recent studies, several oncoplastic techniques have been described by using breast conservation surgery. After BCS was done, breast reshaping by oncoplastic techniques were selected depending on the location and size of the tumor within the breast as well as the size of breast itself.

We applied Round-Block technique and Batwing mastopexy for the periareolar lesions. After central quadrantectomy, linear suture, purse-string suture and inverted T-reduction mammoplasty technique were conducted for the subareolar lesions.

There are various options for the upper quadrant lesions such as Tennis racket method, inferior pedicle reduction mammoplasty and flap rotation (matrix rotation).

Certain tumor localizations, particularly inferiorly located breast cancer, and large tumors carry a high risk of post-operative deformity. The most common consequence, followed by inferior large lumpectomy is a noticeable deformity with excessive protrusion and pointing downward of the nipple, caused by wound fibrosis and retraction.

For the lower quadrant lesions, we used several oncoplastic techniques after partial mastectomy such as 'Wise pattern (inverted T)' reduction mammoplasty, 'vertical pattern' reduction mammoplasty and 'J-pattern' mammoplasty. In order to improve the cosmetic outcome, additional repositioning of the nipple areola complex (NAC) or reshaping of the contralateral breast can be considered.

After removing quite a lot of breast tissue with tumor, it was necessary to use volume replacement techniques. Partial mastectomy (quadrantectomy) and immediate reconstruction with a myocutaneous latissimus dorsi flap allows extensive resection of volume, which fits oncoplastic requirements with lower morbidity and a good cosmetic outcome. We found that thoraco-epigastric flap would be one of good options for the small sized breast patients, who wished to keep her breast intact as much as possible.

Even though the sizes of breast are smaller in Asian women, in selected cases, oncoplastic approach has allowed us to perform wide range of resection and to obtain good oncologic control with favorable cosmesis.

More than 70% of Breast conserving surgery patients were treated with oncoplastic surgery techniques.

The final purpose of post mastectomy reconstruction is a balanced, symmetrical, pleasing appearance for both breasts. When reconstruction is considered, equal importance may need to be placed on the contralateral breast. When the unaffected breast is aesthetically pleasing and there is a low risk cancer in the contralateral breast, matching the reconstruction to the remaining breast is the best choice. However, if some woman have an unattractive breast, which is small, ptotic or huge, remodeling of the contralateral breast may be desirable.

Numerous options may be available to the patient depending upon the individual anatomic and oncologic status for symmetrical shape. Surgical options available for the contralateral breast included breast augmentation with implant, mastopexy, and reduction mammoplasty.

The administration of neoadjuvant chemotherapy should not constitute a contraindication for performing immediate breast reconstruction following mastectomy in patients who were not converted to lumpectomy candidates.

Autologous tissue reconstruction is preferred over implant reconstruction in patients with large, operable, and locally advanced breast cancer who would likely need adjuvant radiotherapy, given that irradiation of breast implants is associated with an increased risk of capsular contracture.

On the other hand, radiotherapy can be given safely to high-risk patients following autologous tissue breast reconstruction, with excellent cosmetic results.

Several studies have shown that in patients who have received prior neoadjuvant chemotherapy, immediate breast reconstruction with autologous tissue is safe, does not delay further adjuvant therapy, and is not associated with an increase in local recurrence or with a delay in detecting such a recurrence.

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Risk Assessment of Developing Breast Cancer in Japanese Women

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The risk assessment tool, the Gail model, is currently available for counseling and/or chemoprevention of breast cancer in USA. Very recently, a web-based risk assessment tool for breast cancer has been developed for Korean women (Chang M-C, et al. Kyoto Breast Cancer Conference 2009). We present the development and validation of a logistic regression model as a tool for breast cancer risk assessment in Japanese women.

To assess the risk factors for breast cancer in Japanese women, a case-control study comparing 3,434 breast cancer patients with 2,427 healthy controls was conducted. Factors examined included use of hormone replacement therapy, body mass index, alcohol intake, physical exercise, parity, past history, history of breast screening, history of benign breast diseases or breast biopsy, family history of breast cancer, history of breast feeding, ages of menarche and menopause, use of oral contraceptives and educational background. Based on the significant risk factors thus identified, a logistic regression model for risk assessment was developed.

In general, risk factors for breast cancer in Japan are similar to those in Western populations. However, some discrepancies were observed; for example, surprisingly, there was no statistically significant correlation between hormone replacement therapy and breast cancer in Japanese women. In addition, another case-control study suggested that soybean intake might prevent breast cancer in Japanese women.

The risk assessment tool for Japanese women thus developed will be further validated for another cohort. Considering there are close similarities in the etiology of breast cancer in Asia, it is our hope to exchange information with Asian countries.

Toward Anthracycline-Free in Adjuvant Treatment

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Adjuvant chemotherapy has long been the mainstay of post-operative breast cancer treatment over 30 years. Anthracyclines and taxanes are two major classes of cytotoxic drugs whereas their different combinations have evolved since 19th century. Although there are still a lot of studies on the sequence, dosage, duration and combination of anthracycline- and/or taxane-based chemotherapy which is the key anti-cancer treatment for breast cancer, in recent years, a number of new specific biological agents entered into clinical practice and gradually replaces the non-specific cytotoxic agents. The evolution originates from the advancement of molecular biology and genetic expression profiling which together help to further classify breast cancer into molecular subtypes. As different types of cancer respond to different types of therapy, the widespread use of anthracyclines and/or taxanes may over-treat patients who might even experience unnecessary toxicities. The exercise of histopathological evaluation of resected tumor is now important to provide clinicians with clues on selection of appropriate adjuvant treatments such as hormonal therapy and anti-HER2 therapy for particular subtypes of breast cancer rather than exclusive chemotherapy. However, considering the highly mutating and aggressive malignant tumor, the development of chemotherapy is still underway to ensure a provision of effective and safe systemic treatments after surgery. In view of the concerned anthracycline-induced cardiotoxicity and the recently published results on the superiority of docetaxel-cyclophosphamide over doxorubicin-cyclophosphamide combination therapy in adjuvant setting, taxane might be able to put adjuvant treatment into anthracycline-free apart from the incorporation of “targeted” agents. Given that the cardiotoxicity by anthracyclines might jeopardize patients’ survival, further development of taxane-based chemotherapy together with other biological agents are necessary to direct future adjuvant breast cancer treatments.

Adjuvant Taxanes: Maximizing Benefits

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There are two major ways to improve the therapeutic effects of chemotherapy, selection of target patients and enhance the antitumor effect. Recent accumulated data indicate that hormone insensitive tumors are more sensitive to chemotherapy including taxanes as compared with hormone sensitive ones. Therefore, it is reasonable to make a therapeutic plan based on hormonal status individually. In addition, it has been recently underlined that luminal type B tumors are relatively more effective to chemotherapy rather than luminal type A tumors, indicating that a different therapeutic strategy needs to be taken for these estrogen receptor (ER) positive tumors. Tumor proliferation activity and gene signatures help to characterize the tumor properties. In order to enhance the activity of taxanes, the combination with other chemotherapeutic agents such as cyclophosphamide and capecitabine seem to be promising. Currently numbers of clinical trials with these regimens are on going for primary breast cancers. We are also conducting several preoperative trials in the Japan Breast Cancer Research Group (JBCRG). Regarding the combination with biological agents such as trastuzumab, several new findings were reported recently. These issues will be also discussed.

Clinical and Therapeutic Implications of Triple Negative Breast Cancer

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Triple negative (ER negative, PR negative, HER2 not overexpressed) breast cancer is recently recognized a subtype of breast cancer with distinct pathologic and clinical features of relatively poor prognosis, aggressive behavior and lack of targeted therapies.

This subgroup accounts for 15% of all types of breast cancer. Although not synonymous, the majority of triple-negative breast cancers carry the “basal-like” molecular profile on gene expression arrays.

When diagnosed, triple-negative breast cancers illustrate preferential relapse in visceral organs, including the central nervous system. Relapse is early and common among triple negative breast cancer despite initial response to chemotherapy might be more profound. Although effective tailored have been developed for hormone receptor positive and HER2+ disease, chemotherapy is the mainstay treatment for this subgroup at the moment.

The armamentarium of “targeted therapeutics” for triple negative breast cancer is evolving and includes strategies to inhibit angiogenesis, epidermal growth factor receptor, and other kinases, Finally, inhibition of poly (adenosine diphosphate-ribose) polymerase-1 is an attractive therapeutic strategy that is in active study as positive associations between triple-negative disease and BRCA mutations have been repeatedly demonstrated.

Molecular Profiling of Breast Cancer

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Communication and Care Roles of Family Across the Cancer Care Continuum

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Cancer invades one body but affects many. For women with breast cancer, the ordeal of diagnosis and treatment is infrequently faced alone. A recent Belgian study suggests that over 80% of women seeking care for breast cancer were accompanied to their initial oncology visit by a family member or spouse. It is very likely that many of these women are routinely accompanied to every treatment and follow up visit, especially those over the age of 65, with limited education and in poor physical or emotional health. The objective of this talk is to discuss specific communication roles in medical visits adopted by family members to facilitate care

A review of relevant studies, conducted in the US, Asia and Europe will be presented.

Patient companions, most usually a spouse or adult child, are often actively engaged in the medical dialogue and facilitate the exchange of health information between patients and their physicians, provide emotional support and act as a patient advocate. Results of observational studies and surveys in the US, Asia, and Europe, point to a common set of facilitative communication roles played by family companions during medical visits.

For instance, the majority of companions in a US study of patients over the age of 65, reported to directly facilitated visit communication by engaging in at least one of the following activities (and very often more than one): writing down physician instructions, providing information regarding patients' medical conditions or needs, asking questions or reminding the patient to ask questions, or explaining physicians' instructions to the patient. Visit companions were also reported to be present for company and moral support, and to assist with logistics such as transportation, scheduling appointments and physical assistance. Similar findings in regard to companion roles were also reported in a parallel Japanese study of elderly medical patients.

Especially noteworthy and relevant to survivorship are findings that visit companions have a significant impact on patients' experience of care. Patient satisfac-

tion with physicians' interpersonal skills and ability to communicate information in an understandable and useful way, are a positive function of the intensity of companions' involvement in visit communication. The strength of this relationship is most evident among individuals with the worst self-rated health such that the common inverse relationship between health status and satisfaction, that is the sicker patients are, the less satisfied they are with their care, appears to be attenuated with greater companion involvement in visit communication.

Other observational studies have linked the presence of active companions to more patient engagement in decision making and recall of treatment information. Clayman and colleagues, in a US study, concluded that older medical patients with companions who engaged in facilitating communication behaviors were 4 times more likely to be active in decision making (active decision-making was defined as discussing treatment alternatives, risks and benefits, uncertainties, preferences, or making an explicit request) than patients whose companion was passive during the visit. Other studies, for instance, Jansen et al in the Netherlands have demonstrated a benefit to accompanied cancer patients in their ability to accurately recall treatment related information communicated to them preceding chemotherapy treatment.

Family members play an important communication role during oncology visits across the entire care spectrum. Although largely unacknowledged, this aspect of family involvement in care undoubtedly contributes to survivorship. The challenges ahead are to identify ways to optimize the power of family involvement through the fostering of effective models for patient-companion communication and to develop training programs that prepare physicians to take advantage of the resource companions represent in patient visits.

The Cancer Paradigm Shift-Who Will Take Care of the Breast Cancer Survivor

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Purpose: 1) Provide statistics showing oncology specialist shortage that is projected for 2020 (increased need of 48%; onc work force will only grow by 14% however, creating the shortfall). 2) Provide data comparing recurrence rates and long term survival of patients followed long term by oncologist vs. generalist. 3) Provide statistics projecting aging population with increase in cancer survivors in general. 4) Overview of survivorship issues that must be addressed: a. 53%-secondary health problems b. 49%-non-medical problems are unmet c. 53%-suffering with emotional problems as result of diagnosis and treatment d. 70%-emotional support-depression e. 58% loss of sexual desire or function f. financial issues-43% decrease in income; 25% in debt due to treatment expenses. 5) Need to establish clinical practice guidelines for survivorship. 6) Long Term Follow Up Needs a. chronic side effects from chemo, targeted therapy, hormonal therapy b. late effects of radiation and/or surgery c. risk of secondary cancers d. other long term health issues e. psychological burden. 7) Survivorship care a. prevention of recurrence of breast cancer b. prevention of secondary malignancies c. promote health and recovery d. ease side effects from treatment e. enhance quality of life and relationships with others. 8) Role of the NP in a comprehensive breast center including a collaborative team approach in assessment and management of acute patients and long term survivors. 9) Discussion of a survivorship care model that may be applied based on the volume of breast cancer patients seen and treated. 11) Q&A regarding models that are being used-PCPs, Gynecologists, Oncology nurses serving as the breast cancer survivor provider.

Methods: Lecture and examples of models in use and being developed.

Result: The necessity to implement new models for delivering survivorship care must be developed and implemented soon in preparation for the growing volume of women being diagnosed with breast cancer compared to the lack of oncology specialists there will be to manage them. This requires oncologists to discontinue their oversight in the care and monitoring of breast cancer patients soon after their treatment is completed.

Conclusion: Utilizing nurse practitioners as the cancer survivor provider will be the most cost effective model to use, coupled with educating PCPs and gynecologists in the management of these patients long term care needs.

Fostering Breast Cancer Control through Community Engagement: Challenges and Opportunities

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Introduction:

Rates of breast cancer vary yet, there is a global rise of the disease. An estimated 1.3 million new cases were diagnosed around the world last year. As countries modernize, more women may be threatened by breast cancer. It is crucial that women's awareness be bolstered and expectations be raised for family members, frontline health professionals, community, governmental, and policy-linked organizations to engage in the spectrum of breast cancer control.

Presentation Objectives:

The focus of this presentation is to review the spectrum of cancer control and identify strategies that underscore the need for greater community participation in cancer care and outcomes. Challenges and opportunities will be highlighted that include patient and individual-level variables, sociocultural and contextual factors and organizational practices.

Implications:

This presentation is intended to show the importance of community engagement in overcoming persistent barriers experienced by women in transforming perceptions of cancer. Engaged communities can influence shaping policy for improved cancer outcomes.

Beating Breast Cancer Stigma and Discrimination

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Whenever you hear about breast cancer these days, the buzz words are that “early detection saves lives”. Translating this hype is easy: when breast cancer is found in its earliest stages of development, the five-year survival rate is 98%. However, looking past this pink-hued buzz and into my own community, the trends are more disturbing. Less than half of Asian American and Pacific Islander women 50 years and older in the U.S. have had a mammogram or clinical breast examination within the last two years—the lowest rate of screening among all racial/ethnic groups.

Breast cancer is the number one cause of cancer-related mortality for Asian American and Pacific Islander women, who have the lowest rate of both screening and early detection, compared to all other ethnic groups. I have spent most of my career helping to educate women throughout the San Francisco Bay Area about breast cancer and helping them through a cancer diagnosis and into survivorship. But it has been a hard road with a lot of tragedy along the way, especially as that road travels through communities of color.

For us, cancer is still “the big C” and that 98% statistic is a pipe dream. Numerous barriers stand between us and a mammogram, the best method of early detection: lack of health insurance, a limited command of English, cultural and social taboos surrounding our breasts, and a lack of awareness of the screening to detect breast cancer early. We conducted a telephone survey of 798 Chinese immigrants living in San Francisco and found that 25% still believe cancer is contagious. Many also believe cancer is caused by environmental as well as personal action, such as immoral behavior. A logistic regression model indicated that women who are low-income and have resided in the United States for an extended period of time are more likely to believe cancer is contagious.

Community stigma toward breast cancer and breast cancer survivors will prevent some women from seeking early diagnosis. Multimedia education efforts, utilizing print, television and radio may provide a point of entry to reach otherwise unreachable individuals. This concerted educational effort may help to dispel some of the myths regarding cancer, its treatment and prognosis.

Too often, I talk to women who do not pursue screening because they fear finding a lump. For some it's even worse they know they wouldn't be able to afford treatment if they did find one. California has a program that provides screenings and treatment for many underserved women in our state. Lawmakers designed the program, Every Women Counts, to knock down the barriers that prevent early detection, but the program lacks funding to serve all women who lack adequate health coverage. Of the more than 1.2 million women who are eligible for care under the program, the current funding can only provide care to 20 percent of them. Even worse, it is projected that more than 40,000 eligible women seeking breast health services will have to be turned away due to lack of funding next year.

It is important for all women to join together to ask legislators to increase funding for screening programs and make detecting breast cancer a priority. It will ensure that no women seeking care is turned away and it will ensure that thousands of lives will be saved.

One of the actions we have taken in San Francisco on Friday, January 11, 2008 was to invite city officials to turn San Francisco's City Hall pink to celebrate the start of this new push to close the gaps in breast cancer screening and treatment. The following week, hundreds of our volunteers descended on the State Capitol in Sacramento, California to challenge decision makers to close these gaps in policy and funding. This was a good start, but it usually takes more than a week of public action to create political action. We all need to call our legislators and the governor's office and let them know that the lives of our mothers, our wives, our daughters, and our grandmothers are all on the line.

More than 4,000 women in California will die from breast cancer in 2009 how many of these lives can we save.



GBCC 2009

Closing Lecture

The Challenge in Providing Equal Access to Care

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Purpose/Background: The vast burden and impact of cancer around the globe is undeniable. Recent data illustrates that the disease kills more people around the world every year than malaria, AIDS, and tuberculosis, combined [1]. While at one time, cancer was widely thought to afflict only the elderly residing in affluent countries, cancer has now moved beyond high income countries of the developed world to the middle and low income countries of the developing world. In fact, more than 50% of new cancer cases and nearly two-thirds of cancer deaths occur in the low income, lower middle income and upper middle income countries of the developing world [2]. In many of these countries, where incidence of cancer is undoubtedly growing expeditiously, the stigma associated with cancer arising from misinformation, lack of awareness, and deeply-engrained cultural myths (among other instigators) in conjunction with deficient or non-existent national cancer control policies and a lack of resources, often acts as a barrier to treatment and leads to significant levels of mortality.

Methods: I will discuss the Economic Impact Report that LIVESTRONG commissioned the Economist Intelligence Unit to undertake and likewise, I will examine our research into the topic of stigma associated with breast cancer and other cancers impacting people in both developed and developing countries, and the subsequent silence around this stigma that occurs in many communities.

Results: The results of our research could potentially have far-reaching and profound impacts in the arena of cancer control, advocacy, and survivorship, given that the Economic Impact Report is the first of its kind documenting the global burden of cancer in economic terms. Likewise, it also represents the first time that a global treatment expenditure standard has been considered and the spending gap to achieve that has been quantified [3] The results of our studies serve in large part to illuminate the disjuncture between the developed and developing worlds in terms of providing access to treatment and care. Examining this disjuncture then becomes a function of understanding what we as a technologically advanced society are capable of in terms of resource provision, and the geopolitical, economic, and cultural realities that prevent equal access to care for those in low and middle income countries. It also however, underscores the need to find innovative and effective ways of com-

bating stigma in the developed world so that we can comprehensively provide equal access to treatment to all persons marginalized by stigma.

Conclusion: I will be discussing some of the mechanisms which LIVESTRONG, in collaboration with our partners, is utilizing in order to address the barriers to treatment which exist on a global scale. Primarily, I will elaborate on some key aspects of our Global Cancer Campaign with the goal of providing a snapshot of the progressive mediums that large-scale grassroots advocacy and global collaboration provide in reducing the global cancer burden and addressing the need for improved access to treatment around the world by advocating for an investment in health infrastructure and education, encouraging instigation of cancer control policies and programs, and reducing stigma.

References

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GBCC 2009

Free Paper

Application of Analysis of Loss of Heterozygosity on Chromosome 16q to Core Needle Biopsy Specimens from Intraductal Papillary Lesions of the Breast

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Background/Purpose: Loss of heterozygosity (LOH) on chromosome 16q is shown to be frequent in low-grade ductal carcinoma in situ (DCIS), including cribriform and papillary subtypes. Because the differential diagnosis of intraductal papillary lesions on core needle biopsy (CNB) specimens is often difficult, we planned to apply the analysis of LOH on 16q to CNB specimens from intraductal papillary lesions and to examine its diagnostic utility.

Methods: We examined LOH at the D16S419 and D16S514 loci on chromosome 16q in 21 CNB specimens which was histologically diagnosed as indeterminate or suspicious of malignancy at the National Cancer Center Hospital between 2005 and 2008. Five obvious DCIS cases were included as positive control. From 5 to 10 μ m-thick sections of routinely processed formalin-fixed paraffin-embedded tissues, tumor cells were microdissected, subjected to PCR-LOH, and analyzed using an ABI 3130 sequencer. Results of the LOH analysis were compared with final histological diagnosis on excisional biopsy specimens.

Results: In 11 tumors that were finally diagnosed benign, 8 were informative and LOH on 16q was not detected. In 10 tumors that were finally diagnosed as DCIS, e.g., low-grade papillary or solid subtype, seven (70%) were positive of LOH on 16q. In 5 CNB specimens that were diagnosed as DCIS, three were informative and two (67%) were positive of LOH.

Conclusions: Examination of LOH on 16q might be useful as an objective supportive tool for diagnosis of intraductal papillary lesions on CNB specimens.

Clinicopathologic Signature of Triple-negative Breast Cancer Patients with Good Prognosis

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Background/Purpose: We analyzed the molecular subtypes of breast cancer using Korean Breast Cancer Society Registration Program data during 1993-2008 to compare the clinical feature and prognosis for 'triple-negative' breast cancer with other types of breast cancer. We also compared patients deceased from breast cancer within 3 years of diagnosis with the others in triple-negative breast cancer patients to find clinicopathologic variables influencing prognosis.

Methods: We studied a cohort of 38,356 breast cancer patients, with assessable data for ER, PR, and Her-2/neu status. The median follow-up period was 75.6 months.

Results: Those with triple-negative breast cancer had an increased propensity of early death within 5 years of diagnosis. But, thereafter, the risk of death declined rapidly. In the luminal A and B groups, the risk of death was constant over 7 years of follow-up. Overall, the triple-negative group had a 'good' long-term prognosis. Two thousand eight hundred thirty one triple-negative breast cancer patients had assessable follow up data over 3 years. Two hundred eighty three patients deceased from breast cancer within 3 years of diagnosis. Tumor size, nodal status, histological grade were correlated with breast cancer specific mortality by the univariate analysis with triple-negative breast cancer patients. Histological grade was the only factor correlated with the breast cancer specific mortality in multivariate analysis.

Conclusions: Triple-negative breast cancer has more aggressive clinical course than any other forms of breast cancer. It is necessary to develop new prognostic marker and effective therapeutic strategy.

Comparison of Outcomes for the Patients with Pathologically Node-Negative Breast Cancer and who were Treated with either with Sentinel Lymph Node Biopsy Only or with Conventional Axillary Lymph Node

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Background/Purpose: The purpose of this study was to compare results after performing only an SLNB as compared with performing conventional axillary lymph node dissection (ALND) without an SLNB in pathologically node negative (pN0) breast cancer patients.

Methods: From 2004 to 2007, SLNBs were performed for patients with primary breast cancer who had no clinical evidence of a lymph node metastasis. A total of 272 patients were treated with only an SLNB. During the same period, 278 patients were confirmed as pN0 after conventional ALND without an SLNB. A prospectively collected database and medical records of these patients were reviewed.

Results: For patients that had undergone only an SLNB, there was no local or regional recurrence. A distant metastasis developed in four patients (1.5%). In patients that had undergone ALND without an SLNB, a recurrence was found in 13 patients (4.7%). Patients that had undergone only an SLNB showed significantly better disease-free survival as compared to patients that had undergone ALND without an SLNB ($p=0.032$).

Conclusions: pN0 patients treated with only an SLNB showed a significantly better outcome as compared to patients treated with conventional ALND without an SLNB. These results suggest that performing an SLNB might result in the upstaging of a subset of patients who would have been under-staged by the use of conventional ALND.

Association of Genetic Polymorphisms of Genes Involved in the Lipid Metabolism Pathway and Breast Cancer Risk by Menopausal Status

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Background/Purpose: Obesity and dyslipidemia has been suggested to be associated with breast cancer risk. Enzymes and molecules in the reverse cholesterol pathway play a key role in lipid metabolism. We aimed to examine the effect of genetic polymorphism of the enzymes and molecules in the lipid metabolic pathway on breast cancer risk.

Methods: In a case-control study, 456 incident breast cancer cases diagnosed from August 2002 to December 2003, and 461 control subjects who participated in a cancer screening program during the same period were included in the analysis. Twenty-one single nucleotide polymorphisms (SNPs) were examined for four genes, which were apolipoprotein E (ApoE), low density lipoprotein receptor (LDLR), cholesterol ester protein (CETP), and scavenger receptor B (SR-BI).

Results: Mean body mass index (BMI) was 23.9 kg/m² in cases and 23.0 kg/m² in controls, and the difference were statistically significant ($p < 0.01$). Genotype GA and GG of LDLR rs5927 was associated with reduced risk for breast cancer (OR 0.60, 95% CI 0.40-0.91). Genotype TT of CETP rs289716 was associated with reduced risk for breast cancer (OR 0.55, 95% CI 0.34-0.91) only among premenopausal women. Genotype GG of SR-BI rs838867 was also associated with increased risk (OR 1.94, 95% CI 1.16-3.24) only among premenopausal women.

Conclusions: SNPs of LDLR, CETP, and SR-BI genes were significantly associated with breast cancer risk, and the association was differed by menopausal status.

Diallyl Trisulfide Induces Apoptosis in Human Breast Cancer Cells through Ros-mediated Activation of JNK and AP-1

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Background/Purpose: Chemopreventive effects of garlic have been attributed to its oil-soluble sulfur ingredients, such as diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS), but their underlying molecular mechanisms remain largely unresolved.

Methods: Breast cancer MCF-7 cells were used for this study. The cell viability was determined by conventional MTT reduction assay. Measurement of sub-diploid DNA, phosphatidylserine externalization, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL), and western blot analysis were conducted to detect apoptosis. Accumulation of reactive oxygen species (ROS) in MCF-7 cells treated with allylsulfides was monitored using the fluorescence generating probe DCF-DA. To measure the mitochondrial transmembrane potential (μm), the lipophilic cationic probe TMRE was used. Pharmacological inhibitors of JNK, transfection of the cells with dominant negative JNK, and N-acety-L-cysteine were used to determine the relationship between activation of JNK and ROS generation in the cells treated as determined by kinase assay and western blot analysis. Immunocytochemistry was conducted to detect the expression and nuclear localization of c-jun.

Results: In the present study, we have compared the anti-proliferative effects of DAS, DADS, and DATS in human breast carcinoma (MCF-7) cells. When MCF-7 cells were treated with each of aforementioned allylsulfides, DATS showed most potent anti-proliferative effects. MCF-7 cells treated with DATS (50 μM) underwent apoptotic death as revealed by a progressive increase in the sub-G0/G1 cell population, a typical pattern of annexin V/propidium iodide staining, positive TUNEL staining and perturbation of the mitochondrial transmembrane potential (μm). DATS induced down-regulation and phosphorylation of Bcl-2, and increased expression of Bax in MCF-7 cells. DATS treatment preferentially inactivated ERK1/2 and Akt, but activated c-jun N-terminal kinase (JNK). DATS-induced apoptosis was blunt-

ed in MCF-7 cells treated with a specific JNK inhibitor SP600125 or transiently transfected with dominant negative JNK. DATS treatment resulted in enhanced accumulation of reactive oxygen species. DATS-induced apoptosis as well as activation of JNK was abrogated by the antioxidant N-acetyl-L-cysteine (NAC). Furthermore, DATS induced phosphorylation or expression of c-Jun, which were attenuated by NAC treatment. DATS treatment also led to increased DNA binding activity of AP-1, which was blocked by NAC and the JNK inhibitor. The proapoptotic effects of DATS were blunted by transfection of the MCF-7 cells with the antisense oligonucleotides for c-Jun. We also observed that oral administration of 5 μ mole/kg DATS to female Balb/c mice three times a week for 12 weeks inhibited the growth of human MCF-7 cell tumor xenografts by up to 86%.

Conclusions: These results suggest that DATS-induced apoptosis is mediated by ROS capable of activating JNK and AP-1.

Application of Skin Adhesiolysis Manipulation for the Limb Function Rehabilitation in Post-Operative Breast Cancer

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Background/Purpose: Along with the improved survival rates, the recovery of upper limb activities of daily living (ADL) has become an important issue in postoperative breast cancer patients. To assess safety and efficacy of Skin Adhesiolysis Manipulation (SAM) for function rehabilitation of affected limbs after operation, further improving patients' ADL.

Methods: 123 depressed breast cancer patients received different types of surgery, failed normal rehabilitation treatment in more than six months. Average age 43 (32-75) years old, 117 received chemical therapy, 24 received radiotherapy, 68 received endocrinotherapy. Radical mastectomy, 19; Modified radical mastectomy, 99; Breast-conserving surgery, 10; Bilateral breast cancer operation, 5. SAM created by the author in clinical practice exerts adhesiolysis on correlated skin area through lifting, pushing and sliding. Generally one needed three to six times of procedures. The results were compared before and after manipulation by far infrared thermometer.

Results: 1. After treatment, function of shoulder joints was improved in 90% patients, with 30% complete response and 60% partial response. Local pain was relieved in 85% patients, with 40% complete relief and 45% partial relief. Lymphedema in upper limbs was eliminated in 40% patients, with 6% complete elimination and 34% partial elimination. 2. We found through far infrared thermometer measurement, skin temperature was increased after treatment significantly.

Conclusions: SAM was completely effective and safe for the recovery of upper limb ADL in postoperative breast cancer patients. Whether long or shortly after operation, it is an expedient, economic and easy-to-apply new method, suitable for our country. It needs further consummation and investigation in some aspects.

Chinese Validation Study of Genesearch® Breast Lymph Node Assay for the Diagnosis of Sentinel Lymph Nodes of Breast Cancer: CBCSG-001A

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Background/Purpose: With the adoption of sentinel lymph node (SLN) biopsy as the standard of care, there is an increasing need for the rapid and accurate intra-operative diagnosis of SLNs. CBCSG-001A is a prospective multicenter trial to validate the GeneSearch® Breast Lymph Node (BLN) Assay in China.

Methods: Started from February 2009, CBCSG-001A is being conducted at 6 centers with a total enrollment of 540 cases by June 2009. SLNs are cut into alternating ~2 mm sections. One half of the sections are sampled for H&E. The other half is fully tested with the BLN assay. The assay detects the presence of cytokeratin-19 and mammaglobin to assess if metastases are in SLNs. Predetermined cutoffs are calibrated so only metastases >0.2 mm are detected.

Results: Interim results are based on 20% (114/540) of the planned cases for the study. Current histologic positive rate is 30%. The BLN assay shows high performance as compared to H&E. The results are also very similar to those seen in the US validation trial.

Conclusions: Interim results indicate that the BLN assay has high performance as compared to H&E, indicating the assay performance is fairly robust with the advantage of being an intra-operative, objective and standardized test that examines a larger portion on the nodal tissue, and allowing simultaneous axillary lymph node dissection, if needed. The results of 550 cases will be presented at the GBCC2009 & 7th ABCS.

Study ^a	N ^a	Sensitivity ^a (95% CI) ^a	Specificity ^a (95% CI) ^a	PPV ^a (95% CI) ^a	NPV ^a (95% CI) ^a
Chinese Validation Study ^a	114 ^a	91% ^a (76-98) ^a	93% ^a (84-97) ^a	84% ^a (68-93) ^a	96% ^a (89-99) ^a
US Validation Study ^a	416 ^a	88% ^a (80-93) ^a	94% ^a (91-97) ^a	86% ^a (79-91) ^a	95% ^a (92-97) ^a

Fig. 1.

Immunoprofile of Sentinel and Axillary Nodes in Early Breast Cancer

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Background/Purpose: Sentinel lymph node (SLN) biopsy allows recognition of the first lymph node into which a primary tumor drains. While lymph node metastasis is among the most important predictors of disease-free and overall survival for patients with breast cancer, the immunological nature of tumor-draining lymph nodes is often overlooked.

Methods: We performed immunohistochemical analysis of 193 sentinel nodes and axillary lymph nodes from 55 early breast cancer (T1/T2 and N0/N1) patients who were done SLN biopsy or followed axillary dissection between 2000 and 2003 with 5-year follow-up to determine if alterations in CD4, CD8 and CD1a cell populations predict distant metastasis or disease-free survival and retrospectively evaluated clinical data.

Results: Recurrent disease developed in 6 (42.9%) of 14 patients during follow-up of 5 y; 2 of 6 occurred at distant sites, 3 developed locoregional relapse, and one recurred both at a distant site and locally. Group 2/3 Patients correlated with disease recurrence and distant metastasis more closely than group 1 patients ($P=0.003$). Expression of CD1a was decreased in the group 2/3 patients than group 1 patients and there was a statistical significance ($P=0.0424$). Among group 1 patients, there was a statistical significance between tumor size and CD1a, CD8 expression (CD1a, $P=0.0097$ and CD8, $P=0.0324$).

Conclusions: We can recognize that expression of CD1a was decreased in the group 2/3 patients than group 1 patients. And the larger the tumor size is, the more the expression of CD1a, CD8 is increased in group 1 patients. Analysis at 10-year post-surgery is required to investigate the association further.

Papillary Lesions Diagnosed by Core Needle Biopsy

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Background/Purpose: Papillary lesions of the breast include a broad spectrum of lesions from benign papillomas to papillary carcinomas. It is difficult to determine whether a lesion is benign or malignant, based on the fragmented materials by core needle biopsy (CNB). The aim of this study was to evaluate the patients with papillary lesion obtained by CNB.

Methods: We retrospectively reviewed 33 papillary lesions diagnosed by CNB between 2004 and 2007. Clinical findings of papillary lesions were compared between benign and malignant lesion.

Results: An average age was 48.9 years old. 12 patients presented with discharge and 8 patients presented with a lump. 8 patients were asymptomatic. The initial diagnosis on CNB of the 33 lesion was 24 intraductal papillomas, 4 intracystic papillomas, 3 papillomas and 2 adenomas. After CNB, excisional biopsy was carried out for 22 patients and biopsy by Mammotome was carried out for 2 patients. Periodical follow up was carried out for 9 patients. Five (15.2%) of 33 patients with papillary lesions were finally diagnosed as breast cancer. Average distance from the nipple to the tumor diagnosed as malignant was 2.46 cm, which was longer than that diagnosed as benign.

Conclusions: Finally 5 papillary lesions (15.2%) were diagnosed as a breast cancer. It is necessary to perform surgical excision for papillary lesions to avoid missing a malignancy, especially for papillary lesions located far from the nipple.

Regional Lymph Nodes Irradiation after Neoadjuvant Chemotherapy and Surgery in PET Positive Clinical N3 Breast Cancer Patients

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Background/Purpose: To evaluate the efficacy of regional lymph nodes irradiation after neoadjuvant chemotherapy (NEO) and surgery in PET positive clinical N3 (cN3) breast cancer patients.

Methods: PET positive 55 patients with ipsilateral infraclavicular or internal mammary (IMN) or supraclavicular (SCL) lymph nodes were analyzed. The clinical nodal stage at diagnosis was cN3a in 14, cN3b in 12 and cN3c in 29 of patients. All were treated with curative intent NEO, mastectomy or breast-conserving surgery, and radiotherapy (RT). RT was comprised of 60.4 Gy to breast combined with 45~50.4 Gy to SCL for all patients. Additional 5-20 Gy boost RT to PET+SCL or RT coverage of PET+IMN was performed at physician's discretion.

Results: At a median follow-up of 38 months (9-80 months), 20 patients (36.4%) had developed treatment failures. All treatment failures included distant metastases, among which one ipsilateral breast recurrence, six regional failures (RF) and one both IBR and RF were combined. Only four patients (7.2%) failed at initial PET+cN3 lymph nodes. The 5-year locoregional relapse-free survival (LRRFS), disease-free survival (DFS), and overall survival rate was 80.1%, 59.6% and 78.5%, respectively. The SCL dose >55 Gy for cN3c patients did not affect SCL-relapse free survival or 5y DFS, as did not those with RT coverage of IMN for cN3b.

Conclusions: RT including regional lymph nodes after NEO and surgery achieved excellent locoregional control for patients with PET positive cN3 breast cancer patients. Additional boost RT to PET+SCL or coverage of PET+ IMN did not show the additional gain in LRRFS or DFS.

Scalp-Cooling by Dignicap™ System for the Prevention of Chemotherapy-Induced Hair Loss in Breast Cancer Patients

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Background/Purpose: The DigniCap™ system (Dignitana AB, Sweden; Hair Clinic Reve21, Japan) is an established, highly effective and safe device to prevent hair loss by cooling the scalp. This study evaluates the DigniCap™ system and presents the results of scalp hypothermia on breast cancer patients undergoing chemotherapy.

Methods: DigniCap™ is using a digitized system for controlled scalp-cooling with a refrigerator integrated into a control unit with the soft and tight-fitting silicon cap. Scalp temperature was maintained at +5 centigrades throughout drug administration and for at least 30 min after discontinuing the infusion. Photographs of each patient's scalp were taken before starting chemotherapy. The evaluation was made using a visual analogue scale. All patients answered a questionnaire with 15 questions regarding physical and psychological issues.

Results: From August 2007 to May 2009, 203 patients, aged 25-77 yrs (mean 48.7), with breast cancer were examined completely. The patients were treated with either Paclitaxel (60 mg/m² weekly) plus Cyclophosphamide (500 mg/m²) (146 patients) or Paclitaxel plus Herceptin combination (27 patients) or Epirubicin (40 mg/m² biweekly) plus Cyclophosphamide (18 patients). Remaining 12 patients were treated either combination by 5FU, CPT-11, Endoxan and CBDCA. The results were as follows: 119 patients (58.6%) were classed as grade 0, 52 patients (25.6%) as grade 1, 30 patients (14.8%) as grade 2 and 2 patients (1.0%) as grade 3.

Conclusions: DigniCap™ system using scalp-cooling is effective method to prevent chemotherapy-induced hair loss in patients with cancer of the breast.



Fig. 1. The image of Dignicap.

Nodal Ratio is Superior to Absolute Number of Positive Nodes in Prognostication: A Long-Term Study of 1-2 Nodes in T1-2 Breast Cancer Patients

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Background/Purpose: Nodal ratio (NR) is defined as the absolute number of involved nodes to the number of nodes examined. Previous reports in breast cancer have generally analyzed patients with 1-3 positive lymph nodes as a single group often leading to controversy in practical clinical applicability. This study separately analyzed the survival outcomes among T1-2 breast cancer patients based on whether 1 or 2 axillary nodes were pathologically positive.

Methods: Records of 5,996 patients were available for analysis from the population-based Canadian Saskatchewan provincial registry for the period from 1981 through 1995. Since the reliability of nodal assessment depends on the number of nodes sampled, only those 613 patients staged as T1-2, with ≥ 8 nodes examined were further analyzed for overall (OS) and cause-specific survival (CSS). There were 378 patients with 1 involved node, with NR range of 0.03-0.13. Among 235 patients with 2 involved nodes, 110 had a NR of ≤ 0.15 and the remaining 125 patients have a NR of 0.16-0.25.

Results: Patients with 1 and 2 positive nodes had similar survival but CSS was significantly different using NR as a prognosticator (see figure). Patients with NR less than or equal to 0.15 have better prognosis.

Conclusions: NR is superior to absolute number of nodes in our current staging system to separate patients with 1 or 2 positive nodes. The survival data among patients with 1-2 nodes positive reveals clearly relevant differences when separately analyzed. This may affect adjuvant treatment decision-making.

Overall Survival	1 node	2 nodes	NR \leq 0.15	NR=0.16-0.25
5-years	83%	77%	82%	74%
10-years	65%	61%	65%	58%
15-years	49%	48%	50.0%	45%
P value	0.34		0.11	
Cause-specific survival	1 node	2 nodes	NR \leq 0.15	NR=0.16-0.25
5-years	89%	82%	89%	77%
10-years	79%	73%	79%	69%
15-years	73%	69%	73%	64%
P value	0.12		0.01	

Fig. 1. Overall and cause-specific survival rates.

Underweight and Breast Cancer Recurrence and Death: A Report from the Korean Breast Cancer Society

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Background/Purpose: The association between body mass index (BMI) and breast cancer outcome is controversial. Furthermore, the impact of underweight on breast cancer recurrence and death has not been adequately addressed.

Methods: We investigated this issue using a large nationwide database of 24,698 Korean breast cancer patients. This association between body weight status and breast cancer recurrence was further explored using a single institution database containing information on 4,345 patients.

Results: The results from the nationwide database showed significantly lower overall survival (OS) and breast cancer-specific survival (BCSS) in underweight patients compared to those of normal weight after adjusting for known prognostic factors such as age, tumor size, lymph node metastasis, hormone receptor status, histologic grade, and lymphovascular invasion (hazard ratios=1.48 [95% CI 1.15-1.90] for OS and 1.49 [95% CI 1.15-1.93] for BCSS), which were not observed in obese patients. In an analysis of recurrence data from the single institution, underweight women had a significantly higher risk both of distant metastasis and local recurrence of breast cancer (hazard ratios=1.93 [95% CI 1.04-3.58] and 5.13 [95% CI 2.66-9.90], respectively).

Conclusions: Our study suggests that underweight should be considered to be a high risk factor for death and recurrence after breast cancer surgery, especially in Asian breast cancer patients.

Prognostic Impact of [18F] FDG-PET in Operable Breast Cancer Treated with Neoadjuvant Chemotherapy

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Background/Purpose: This study aimed to evaluate the usefulness of serial positron emission tomography (PET) in operable breast cancers receiving neoadjuvant chemotherapy.

Methods: Serial PET was undertaken in 66 breast cancer patients who comprised a subset of the population in a phase III, randomized neoadjuvant trial at National Cancer Center, Korea. We assessed the peak standardized uptake value (SUVp) before/after neoadjuvant chemotherapy and calculated the reduction rate (RR) of SUVp. Using a receiver operating characteristic curve, we identified an optimal cut-off value of RR for predicting the pathologic response and evaluated the prognostic power of this value.

Results: Ten patients (15.2%) achieved a pathologic complete response (pCR) in primary tumor. The mean RRs of SUVp in primary tumors were statistically different by pathological response (89.2% in pCR vs. 66.9% in non-pCR, $p < 0.001$). When 84.8% of RR was used as a cut-off value for predicting pCR, sensitivity and specificity was 70.0% and 69.6%. Ten patients (15.2%) developed recurrence with a median follow-up period of 61.5 (range: 13.5-71.8) months. In univariate analysis, disease free survival (DFS) rate was correlated with clinical T stage (91.1% in T1/2 vs. 71.4% in T3/4, $p = 0.02$), HER2 status (77.8% in positive vs 96.9% in negative, $p = 0.03$), and the 84.8% RR of SUVp (95.8% vs. 78.5%, $p = 0.04$). HER2 positivity was a significant independent prognosticator in multivariate analysis (HR 8.73, 95% CI; 1.03-73.84, $p = 0.04$).

Conclusions: The RR of SUVp in primary tumor was correlated with pathologic response and DFS. This study suggests the possible prognostic value of the RR in PET by neoadjuvant chemotherapy.

Characteristics of Fluorine-18 Fluorodeoxyglucose/ Positron Emission Tomography Imaging on Triple-Negative and ER-Positive/PR-Positive/ HER2-Negative Breast Cancers

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Background/Purpose: In this study we investigated Fluorine-18 Fluorodeoxyglucose/Positron Emission Tomography Imaging parameters of triple negative (TN) breast cancers and compared the results with ER+/PR+/HER2- breast cancers showing favorable prognosis.

Methods: 189 breast cancer patients who had undergone dual-time-point FDG-PET before any treatment from April 2008 to April 2009 and were identified as either TN (51 patients) or ER+/PR+/HER2- (control group, 138 patients) through tissue biopsy, were analysed Breast cancer lesions were imaged twice at 60 minutes and 180 minutes after administration of FDG. Maximum standardized uptake values (SUVmax) were measured at both time points (SUVmax1 and SUVmax2) In addition, we evaluated tumor size, histopathologic subtype, grade and stage, and compared with SUVmax1 and SUVmax2.

Results: In the TN group (26.9%), mean age was 52 years, mean tumor size was 2.89 cm and 44 cases were invasive ductal carcinomas. Based on the calculation FDG-PET parameters of both subtypes, the mean SUVmax1 of the primary lesion for the TN group was 4.17, the mean SUVmax2 was 2.66. In the control group, the mean SUVmax1 and mean SUVmax2 were 2.96 and 2.11, respectively. SUVmax1 in the TN group was significantly higher compared with the values in the control group ($p=0.001$). Comparison between the 2 subgroups demonstrated a statistically high significant difference in tumors that measured ≤ 2 cm ($p=0.017$). In the TN group grades were not correlated with SUVmax1. According to stages, the TN group appeared to have a higher mean SUVmax1 compared with the values in the control group.

Conclusions: TN breast carcinomas were associated with enhanced FDG-PET imaging representing aggressive biology, which were detected with high sensitivity.

Disease Free Survival Significantly Prolonged in ER- Breast Cancer Patients on UFUR® (Tegafur-Uracil) Maintenance after Adjuvant Chemotherapy- A Retrospective Analysis

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Background/Purpose: The purpose of this retrospective study is to document disease free and overall survival of breast cancer patients who received 6 months UFUR® as maintenance chemotherapy after standard adjuvant chemotherapy.

Methods: Early breast cancer patients from 3 hospitals were given unselected conventional multi-agent combination chemotherapy after curative resection. This was followed by maintenance chemotherapy of 200-400 mg/day UFUR® (Tegafur-Uracil) for at least 6 months. A retrospective analysis for disease free survival and overall survival was performed and the patients were stratified according to ER, PR, and staging.

Results: From February 2002 to December 2008, a total of 173 eligible breast cancer patients were enrolled on study. Stage I/II/III cases made up 30%/50%/20% of the patient population and 70% of cases were ER- or PR-, with potentially higher risk of recurrence. The 3-yr disease free survival rate was 84% overall, and 89%, 84% and 77% for stages I, II, and III patients respectively. The survival results are superior to that of the historical control. When DFS and OS were stratified by ER and PR expression, ER⁺ patient had a significantly improved in disease free survival than ER⁺ patient.

Conclusions: In this retrospective analysis, ER- patients shown to have benefit significantly from UFUR maintenance therapy with prolonged disease free survival, as comparable to ER⁺ patients. The present results suggest that UFUR maintenance therapy in ER- breast cancer patient for 2 years, can be consider as a safe and well tolerated regimen. Larger and prospective trial should be considered for ER- and Triple negative breast cancer patient.

A Risk Stratification by Hormonal Receptors (ER, PgR) and HER-2 Status in Small (≤ 1 cm) Invasive Breast Cancer: Who Might be Possible Candidates for Adjuvant Treatment?

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Background/Purpose: As the use of screening mammography expands, the proportion of cases of invasive breast cancer ≤ 1 cm is increasing. The aims of this study were: 1) to identify risk factors for systemic metastases in patients with ≤ 1 cm invasive breast cancer and 2) to investigate the patient groups at the greatest risk for metastases with such small tumors.

Methods: Data were collected retrospectively from the breast cancer registry of our institution for patients with invasive breast cancer from October 1994 to December 2004.

Results: Of 4,036 patients who received curative breast cancer surgery, we identified 427 patients who had T1a or T1b breast cancer excluding 39 patients who received neoadjuvant chemotherapy. Ipsilateral axillary lymph node involvement was found in 13% (57/427) of patients at the time of surgery. A multivariate analysis was conducted in 370 (T1aN0, T1bN0) patients without lymph node involvement. In a Cox-regression model, HER-2 positive and triple negative groups were identified as independent risk factors to predict DRFS (Hazard ratio [HR] 8.8, $p=0.003$ for HER-2 positive group; HR 5.1, $p=0.026$ for TN group) in T1bN0 tumors. Statistical significance was not maintained when the analysis was limited to T1aN0 tumors.

Conclusions: Even though T1aN0 and T1bN0 tumors have a relatively low risk of systemic failure, anti-HER-2-directed therapy for HER-2 group and new innovative adjuvant systemic treatment for TNBC patients with T1bN0 tumors should be considered. Prospective adjuvant trials are warranted in these subgroups of patients.

The Development and Comparison of Breast Cancer Recurrence Prediction Model

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Background/Purpose: The purpose of this study is to develop prediction model using data mining technique and to compare the accuracy of the purposed model versus Adjuvant! online for recurrence prediction of breast cancer.

Methods: Data from 631 patients with breast cancer from the department of surgery of ajou university hospital were collected and recorded during the period 1994-2007 years. 8 among 64 variables were selected with Pearson chi-square test and medical expert advises (Fig. 1). To obtain a reliable estimate of model accuracy applied the holdout method that divided into 438 patients for training and 193 patients for testing. Purposed model was developed using Support Vector Machine (SVM). Since Cox regression is the most popular algorithm to build a predictive model for time-to-event data, this study compared accuracy with Cox regression. We also compared the accuracy with the well-known Adjuvant! online for recurrence prediction of breast cancer.

Results: The recurrence probability for each patient in the test set was calculated using each model (purposed model, Adjuvant! online). The predictive accuracy of each model was computed using the area under ROC curve (AUC). The purposed model (AUC=0.842) was higher AUC than Cox regression model (AUC=0.648) and Adjuvant online (AUC=0.7) (Fig. 2).

Conclusions: The Purposed model based on SVM showed very efficient with Adjuvant! online when applied to predict recurrence of breast cancer.

Table 1. Characteristics of Patients

Variables	Non-Recurrence	Recurrence	p-Value
Age	46.5±11.3	46.2±12.2	0.27
Histological Grade			< 0.0001
Grade 1	63(19.33%)	10(5.99%)	
Grade 2	153(46.93%)	68(40.72%)	
Grade 3	110(33.74%)	89(53.29%)	
Local Invasion of Tumor			< 0.0001
Yes	12 (2.99%)	48 (26.67%)	
No	389 (97.01%)	132 (73.33%)	
Her2			<0.05
Positive	136(60.18%)	64(51.2%)	
Negative	90(39.82%)	61(48.8%)	
Number of Tumor	1.00±0.32	1.22±0.79	< 0.0001
Tumor Size (cm)	3.09±2.42	4.05±3.5	< 0.0001
Lymphovascular Invasion			< 0.0001
Yes	83(44.15%)	78(65%)	
No	105(55.85%)	42(35%)	
Estrogen Receptor			<0.05
Positive	228(67.86%)	94(58.02%)	
Negative	108(32.14%)	68(41.98%)	
Number of Metastatic Lymph Node	2.2±5.7	7.3±10	< 0.0001

Fig. 1. Characteristics of Patients.

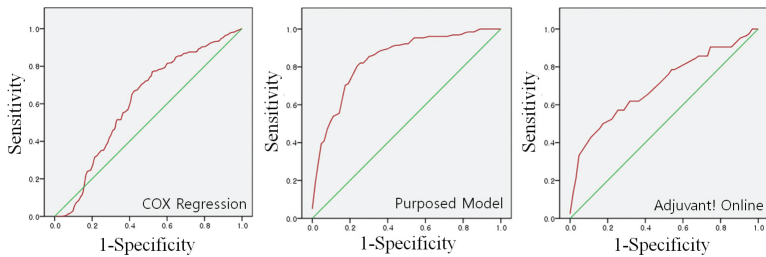


Figure 1. Receiver operating characteristic (ROC) curves of purposed model, Cox regression, and Adjuvant! online

Fig. 2. ROC curves of purposed model, Cox regression, and Adjuvant online.

Lapatinib Combined with Letrozole vs. Letrozole Alone for Front Line Postmenopausal Hormone Receptor Positive (HR +) Metastatic Breast Cancer (MBC)

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Background/Purpose: EGF30008 is a double-blind, placebo-controlled, first-line phase III trial with letrozole +/- lapatinib in pts with HR+ postmenopausal MBC to see if lapatinib enhances endocrine responsiveness and delay the onset of resistance.

Methods: 1286 postmenopausal women with HR+ untreated MBC were randomized to letrozole 2.5 mg/day +/- lapatinib 1,500 mg/day with stratification factors 1) visceral vs bone only disease and 2) time since completion of prior adjuvant endocrine tamoxifen therapy (<6 mo or 6 mo/never received). 219 pts were ErbB2+ (IHC 3+ and/or FISH amplified). The primary and secondary endpoints included PFS in the HR+ ErbB2+ population and that in the overall ITT population in closed hierarchical testing procedure.

Results: Median PFS in the ErbB2+ population was increased from 3.0 mos in the letrozole group to 8.2 mos in the lapatinib+letrozole group (HR 0.71, p=0.019). Median PFS in the ITT population increased from 10.9 mos to 11.9 mos, respectively (HR 0.86, p=0.026). ORR in the ErbB2+ population was significantly increased from 14.8% to 27.9% in the combination group (OR 0.4, p=0.021), with a clinical benefit rate (CBR) improvement from 28.7% to 47.7% (OR 0.4, p=0.003). With 41% of pts still being followed, a possible overall survival trend as analyzed by Cox model was noted in the ErbB2+ group (HR 0.77, p=0.185). The combination of letrozole and lapatinib was well tolerable and manageable.

Conclusions: Through combined endocrine and targeted ErbB1/ErbB2 inhibition, lapatinib significantly improved the clinical efficacy of an aromatase inhibitor in patients with known HR+HER2+MBC.

The Effect of Breast Self-examination Program for Young Korean Women Instructed by Breast Cancer Survivors

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Background/Purpose: With the prospect of increasing incidences of breast cancer worldwide, the situation of women with breast cancer in Korea is worse than those of developed countries. First of all, the rate of early detection of breast cancer is low. Second, the incidence rate of breast cancer in young women is higher in Korea. Thus, breast self examination (BSE) would play an important role in screening and detecting breast cancer in an early stage. The purpose of the study was to evaluate the effect of BSE educational program given by breast cancer survivors who were educated to perform as instructors.

Methods: The study used a one group only experimental design. The subjects were asked about their health belief, self efficacy, and performance of BSE along with knowledge and attitude on BSE before the class, and 1 and 3 months after the class. A total of 102 young women enrolled in the first class, however 34 responded at the 2nd mail survey and 25 to the 3rd survey.

Results: Average age was 24.8 years. BSE knowledge, self-efficacy, and attitude improved significantly. The health belief score had increased, though statistically insignificant. Knowledge was a main variable to correlate other variables.

Conclusions : The results of the study suggest that the BSE program instructed by breast cancer survivors should be expanded nationwide in order to increase awareness of breast cancer and to increase BSE practice among healthy young women in Korea.

A Study of Validation of the Quality of Life Family Version (QOL-F) for Spouse of Women with Breast Cancer in Korea

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Background/Purpose: The aims of this study were to adapt culturally and to evaluate its construct validity of the English version of the QOL-F developed by Ferrell (2000).

Methods: This study design was descriptive study. We have evaluated by exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) for construct validity. The sample consisted of 201 spouses of women with breast cancer. Data were collected between February, 28 and April, 30, 2008 using structured self-report questionnaire including demographic characteristics and QOL-F at one university hospital in Seoul. Collected data were analyzed by SPSS 12.0 Win program for descriptive statistics, Common factor analysis for construct validity and Cronbach's alpha coefficient for reliability.

Results: Six factors were identified with eigenvalues >1, explained 58.79% of the total variance. Based on findings from the EFA, a five-factor was tested for the CFA. Extracted five factors were explained 55.76% of the total variance and the range of factor loadings was 0.444~0.893. Internal reliability coefficients of these five factor-based scales, 30 items, were found to be substantial, ranging from 0.78 to 0.95. Certain items such as overall physical health, initial diagnosis distress, support from others, overall social well being, religious activities, personal spiritual activities, positive changes in life were deleted from the extraction of factors in this study.

Conclusions: The QOL-F had good construct validity and reliability and could be used to measure quality of life of spouse of women with breast cancer in Korea. This scale should be further evaluated in different regions relating to cultural differences.

A Pharmaco-Economic Analysis of Inoperable Advanced Breast Cancer (ABC) Patients Receiving Capecitabine in Taiwan

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Background/Purpose: Capecitabine is currently the only treatment licensed for patients who failed anthracyclines and taxanes in Taiwan. The aim of this study was to investigate the healthcare resource utilization and direct medical costs of ABC patients treated with capecitabine in Taiwan from the Bureau of National Health Insurance (BNHI) perspective.

Methods: A retrospective year-cohort design was used with data from the National Health Insurance Research Database (NHIRD), which covers the entire population in Taiwan. Three year-cohorts were studied: 2004/05, 2005/06 and 2006/07 based on the year of diagnosis. A generalized linear model (GLM) was employed to compare the differences in healthcare resource utilization between groups with different duration of capecitabine use.

Results: For ABC patients treated with capecitabine for <3 months, the average annual outpatient visits and times of Capecitabine prescriptions showed an increasing trend (Fig. 1), and annual treatment fee and annual total medical cost also showed an increasing trend (Fig. 2). However, the average annual inpatient admissions showed a decreasing trend (Fig. 1) whilst the trend of annual drug cost was inconclusive (Fig. 2).

Conclusions: The total medical costs of treating inoperable ABC patients treated with capecitabine in Taiwan showed an increasing trend in recent years, which may be a result of the shift in treatments pattern from inpatient to outpatient and increasing prescriptions of Capecitabine.

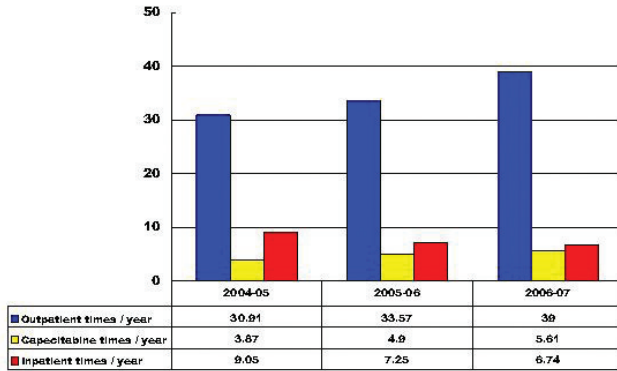


Fig. 1.

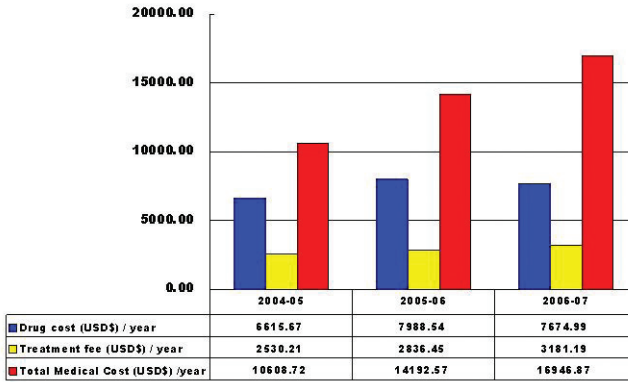


Fig. 2.

The Impact of Breast Cancer on Mother-Child Relationships in Korea

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Background/Purpose: Breast cancer is the number one cancer among Korean women, with 57.4% between the ages of 30-49. The situational crisis of a cancer diagnosis may compound the developmental task of caring for dependent children, especially in cultures such as Korea where family traditionally centers on children. However, despite growing research on parent-child relationships following a cancer diagnosis in the West, there have been no studies in Korea to identify patterns of relationship changes and meanings. The purpose of this explorative study was to explore the impact of breast cancer on Korean mothers and their children and to suggest points for practice.

Methods: This explorative study explored experiences and meanings of the mother-child relationship following breast cancer diagnosis among Korean women younger than 50 years. Following IRB approval, participants were recruited through postings, referrals, and snowballing and interviewed in-depth for 60-90 minutes. The main question posed was “What is your experience of your relationship with your child following diagnosis of breast cancer?” Interviews were recorded with participants’ consent and transcribed verbatim for content analysis to identify themes and domains following Colaizzi’s (1978) guidelines.

Results: The study is ongoing and preliminary results suggest that there are adaptation issues following diagnosis that are entwined with changes in attitudes towards children. Cultural influences are also noted, with different points of emphasis according to developmental stage of the child.

Conclusions: Findings are expected to inform health care professionals in providing relevant anticipatory guidance for Korean women with breast cancer on their relationship with their children.

The Mediating Effect of Coping on the Relation between Optimism and Psychosocial Adjustment in Korean Early Breast Cancer Women

Hyang Sook So¹, Hae Young Kim², Eun Ko³, Young Hee Noh⁴

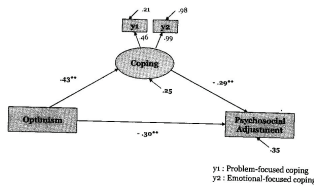
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Background/Purpose: The purpose of the study was to identify the mediating effect of coping between optimism and psychosocial adjustment in early breast cancer women. For this, we formulated a mediating model derived from the literature on optimism, coping, and psychosocial adjustment.

Methods: Subjects were 198 breast cancer women who had already had post-surgical radiation therapy or chemotherapy, and recruited from outpatient clinic of C National University Hospital in Southwestern Korea. Data were collected through self reporting questionnaires such as Life Oriented Test-Revised (LOT-R), Ways of Coping Checklist (WCCL), and Psychosocial Adjustment of Illness Scale-Self Report (PAIS-SR). Collected data were analyzed using SPSS 12.0 by correlation analysis. In addition, the goodness of fit of the mediating model was measured and directly, indirectly, and total effect of mediating effect was tested using AMOS 7.0.

Results: In the results of measuring the overall goodness of fit of the mediating model, all fitness indices showed that the model was acceptable. Also, optimism and coping had significantly direct, indirect and total effects on psychosocial adjustment. Thus, coping was found to have a partial mediating effect on the relation between optimism and psychosocial adjustment among early breast cancer women.

Conclusions: Based on the results, to enhance early breast cancer patients' psychosocial adjustment, we need to apply an intervention strengthening their coping by giving the patients positive and optimistic beliefs.



<Figure 1> The Mediating Effect of Coping between Optimism And Psychosocial Adjustment

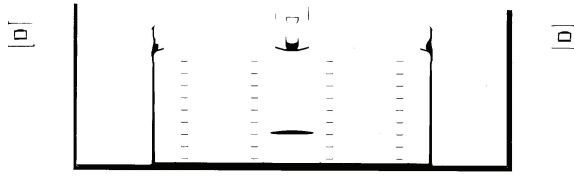
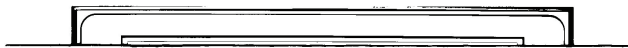


Fig. 1. The mediating effect of coping between optimism and psychosocial adjustment.



<Table 1> Effect Coefficient of Structural Model by Mediating Effect of Coping

Variables	(n=198)		
	Direct Effect	Indirect Effect	Total Effect
Coping			
Optimism	.43**	-	.43**
Psychosocial Adjustment			
Optimism	-.30**	-.13**	-.43**
Coping	-.29**	-	-.29**



Fig. 2. effect coefficient of structural model by mediating effect of coping.



GBCC 2009

Poster Discussion

Systematic Review and Meta-analysis of the Prevalence of BRCA1 and BRCA2 Germline Mutations in Women with Breast Cancer in Asia

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Background/Purpose: BRCA1 and BRCA2 germline mutations have been found to account for women's increased risk of breast cancer in White U.S. population. In this study, we assessed the prevalence of BRCA1 and 2 germline mutations in women with breast cancer in Asian countries by performing a systematic review and meta-analysis.

Methods: We searched PubMed and EMBASE for English publications since 1990. We reported a range of prevalence for each country, regardless of risk factors. Random effect meta-analysis was conducted to get pooled prevalence of BRCA1 and BRCA2 mutations and stratified by family history or early-onset breast cancer.

Results: A total of 46 papers were included in this review. Meta-analysis result showed a pooled prevalence of BRCA1 mutation of 10% and 8% for BRCA2 mutation. For breast cancer women with family history, prevalence for BRCA1 and BRCA2 mutations are 13% and 9%. For early onset breast cancer women, the prevalence for BRCA1 and BRCA2 mutations are 6% and 3%.

Conclusions: We found that the pooled prevalence of Asian population is higher than White population (2-4%), which may be due to higher proportion of high risk population included in this review. More population-based studies are needed to assess the prevalence of BRCA1 and BRCA2 mutations in women with breast cancer in Asia.

Graph 1. Prevalence of BRCA1 and BRCA2 Germline Mutations among Breast Cancer Women in Asia

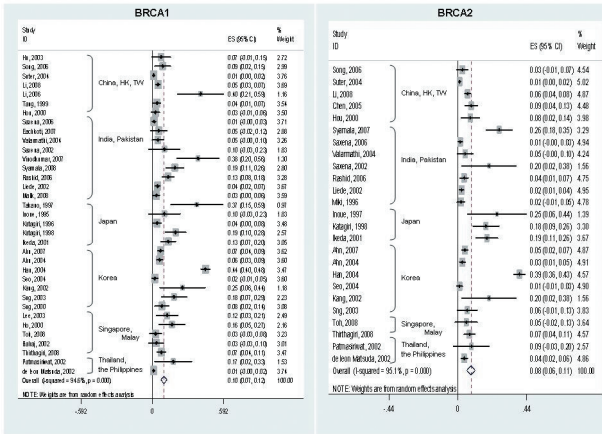


Fig. 1

Table 1. Random Effect Meta-analysis Result of Pooled Prevalence for Breast Cancer Women in Asia

	Number of studies	Prevalence [95% CI]		
		BRCA1	BRCA2	BRCA1or2
Total (regardless of risk factors)	36	0.10 [0.01-0.12]		
	25		0.08 [0.06-0.11]	
	17			0.10 [0.08-0.11]
Early onset	12	0.06 [0.04-0.08]		
	6		0.03 [0.02-0.04]	
Family history	19	0.127 [0.10-0.16]		
	12		0.09 [0.06-0.12]	
	5			0.26 [0.17-0.35]
Family history and early onset	11	0.06 [0.04-0.08]		
	7		0.04 [0.02-0.06]	
	4			0.10 [0.04-0.16]

Fig. 2

The Effect of a Community Outreach Mammogram Program for Non-insured Korean American Women

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Background/Purpose: The mammogram screening rates for Korean-American women are far below the rates for California women over the age of 40. One of the main reasons they do not get mammogram screening is due to lack of proper insurance coverage. The purpose of this study is to describe the effective collaborative community outreach program of mammogram breast cancer screening and to provide screening and detection of breast cancer in Korean American women.

Methods: Through community outreach efforts (i.e., church, small business, ethnic media) for one year, 152 women responded and received initial phone screening for eligibility of age, income, and insurance coverage, after the initial screening, 19 women were not eligible. The eligible participants received a clinical breast exam and screening mammogram at the collaborated hospital through the California Cancer Detection Program. Abnormal test results were reviewed by the study coordinator and participants were notified via phone, otherwise normal test results were mailed to the participants. The program coordinator navigated the patients who had positive test results to receive further evaluation.

Results: 133 women (mean age=50 ± 6.6) with no insurance coverage and limited English proficiency were screened. Eighteen percent (n=18) of women were recommended for further diagnostic testing due to abnormal findings, 9% (n=12) of women received additional ultrasound testing, approximately 5% of women (n=6) received biopsy, and finally 3% of women (n=4) were diagnosed with breast cancer and received surgery.

Conclusions: The community outreach program successfully detected breast cancer for non-insured women in underserved immigrant Korean-American women.

Knowledge, Attitudes, and Practice of Obstetrics and Gynecology Nurses about Breast Cancer and Breast Self-Examination

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Background/Purpose: This study aims to determine obstetrics and gynecology (OBGY) nurses' knowledge, attitudes, and practice about breast cancer and breast self-examination (BSE); and contribute to the breast health management that integrates breast-feeding with early detection of breast cancer.

Methods: This descriptive study involves 163 consented nurses in OBGY using a self-questionnaire on knowledge, attitudes, and practice about breast cancer and BSE, collected between May 11th and June 5th in 2009.

Results: The mean scores of knowledge and attitude were 71 ± 12.7 (out of 100) and 3.06 ± 4.24 (out of 5), respectively. While most nurses (99%) recognized the importance of BSE, 58.3% had performed BSE and only 5.7% performed every month. The mean practice level of BSE was 8.35 ± 1.96 (out of 12). Only 24.3% of the participants recommended BSE to clients. Knowledge and attitude were independent of participants' general characteristics. Practice level, however, showed significant differences according to marital status, breastfeeding experience, and education level. Nurses with experience of mammogram or breast ultrasonogram scored higher knowledge. Attitude was higher for nurses who received recommendation for BSE, performed BSE, received BSE education, or recommended BSE to clients; and practice level was higher for nurses who received BSE education or willing to perform BSE in future. Practice level had a positive correlation with attitude and no correlation with knowledge.

Conclusions: OBGY nurses need continuing education for practical BSE experience using high fidelity simulators. Practical BSE education can not only promote the preventive behavior of nurses, but it can also improve the breast health management of pre- and post-natal clients.

Postoperative Treatment Strategy and Follow-Up Management for Breast Cancer Patients in Korea

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Background/Purpose: The risk for recurrence of breast cancer continues over 15 years. So, adjuvant therapy and follow up examination in breast cancer are very important after surgery. We investigated current practice of post operative follow up management for breast cancer after curative resection through nationwide survey in Korea.

Methods: From December 2008 to February 2009, a questionnaire was sent out to 307 members of Korean Breast Cancer Society (KBCS). A questionnaire was composed of cover letter, general information and main questionnaire about follow-up schedules and contents.

Results: 21.2% (65/307) of the members of the KBCS returned the survey. Most common responders described that subject of follow up was department of surgery with or without adjuvant chemotherapy. Reference guidelines for decision of adjuvant therapy were similar in distribution among NCCN, ASCO and KBCS guidelines. Most common follow up schedule was every 6months exam for first 5 years after primary surgery and then annually exam. Mammogram, sonogram, bone scan were tend to consider essentially and PET CT, MRI were considered alternatively. CA15-3, CEA and some of blood chemistry were also essential orders in most responders.

Conclusions: It seems that clinicians treating breast cancer in Korea showed some different trend with international guidelines. Therefore, a multicenter randomized trial is needed to confirm the different modality for follow up and our results could give an aid to design such study.

The Korean Hereditary Breast Cancer (KOHBRA) Study: Protocols and Interim Report

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Background/Purpose: The primary aims of KOHBRA study are to estimate the prevalence of BRCA1/2 mutation and ovarian cancer among the high risk group of hereditary breast cancer patients and their families.

Methods: The KOHBRA study is a prospective multi-center cohort study for cases and their families. From May 2007 to May 2010, the KOHBRA study is planning to enroll about 2000 subjects. All participants have been receiving BRCA genetic testing and counseling and collecting clinical information and blood sample for blood banking. Interim analysis of the prevalence of BRCA1/2 mutation and the prevalence ovarian cancer in Korean was done from initial 975 patients.

Results: From 33 centers, total 220 mutation carriers (51 unaffected) were identified. One hundred eighty three family members were enrolled from 156 families. Among 428 patients with family history of breast/ovary cancer 106 patients had BRCA mutation (24.8%). For early onset (<35) breast cancer patients without family history, the prevalence of BRCA mutation was 11.3% (24/212). The prevalence of BRCA1/2 mutation was 25.5% (17/68) in bilateral breast cancer patients, 8.3% (1/12) in male breast cancer patients, 33.4% (1/3) in patients with breast and ovarian cancer.

Conclusions: This results in interim analysis suggest that the prevalence of BRCA mutation in Korean is similar to that of Western country and the study population in this interim analysis is the largest number among non-Jewish Asian data examined BRCA1 and BRCA2 until now. More confident prevalence of BRCA mutation will be available after the completion of the KOHBRA study.

Breast Cancer: 8 Year Experience of South Egypt Cancer Institute (SECI)

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Background/Purpose: To study the characters of breast cancer in south Egypt cancer institute and study the change in surgical management.

Methods: It is retrospective study conducted on patients with breast cancer admitted to south Egypt Cancer Institute during the period from 2001 to 2008. Each patient reviewed for gender, age, laterality, presenting symptoms, clinical and pathological staging, operative procedure, histopathology types.

Results: During this period 616 patients with breast cancer were admitted to SECI, 40 patients were admitted during year 2001 with steady increase in incidence 124 patients were admitted during year 2008. 588 (95.5%) patients were female and 28 (4.5%) patients were male, the age range from 23-85 years with the mean age 47 years, left side was affected in 335 (54%) patients, right side was affected in 270 (44%) patients while bilateral cases affect 11 (2%) patients, 226 (37%) patients were either single or divorced or widow while 390 (63%) patients were married. 590 patients presented by breast lump, stage I 70 (11.4%), stage II 340 (55.2%), stage III 152 (24.7%), stage IV 50 (8.1%). Modified radical mastectomy was done in 511 (83%) patients, 40 (6.5%) underwent breast conservative surgery, latissimus dorsi flap reconstruction done in 12 (2%), pedicle tram flap reconstruction in 23 (3.7%) patients. Histopathological finding, infiltrated duct carcinoma 520 (84.4%).

Conclusions: The incidence of breast cancer is steady increase with tendency to occurs in younger age groups and with advanced stages in Egypt, in recent years the we gradually shifted to more conservative and reconstructive surgical techniques.

Chinese Women's Breast Cancer Screening and Health Promoting Behavior

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Background/Purpose: The purpose of this study was to identify the present state about breast cancer screening and the relationship between breast cancer screening and health promoting behavior of Chinese women whom located in 5 cities (The west coast, Beijing, Shanghai, Yanji, Guangzhou) in China.

Methods: This study was a cross-sectional study. Data were collected using self-reported questionnaire consist of general characteristics, items about breast cancer screening and HPLP. Participants were 1,290 women who live in China. Data were analyzed with SPSS Win 14.0 program using descriptive statistics and Person's correlation coefficient.

Results: 57.6% of women were performed breast cancer screening. Types of breast cancer screening were breast self examination (37.4%), sonogram (30.4%), mammography (19.2%). And 45.3% of women was received an education about breast cancer screening. Among those who participated in breast cancer screening, the score of health promoting behavior was higher than those who didn't ($t=3.024$, $p=0.003$).

Conclusions: These results suggest the needs for education about importance of breast cancer screening and health promoting behavior in China.

Estrogen Receptor α Induces Down-regulation of PTEN through PI3K Activation in Breast Cancer Cells

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Background/Purpose: Breast cancer cells do express estrogen receptor- α (ER α) and ER β . ER α stimulates growth signal involving PI3K/Akt in breast cancer cells and PTEN is one of the major tumor suppressors. Recently it has been known that ER α directly activates PI3K, its downstream effector is inhibited by PTEN. Here, we investigated whether ER α overcomes PTEN inhibition through PI3K activation in breast cancer cells.

Methods: Human breast cancer cell lines (MCF-7 and MDA-MD-231) were obtained from the American Type Culture Collection (Rockville, MD, USA). The effect of ER α and PI3K on PTEN expression in breast cancer cell lines were analyzed by Western blots and real-time PCR.

Results: Inhibition of PI3K with wortmannin caused a dose-dependent increase in PTEN levels of ER α positive MCF-7 cells, but those of ER α negative MDA-MB 231 cells were not changed, suggesting that ER α induces down-regulation of PTEN through PI3K activation in ER α -positive breast cancer cells. We found that MCF-7 cells revealed low PTEN protein levels compared to MDA-MB 231 cells, which was correlated with high levels of p-Akt and PIP3. However, PTEN mRNA expression showed no differences in both cells. Interestingly, CK2 (casein kinase 2) and p-PTEN level of MCF-7 cells were low compare to that of MDA-MB 231 cells, indicating that PTEN of MCF-7 cells has low stability compared to MDA-MB 231 cells.

Conclusions: The results presented here provide the first evidence that ER α /PI3K signaling regulates stability of PTEN in breast cancer cells. Our findings may also help therapeutic strategy for ER α positive breast cancer.

Silibinin Prevents 12-O-Tetradecanoyl Phorbol-13-Acetate-Induced MMP-9 and VEGF Expression by Inactivation of the RAF/MEK/ERK Pathway in MCF-7 Human Breast Cancer Cells

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Background/Purpose: Matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF) expression are pivotal steps in cancer metastasis. Herein, we investigated the effect of silibinin on 12-O-tetradecanoyl phorbol-13-acetate (TPA)-induced MMP-9 and VEGF expression in MCF-7 human breast cancer cells.

Methods: The expression of MMP-9 and VEGF in response to TPA was increased, whereas TPA-induced MMP-9 and VEGF expression was decreased by silibinin. To investigate the regulatory mechanism of silibinin on TPA-induced MMP-9 and VEGF expression, we pretreated cells with various inhibitors, such as UO126 (MEK1/2 inhibitor), SP600125 (JNK inhibitor), and SB203580 (p38 inhibitor).

Results: Interestingly, TPA-induced MMP-9 expression was significantly inhibited by UO126, but not by SP600125 and SB203580. In addition, we pretreated cells with 100 μ M silibinin prior to TPA treatment. TPA-induced MEK and ERK phosphorylation was significantly decreased by silibinin in MCF7 cells. TPA-induced VEGF expression was also suppressed by UO126. On the other hand, we found that adenoviral constitutive active-MEK (Ad-CA-MEK) significantly increased MMP-9 and VEGF expression.

Conclusions: Taken together, we suggest that the inhibition of TPA-induced MMP-9 and VEGF expression by silibinin is mediated by the suppression of the Raf/MEK/ERK pathway in MCF-7 breast cancer cells.

Myeov Selected by Array CGH Is Up-Regulated in Breast Cancer

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Background/Purpose: We tried to validate the expression level of MYEOV selected as a candidate gene for the invasion and metastasis of breast cancer by the analysis of array comparative genomic hybridization (array CGH).

Methods: MYEOV gene was selected as the candidate gene for the invasiveness, metastasis of breast cancer by the analysis of previous results of array CGH. We performed RT-PCR to validate the expression of MYEOV in paired normal and cancer tissues of 20 breast cancer patients, and in 7 breast cell lines including 1 normal breast cell lines (MCF10A) and 6 breast cancer cell lines (MCF7, T47D, MDA-MB453, HCC1954, BT20, MDA-MB231).

Results: The expression of MYEOV in cancer tissue is up-regulated in 11 samples (55%), same in 5 samples (25%), and down-regulated only in 4 samples (20%) compared to normal breast tissues. All samples with triple negative breast cancer (n=6, 30%) showed up-regulated expression and 8 (89%) of 9 samples with hormone receptor negative breast cancer showed up-regulated expression. Only MCF10A and MDA-MB453 showed weak expression and all other cell lines showed strong expression. All of 3 cell lines with triple negative phenotype (HCC1954, BT20, MDA-MB231) showed strong expression of MYEOV.

Conclusions: The expression level of MYEOV in cancer is up-regulated compared to normal breast tissue and this phenomenon is prominent in triple negative breast cancer.

SN	histology	age	T stage	N stage	Stage	ER	PR	HER2	NG	HG	recurrence
1	IDC	50	3	3	3C	0	0	1	3	3	systemic
2	IDC	37	3	3	3C	1	1	1	2	2	0
3	IDC	82	4	3	3C	1	1	0	3	3	local
4	IDC	64	3	2	3A	1	0	1	3	3	0
5	IDC	62	2	0	2A	0	1	0	3	2	0
6	IDC	83	2	1	2B	1	1	1	3	2	0
7	IDC	48	3	3	3C	0	0	1	3	3	systemic
8	IDC	50	2	2	3A	1	0	1	2	2	systemic
9	IDC	57	3	1	3A	1	1	0	2	?	0
10	IDC	56	2	1	2B	1	0	0	3	3	0
11	DCIS	49	0	0	0	0	0	0	?	?	0
12	IDC	60	2	0	2A	0	0	0	3	3	0
13	IDC	73	2	2	3A	0	0	0	3	3	systemic
14	IDC	45	4	1	3B	0	0	1	3	3	0
15	IDC	73	2	1	2B	1	0	1	2	2	0
16	IDC	47	3	3	3C	0	0	0	3	3	0
17	IDC	47	3	2	3A	1	1	1	3	2	0
18	IDC	65	2	0	2A	0	0	0	3	3	0
19	IDC	65	2	2	3A	1	0	1	2	3	0
20	IDC	69	2	1	2B	0	0	0	2	2	0

Fig. 1.

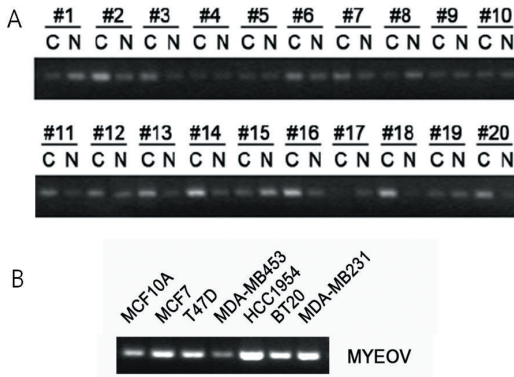


Fig. 2.

Endorepellin LG3 Fragment and Breast Density: A Potential Combination with Screening Mammography in Women with Dense Breast Tissue

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Background/Purpose: To assess the potential of the endorepellin LG3 (ERLG3) fragment as an adjunct to screening mammography, we investigated the association between circulating ERLG3 fragment levels and various clinicopathologic variables including mammographic breast density.

Methods: ERLG3 fragment levels were determined by competitive ELISA in plasma samples from a prospectively constructed study cohort of 258 women diagnosed with primary breast cancer and 201 healthy females. Circulating ERLG3 fragment levels and mammography results were evaluated individually and in combination for their efficacy as screening tools to identify breast cancer.

Results: Lower ERLG3 fragment levels were observed in breast cancer patient plasma than healthy control plasma ($p=0.001$; mean \pm SD: 29.5 ± 9.1 ng/ml and 31.9 ± 6.3 ng/ml, respectively). The lower levels were prominent in patients with negative axillary lymph node (ALN) metastasis (ALN negative versus positive; $P_{\text{age adjusted}}=0.033$, mean \pm SD: 28.8 ± 9.1 ng/ml and 31.3 ± 9.0 ng/ml, respectively) and dense breast tissue (mammographic density grade 3 or 4 versus 1 or 2; $P_{\text{age adjusted}}=0.03$, mean \pm SD: 28.3 ± 8.9 ng/ml and 33.7 ± 8.7 ng/ml, respectively). Receiver operating characteristics (ROC) curve analysis showed that ERLG3 fragment analysis significantly improved the discriminating performance of mammography in patients with dense breast tissue showing non-calcification type mammographic abnormalities. The sensitivity increased from 59% to 71.8% (AUC_{ROC} change 0.05; and $p=0.017$), although it is less sensitive than mammography as a single marker ($AUC_{\text{ROC}}=0.617$; sensitivity=27.4%; specificity=97.1%; and $p=0.0008$).

Conclusions: ERLG3 fragment levels are a useful diagnostic biomarker for breast cancer as an adjunct to screening mammography, particularly when used for young women with dense breast tissue for whom mammography is less effective.

Clinical Use of Serum HER2/Neu Level as a Tumor Marker in Breast Cancer

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Background/Purpose: Tumor markers should be useful for detecting cancer at early time and for monitoring the clinical outcome of anti-cancer therapeutics. Although CEA, CA15-3, NCC-ST439 and BCA225 are now used in breast cancer, positive rates of cancer by these markers are not sufficiently high in clinical use. We examined serum HER2/neu oncoprotein levels in patients with breast cancer and assessed its clinical usefulness as a novel tumor marker.

Methods: Concentrations of HER2/neu extracellular domain (HER2 ECD) in sera from 239 patients with breast cancer ranging in clinical stages from 0 to 4 were measured by the ADVIA Centaur HER2 assay. The positivity of this marker was compared with that of other conventional markers.

Results: Positive rates (16.3%) by HER2 ECD were compatible with those by other markers. In patients with HER2-negative stage 4 cancer, 74.2% of the patients were positive for at least one of the 4 conventional markers. Addition of HER2 ECD did not greatly increase the positive rate. In patients with HER2-positive stage 4 cancer, although cancer was detected by the conventional markers in only 46.2% of the patients, HER2 ECD showed 61.5% positivity in this population. Serial changes in tumor marker levels in patients who received chemotherapy were observed. The HER2 ECD levels showed a significant decline or normalization in all of the responders. The HER2 ECD levels were well correlated with clinical status of the patients.

Conclusions: HER2 ECD is a useful tumor marker especially in HER2-positive breast cancer, which has a low detectability by conventional tumor markers.

Significance of E-Cadherin Expression in Triple-Negative Breast Cancer

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Background/Purpose: Triple-negative breast cancer (TNBC), a subtype of breast tumor with estrogen receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (HER2) negative, shows poor prognosis because of frequent metastasis and recurrences. E-cadherin expression is associated with cancer cell invasion and metastasis. To clarify the correlation between E-cadherin and TNBC, we examined the E-cadherin expression in breast cancers.

Methods: A total of 574 patients who had undergone resection of primary breast cancer at our institute were enrolled. ER, PR, HER2, and E-cadherin expression were assessed by immunohistochemistry. We examined the association between TNBC and other clinicopathologic variables, and evaluated the significance of E-cadherin expression.

Results: Of informative 574 breast cancer patients, 123 showed triple-negative phenotype. TNBC showed larger tumor size ($p=0.012$), more frequent lymph nodes metastasis ($p=0.024$) and frequent lymphatic invasion ($p=0.015$). TNBC showed poorer prognosis ($p<0.001$, Log-Rank). Reduction of E-cadherin was found in 238 (41.5%) of 574 breast cancers. Reduction of E-cadherin was significantly frequent in TNBC ($p<0.001$) and lymph node metastasis ($p=0.032$). In TNBC, the prognosis of patients with E-cadherin negative expression was significantly worse than that of E-cadherin positive ($p=0.0265$, log-rank). And loss of E-cadherin expression was an independent prognostic factor ($p=0.046$).

Conclusions: E-cadherin expression might be a useful predictive marker in TNBC.

Induction of Specific Anti-cancer Immune Response by Trastuzumab Administration in Patients with Advanced Breast Cancer

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Background/Purpose: Trastuzumab (Tr) is able to induce molecular changes in Her2+ breast cancer cells that make them to induce an antigen specific cytotoxic T cell (CTL) response. We investigated the immunological activity of Tr that was administered in pts with breast cancer.

Methods: CTLs were generated in vitro by incubation of peripheral blood lymphocytes (PBL) with the irradiated autologous tumor cells. The specimens were removed from 14 patients with a recurrent breast cancer (7 HER2/neu+; 7 HER2/neu-) and they all failed the conventional chemo-radiotherapy. The cultured CTLs were analyzed their surface markers, and the killing activity. CTLs were administered into recurrent tumor directly by intra-peritumoral injection biweekly and Tr (2 mg/kg) was infused systemically every week.

Results: Following 2-week's coculture, these immune cells containing a preponderance of CD3+ CD4+ or CD3+ CD8+ T cells and CD56+ NK cells, expressed significant degrees of cytotoxicity against autologous tumor cells and the allogenic tumor cell lines. Antibody-dependent cell-mediated cytotoxicity (ADCC) was enhanced in 4 of 6 cases. After stimulation of Tr, the vaccinations with peptide-loaded DCs result in an increased in the number of breast cancer specific CD8+ T cells in cocultured T cells, as documented by IFN-g ELISPOT assay.

Conclusions: Cellular specific anti-cancer immune response might be augmented by anti-Her2 mAb, and it might be in part due to the involvement of mAb in the ability of DC cross-presentation followed by the enhancement of antitumor cellular immunity.

The Role of 14-3-3 Sigma in Human Breast Cancer with Emphasis on the Mechanism of its Regulation

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Background/Purpose: 14-3-3 sigma (σ) is considered to be an important tumor suppressor with the decreased expression reported in various cancers. Its level was reported to be decreased either by hypermethylation at its promoter or ubiquitin-mediated proteolysis by estrogen-responsive ring finger protein (Efp). In this study, we tried to investigate the significance of the 14-3-3 σ expression in human breast cancer and the mechanism of its regulation.

Methods: Efp was downregulated using siRNA in MCF-7 breast cancer cell line to examine its influence on the level of 14-3-3 σ protein. The methylation status of the promoter of 14-3-3 σ was also evaluated by methylation-specific PCR. The expression of Efp and 14-3-3 σ in 220 human breast carcinoma tissues was assessed by immunohistochemistry. Other clinicopathological variables were evaluated together.

Results: Silencing of the Efp in MCF-7 breast cancer cell line resulted in increased expression of the 14-3-3 σ . The Efp-positive human breast cancers were more frequently 14-3-3 sigma-negative (60.5% vs. 39.5%). Hypermethylation of the 14-3-3 σ was common (64.9%) and had a tendency of inverse association with the 14-3-3 σ positivity ($p=0.07$). Positive 14-3-3 σ expression was significantly correlated with poor prognosis.

Conclusions: Our data suggests that in human breast cancers, the regulation of 14-3-3 σ may be involved by both mechanisms. Interestingly, 14-3-3 σ turned out to be a very significant poor prognostic indicator, which is on the contrary to its previously known function as a tumor suppressor, suggesting a different role of 14-3-3 σ in breast cancer.

Natural Triterpenoid Suppresses HER2/Neu (ERBB-2) Expression and Induces Apoptosis in Human Breast Cancer Cells with HER2/Neu Oncogene Amplification

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Background/Purpose: Overexpression/amplification of HER2/neu (c-erbB-2) oncogene is seen in approximately ~25% of breast cancer patients and plays a causal role in mammary carcinogenesis. HER2 overexpression, which confers resistance to various therapeutic regimens, correlates with a poor clinical prognosis. However, little is known about HER2 down-regulators from natural sources in breast cancer. In this study, we tried to explore the pharmacological activities using a natural triterpenoid (corosolic acid, CRA) and its effects in HER2 signaling playing a critical role in breast cancer development, progression and metastasis.

Methods: We examined the down-expression of HER2 by CRA in SKBR3 human breast cancer cell line, which naturally exhibits amplification of the HER2 oncogene. Using western blotting, cell growth and proliferation inhibition assay, cell cycle analysis, and caspase 3-dependent poly-ADP ribose polymerase (PARP) cleavage assay, we characterized the pharmacological effects of CRA on HER2-directed signaling pathways and apoptosis.

Results: CRA dramatically inhibited HER2 expression in a dose-dependent manner (0-50 μ M) for 24 h treatment. CRA effectively inhibited cell proliferation and induced G1 arrest through induction of p27^{kip1} and cyclin D down-regulation playing a key role in the onset and progression of HER2-related breast cancer. CRA exposure enhanced apoptotic cell death, as confirmed by caspase 3 and PARP cleavage activities. In addition, CRA inhibited signaling pathways downstream of HER2, including phospho-proteins such as AKT and MAPK.

Conclusions: These findings demonstrated, to the best of our knowledge, for the first time, that CRA, a natural triterpenoid, suppressed HER2 overexpression, which in turn promoted apoptotic cell death of breast cancer cells with HER2 oncogene amplification.

Regulatory Role of P53 in Cancer Metabolism through Synthesis of Cytochrome C Oxidase 2 (SCO2) and Tp53-Induced Glycolysis and Apoptotic Regulator (TIGAR) in Human Breast Cancer

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Background/Purpose: Cancer cells showed higher rate of anaerobic respiration than normal cells. The exact mechanisms for this higher rate of glycolysis in cancer cells remain to be elucidated. Recent researches suggest that p53, the most commonly mutated tumor suppressor gene, might play an important roles in the regulation of energy generating metabolic pathways that switch from oxidative phosphorylation to glycolysis through synthesis of cytochrome C oxidase 2 (SCO2) and TP53-induced glycolysis and apoptotic regulator (TIGAR).

Methods: We investigated the expression of p53, SCO2, TIGAR and cytochrome C oxidase (COX) in 95 cases of invasive ductal carcinoma using immunohistochemistry.

Results: Overexpression of p53, SCO2, TIGAR and COX was observed in 27.4% (26 cases), 82.1% (78 cases), 76.8% (73 cases), and 77.9% (74 cases) respectively. Overexpression of p53 was significantly associated with decreased expression of SCO2 ($p=0.009$), COX ($p=0.001$) and TIGAR ($p=0.03$).

Conclusions: These results suggest that p53 can modulate the metabolic pathways via SCO2 and TIGAR in human breast cancer.

Microsatellite Instability and P53 Gene Loss of Heterozygosity in Invasive Ductal Carcinomas

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Background/Purpose: Microsatellite alterations, especially microsatellite instability (MSI) and loss of heterozygosity (LOH), have been elucidated as novel mechanisms of carcinogenesis and as a useful prognostic factor in kinds of malignant tumors. The p53 gene is believed to play an important role through the mutation or allelic loss in the progression of various human malignant tumors. Our objectives were to evaluate MSI and p53 gene related LOH in invasive ductal carcinomas (IDC) and to correlate with various clinicopathological factors.

Methods: The MSI analysis was performed by using polymerase chain reaction with five polymorphic microsatellite markers (BAT25, BAT26, D2S123, D5S346 and D17S250 loci recommended in 1998 NCI International Workshop on Microsatellite Instabilities and RER phenotypes) in 50 surgically resected tumors and each non-tumorous counterpart. p53 gene LOH was detected with 4 markers (D17S796, TP53, D17S5, and D17S513).

Results: MSI and p53 LOH were detected in 22% and 60%, respectively. MSI was mostly detected in BAT25 and BAT26 markers (20.5% and 17.1%). MSI was more frequently detected in tumor grade I, T-stage I, non-metastatic tumor and tumor stage I. The LOH frequency correlates well with the tumor size and stage. Reverse correlation between MSI and p53 gene LOH tends to show.

Conclusions: MSI may be involved partly in mammary carcinogenesis and tumor invasion. p53 gene LOH may contribute to the development and invasion of IDC. Combined use of both MSI and p53 gene LOH may be useful clinical indicator in determining prognosis among patients with IDC.

Prognostic Value of Lymphovascular Invasion in Chinese Women with Invasive Breast Cancer

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Background/Purpose: To determine if the presence of lymphovascular invasion contribute further independent prognostic information to the management of invasive breast cancer.

Methods: Age, tumor size, tumor grade, nodal status, ER status, PR status, C-erb B2 status, metastatic disease on presentation, local relapse, distant relapse, cancer-related mortality and lymphovascular invasion were correlated with local relapse, distant relapse and survival. The impact of lymphovascular invasion on survival in node negative patient was evaluated.

Results: 400 patients with primary operable invasive breast cancer between Jan 2000 and Dec 2003 were included. The median follow up was 59 months (1-84 months). Lymphovascular invasion (LVI) were identified in 155 patients (38.7%), which was significantly correlated with tumor size, high tumor grade, nodal involvement, local relapse, distant relapse and metastatic disease on presentation. On multivariate analysis, both local relapse and distant relapse significantly correlated with presence of LVI ($p < 0.001$). Univariate analysis of overall survival found significant correlation with tumor size, nodal status and LVI positivity although on multivariate analysis only tumor size ($p < 0.001$) and LVI positivity ($p = 0.025$) were significant. The difference in cumulative 5-year survival for patients with LVI positivity vs LVI negativity was also statistically significant ($p < 0.05$). The presence of LVI significantly results in a worse prognosis. The presence of LVI in node negative patients was associated with a worse 5-year survival.

Conclusions: Lymphovascular invasion adds prognostic information to Chinese women with invasive breast cancer including those who have node negative disease. LVI should be taken into account in decision-making on adjuvant therapy in management of breast cancer patients.

Direct Interaction of ROR-alpha with Aromatase Promoter in Breast Cancer Cells

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Background/Purpose: Aromatase plays an important role on the progression of estrogen-dependent breast cancer. Nevertheless, mechanisms controlling the aromatase gene expression have not yet been fully clarified. On the other hand, retinoic acid receptor-related orphan receptor (ROR) α plays an important role on the growth and differentiation of many organs by regulating transcription of target genes. In the present study, we examined the effect of ROR α on the aromatase gene expression.

Methods: ROR α expression vector was transfected into MCF7 cells. Expression of aromatase mRNA was examined using quantitative real time RT-PCR. Chromatin immunoprecipitation (ChIP) assay was performed to identify the interaction of ROR α with aromatase gene promoter region. Surgical specimens of breast cancer were obtained from female patients, after approval of the Ethics Committee of Gunma University.

Results: ROR α transfection significantly augmented the aromatase mRNA levels, particularly those containing exon I.4. Reporter gene assays using a promoter fragment at exon I.4 showed an augmentation of transcription by ROR α , particularly through -147~+14 bp. ROR α bound to a fragment containing -119~-107 bp of the promoter in vitro. ChIP assay showed the in vivo binding of ROR α to the region containing this site. These results indicate a novel ROR response element at this region. Moreover, we observed a significant positive correlation between ROR α and aromatase mRNA levels in the breast cancer specimens.

Conclusions: ROR α may directly activate the aromatase gene expression, which may provide a new insight into our understanding on the molecular mechanisms regulating progression of breast cancer.

Promoter Hypermethylation is an Early Event in Breast Carcinogenesis

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Background/Purpose: Aberrant methylation of CpG island in the promoter region of tumor suppressor genes has become established as an important epigenetic mechanism for gene silencing. Promoter hypermethylation in precursor lesions at risk for progression to invasive cancer may be biomarkers of cancer risk and targets for cancer chemoprevention. In breast cancer, promoter hypermethylation has been described for several genes covering all aspects of cellular function. However, the methylation studies of precursor lesion of the breast are rather sparse and mostly done in a purely qualitative manner.

Methods: To evaluate the significance of alterations in promoter hypermethylation during multistage carcinogenesis of the breast, quantitative multiplex methylation-specific PCR of six genes (APC1, Cyclin D2, HIN-1, RAR- β , RASSF1A, and Twist) was performed on DNA from 15 normal breast tissues, 21 usual ductal hyperplasia (UDH), 48 ductal carcinoma in situ (DCIS), and 35 stage I invasive ductal carcinoma (IDC), not otherwise specified.

Results: We found null to very low levels of promoter methylation in normal samples. In general UDH, DCIS, and IDC samples revealed varying levels of methylation ranging from 0 to 100%. One-way analysis of variance showed that the methylation levels of all six genes increased significantly according to the progression of breast neoplasia from normal epithelium, through hyperplasia, to DCIS. However, methylation levels were not significantly different between DCIS and IDC.

Conclusions: Our results suggest that promoter hypermethylation is an early event in breast carcinogenesis. Promoter hypermethylation in the precursor lesions of the breast cancer may be used as a target for cancer chemoprevention.

GSTP1 Promoter Hypermethylation during Breast Cancer Development

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Background/Purpose: Promoter hypermethylation in precursor lesions of the breast cancer may be biomarkers of cancer risk and targets for cancer chemoprevention. GSTP1 is inactivated by promoter hypermethylation in invasive breast cancers. However, little is known about epigenetic silencing of GSTP1 gene by promoter hypermethylation in precursor lesions.

Methods: To determine the significance of GSTP1 promoter hypermethylation in breast carcinogenesis, methylation status of GSTP1 gene was studied by nested methylation-specific PCR and GSTP1 expression was studied by immunohistochemistry in invasive ductal carcinoma (IDC), ductal carcinoma in situ (DCIS), usual ductal hyperplasia (UDH) and normal breast tissue.

Results: GSTP1 promoter hypermethylation was detected in 4/24 (16.7%) of UDH, 18/49 (36.7%) of DCIS, and 14/36 (38.9%) of IDC. No hypermethylation was detected in normal breast tissues. GSTP1 promoter hypermethylation was found to be progressively elevated during breast carcinogenesis ($p < 0.01$). GSTP1 promoter hypermethylation was associated with loss of GSTP1 expression ($p < 0.01$ for UDH, $p < 0.001$ for DCIS and IDC).

Conclusions: Our results suggest that GSTP1 promoter hypermethylation is an early event in breast carcinogenesis and appears to functionally silence GSTP1 expression. GSTP1 promoter hypermethylation in the precursor lesions of breast cancer may be used as a target for cancer chemoprevention.

Diallyl Trisulfide-Induced Apoptosis via p53 in MCF7 Breast Cancer Cells

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Background/Purpose: The organosulfur compounds of garlic have antitumor effects, but the mechanisms have yet to be investigated. The present study was undertaken to determine the effect of diallyl trisulfide (DATS), a constituent of processed garlic, on the growth of MCF-7 (breast cancer cells) and MCF12a (normal breast epithelial cells), which has never been reported. We also identified a novel DATS derivative that showed synergetic and additive effect against breast cancer cell lines.

Methods: The effects of DATS were investigated by MTT assay, clonogenic survival assay, ELISA based apoptotic assay, TUNEL assay, immunofluorescence staining, flow cytometry, RT-PCR and western blot analysis.

Results: DATS induced apoptosis in MCF-7 cells more than in MCF-12a cells through abrogation of cell cycle checkpoints. The results from semi-quantitative and real-time RT-PCR indicated that DATS increased the level of FAS and cyclin D1 and decreased the level of Akt and Bcl-2. DATS increased Bax expression and also expression and translocation of p53 from cytoplasm to nucleus in MCF-7 cells.

Conclusions: This work suggested that DATS and its derivative may offer a novel strategy for the treatment of breast cancer.

Tumor Reduction Rate and Early Recurrence among Breast Cancer Patients who Can Not Achieved Complete Response to Primary Chemotherapy

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Background/Purpose: Primary chemotherapy (PC) for breast cancer is effective as postoperative adjuvant therapy, which permits more lumpectomies and can be used to study breast cancer biology. Many reports indicate that the absence of residual cancer after PC has been proposed as a critical favorable prognostic factor for prolonged disease-free and overall survival. However, pathological complete response (pCR) has not been obtained for all cases and the majority of the patients indicate no more than partial response to PC.

Methods: The subjects consisted of 41 breast cancer patients failing to achieve pCR to PC. Enhanced MRI using a 1.5-T system was carried on just before and after PCs, as well as the correlation between tumor reduction rate and occurrence of early event was analyzed retrospectively.

Results: In the median 40 (23-48) months follow-up, 14 recurrences and 7 deaths were observed. Disease-free cases had a greater tumor reduction rate than recurred cases ($p=0.0035$). If the average of 56% was chosen as the cut-off value, the significant difference was found between the groups with high and low tumor reduction rates ($p=0.0036$) with a hazard ratio 2.62. Moreover, cancer-associated deaths were often observed in the cases with the lower tumor reduction rate compared with alive patients ($p=0.0003$).

Conclusions: The evaluation of tumor reduction rates on MRI was considered to be useful for predicting early outcome among breast cancer patients who can not achieve pCR after PC.

Chylous Fistulas in Cases Treated Surgically for Breast Cancer

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Background/Purpose: Chylous fistulas in cases treated surgically for breast cancer only are rare. We encountered eight chylous fistula cases after breast cancer operations and report clinical findings of all cases.

Methods: There were eight cases (0.2%) with chylous postoperative drainage among total of 4,005 breast cancer cases treated surgically between 1998 and 2008 in Aichi Cancer Center Hospital. The all cases were performed axillary lymph node dissection. Axillary lymph node dissection has been standard procedure with or without clinical lymph node involvement until 2004 and was only performed in SLN positive and clearly lymph node involvement cases after 2005.

Results: The age of eight patients ranged from 22 to 76 years (average: 53). The body mass index (BMI) in eight patients was normal range (average: 21.1). All primary breast cancers in eight patients were located in the left breast. Six patients were performed level I and II lymph node dissection and two patients were performed level I, II and III area. Axillary lymph node metastasis was involved in three cases among all cases. The chylous fistula appeared in 2, 2, 3 and one patients at the first, second, third, fourth postoperative day (POD), respectively. The chylous fistulas of these eight cases, even if they were long disappeared by the 29th POD without diet control and surgical treatment.

Conclusions: Chylous fistulas were unrelated to obesity, surgical method or the area of axillary lymph node dissection. All eight cases of chylous fistulas were successfully treated conservatively, without special dietary control and surgical treatment.

Promoting QOL of Early Breast Cancer Patients Treated with Endoscopically Assisted Breast-Conserving Operation

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Background/Purpose: Since August 1996, we have treated 780 patients suffered from early breast cancer surgically with endoscopic procedure in order to promote their postoperative QOL. This procedure has advantages such as minimizing operation scar invisible at front view and reduction of postoperative pain and sensory disturbance.

Methods: As for 780 patients we investigated and analyzed the rate of recurrence and survival. And we asked them by questionnaire how well they are satisfied with body image, operation scar and QOL.

Results: For 13 years at the longest observation we have observed 4 local recurrences and all patients are survived ie., 4 among 780 patients. Local recurrence rate is 0.5% and 5 years survival is 99.5%.

Conclusions: These results indicate that our procedure causes no reduction of curability and reduction of local recurrence compared with the previous reports by conventional method. According to questionnaire for patients, it revealed that endoscopically assisted wide excision is contributed to promoting QOL in early-stage breast cancer patients.

Endoscopy-Assisted Breast Surgery for Breast Cancer: A Comparison with Conventional Breast Conserving Surgery

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Background/Purpose: Endoscopy-Assisted Breast Surgery (EABS) can be performed with small and remote incisions that are inconspicuous after surgery. We report herein the aesthetic and treatment results of EABS in patients with breast cancer compared to conventional breast-conserving surgery.

Methods: A 3-cm axillary skin incision was made along the axillary skin crease; the work space was created with a wound retractor. After the retromammary space was dissected through the axillary incision, we made a periareolar incision to excise tissues, partially or totally, under endoscopic assistance. We also performed a dye- or radioisotope-guided sentinel lymph node biopsy and dissected axillary lymph nodes (level I and II) under endoscopic assistance, and carried out frozen section biopsies to assess tumor invasion at the resection margins.

Results: We retrospectively analyzed 50 consecutive patients with breast cancer between June 2006 and November 2008. Thirty three underwent EABS, and 17 had conventional BCS. There was no significant difference in patient characteristics, tumor characteristics, operation time, or blood tests. In the EABS group, 23 patients underwent BCS and 10 underwent a skin-sparing total mastectomy. Six out of 10 patients had a nipple areola complex sparing mastectomy. Seven patients underwent axillary dissection under endoscopic assistance. Among 82% of the evaluated cases there was good to excellent results. There was a significant difference in the wound scar ($p=0.034$) and patient satisfaction ($p=0.012$) with the cosmetic outcome.

Conclusions: EABS was effective for patients with breast cancer and can be regarded as a surgical option with better aesthetic results.

Neo Adjuvant FEC100 Followed by Weekly Paclitaxel for Locally Advanced Breast Cancer

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Background/Purpose: Sequential administration of anthracyclin and taxane in neoadjuvant chemotherapy (NAC) is now a standard treatment for locally advanced breast cancer. Pathological complete response (pCR) is a significant predictor of overall survival (OS) regardless of treatment. We have retrospectively examined the pCR rate as efficacy and analyzed the characteristic of pCR cases.

Methods: Sixty-six female patients with locally advanced breast cancer who had been administered FEC100 followed by weekly paclitaxel in NAC, between December 2005 and May 2009 at the Osaka City University Hospital, were retrospectively reviewed. The patients were in the age range of 26-71 years (mean 50.4 years), in the tumor size range of 15-60 mm (mean 28 mm) and on stage 2A-3A. This study comprised 53 patients with axillary lymph node metastasis. Twelve of HER-2 positive cases were administered weekly trastuzumab on paclitaxel. We evaluated the size of tumor and axillary lymph node by ultrasonography.

Results: Twenty-seven cases (41%) achieved pCR. Overall response rate was 92%. Only a case had progressive disease. Thirty out of 66 cases (46%) received breast conserving surgery. The pCR rate of patients with extensive lymph node metastasis and negative hormone receptor was significantly high. Febrile neutropenia occurred in 18 cases (27%) including 13 cases (19%) who required 3-7 days admission.

Conclusions: FEC100 followed by weekly paclitaxel as a neoadjuvant chemotherapy regimen is very effective in the aspect of pCR rate especially in the patients with extensive lymph node involvement and negative hormone receptor.

Breast Cancer Shrinkage Mode after Neoadjuvant Chemotherapy by Whole-Mount Serial Sections

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Background/Purpose: The main clinical goal of neoadjuvant chemotherapy (NAC) is to down-stage the primary tumor for breast-conserving surgery (BCS). Due to the uncertain shrinkage modes of the primary tumor, BCS after NAC has been associated with significantly high ipsilateral breast tumor recurrences. The objective of this study is to observe the shrinkage modes for the guidance of BCS after NAC.

Methods: All the 30 LABC patients enrolled received three cycles NAC before mastectomy. Whole-mount serial sections (WMSS) at 3 mm intervals were performed. The WMSS were HE stained, and the residual tumor area was microscopically outlined on each slides. The two-dimensional images were processed with Adobe Photoshop 9.0 and the three-dimensional model of the residual tumor was reconstructed with the 3D-DOCTOR software.

Results: pCR was obtained in one case. Of the other 29 patients, honeycomb shrinkage mode was observed in 28 cases (96.6%) with no significant decrease of the histological tumor range after NAC ($p>0.05$); and concentric shrinkage mode was observed in only one case (3.3%). Diffusive microcalcifications on mammography and more diffusive residual DCIS had a good consistency according to kappa test (76.5% vs. 7.7%, $\kappa=0.670$, $p<0.01$).

Conclusions: Three cycles of NAC was not enough to down-stage the primary tumor for BCS due to the honeycomb shrinkage mode. The shrinkage mode after 6-8 cycles of NAC is worth of further study. With diffusive residual DCIS, patients with diffusive microcalcifications might not suitable for BCS after NAC. WMSS and three-dimensional pathological reconstruction of the residual tumor provided a new platform for research in this area.

Neoadjuvant Chemotherapy with Trastuzumab for HER2-Positive Primary Breast Cancer

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Background/Purpose: Neoadjuvant chemotherapy (NAC) with trastuzumab for primary breast cancer patients with HER2-positive tumors has been evaluated.

Methods: A retrospective analysis of 29 primary breast cancer patients (IIB-IIIc) with HER2-positive tumors treated by NAC was performed. NAC consisted of weekly paclitaxel plus trastuzumab with (PTA group, n=9) or without anthracycline (PT group, n=20). Patients in the PTA group received 4 courses of FEC every 3 weeks followed by concomitant paclitaxel 80 mg/m² and trastuzumab weekly for 12 weeks and those in the PT group received 4 courses of paclitaxel 80 mg/m² weekly (Days 1, 8, 15) followed by a 1-week break and trastuzumab weekly.

Results: Median age of patients was 49 years old. Of 29 patients, 14 (48%) had a pathologic complete response (pCR). Patients with clinical stage IIB breast cancer achieved a significantly higher pCR rate than those with more advanced breast cancer. There was no significant difference in age, clinical stage and clinical response rate between the PTA and the PT groups. The pCR rate of the PTA and the PT groups was 44% and 50%, respectively. At the median follow up of 28 months, there was no significant difference of disease-free survival between the two groups.

Conclusions: Trastuzumab-containing NAC is effective in the treatment of primary breast cancer patients with HER2-positive tumors irrespective of anthracycline-containing regimen.

Intraoperative Frozen-Section Examinations of Surgical Margins: The Implication of Features of Margin-Exposed Tumor Components on Further Surgical Treatment

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Background/Purpose: In breast conserving surgery (BCS), we usually resect additional specimens after the diagnosis of positive margin by intraoperative frozen-section examinations (IFE). If we can predict the absence of residual tumor components by IFE, it may be possible to avoid additional mastectomy. In this study, we tried to identify histological characteristics of margin-exposed tumor components on IFE as predictive factors for the residual tumor components in the additionally resected specimens.

Methods: 1,835 cases underwent BCS between 1999 and 2008 at the National Cancer Center Hospital, Tokyo, Japan. We chose patients who had positive margins determined by IFE and had undergone immediate additional resection.

Results: 220 cases were eligible for this study. Within the additionally resected specimens, residual tumors existed in 114 cases (51.8%) and no tumors existed in 106 cases (48.2%). As characteristics of the primary tumors, invasive lobular carcinoma, pT3, EIC (+) and lymphatic invasion were significantly associated with the residual tumor components. As characteristics of margin-exposed tumor components on IFE, the multiple positive margins, the 6 mm maximum diameter, and the lobular carcinoma components were correlated with the residual tumor components. By a multivariate analysis, the number of positive margins and the maximum diameter were independent risk factors of the residual tumors.

Conclusions: IFE of surgical margins was useful for the prediction of the residual tumors, and three histological properties of margin-exposed tumor components were correlated with the absence of residual tumor components. It may be possible to consider stratification of additional surgical therapy according to the characteristics of margin-exposed tumor components on IFE.

The Role of Postmastectomy Radiation Therapy for T1-2N0 Patients with Lymphatic Invasion: Comparison with Patients Undergoing Conserving Surgery

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Background/Purpose: To evaluate the efficacy of postmastectomy radiation therapy for T1-2N0 patients with lymphatic invasion.

Methods: We analyzed 1646 T1-2N0 patients who underwent breast conserving surgery (BCS) or mastectomy from 1989 to 2006. Of 1,646, lymphatic invasion was identified in 125 mastectomy and 139 BCS patients. All patients who underwent BCS received postoperative radiotherapy. We compared a local recurrence rate (LR), local recurrence free survival (LRFS), disease free survival (DFS) and overall survival (OS) between mastectomy and BCS.

Results: There was no difference of local recurrence rates between BCS and mastectomy among patients without lymphatic invasion. In patients with lymphatic invasion, LR rate was higher in mastectomy group (8.0% vs. 2.2%, $p=0.043$). 5-year LRFS rates were 98.1% for BCS patients and 87.3% for mastectomy patients respectively ($p=0.035$). 5-year DFS rate was higher in BCS patients (93.7% vs. 77.6%), but the difference of rates was not statistically significant ($p=0.064$).

Conclusions: Postmastectomy radiotherapy seems to be able to reduce local recurrence rate for T1-2N0 patients with lymphatic invasion and a larger prospective trial is needed to establish the efficacy of radiotherapy for those patients.

Study of S-1/Trastuzumab Combination Therapy for HER2-Positive Metastatic Breast Cancer

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Background/Purpose: S-1 is an oral fluoropyrimidine antitumor drug, which is one of the key drugs for treating metastatic breast cancer. In this study, we examined the efficacy, safety, and PK of Trastuzumab (T) and S-1 combination therapy (ST) for HER-2-positive MBC. Furthermore, we also retrospectively examined the cross-resistance to Capecitabine (X), which is also fluoropyrimidine derivative.

Methods: The subjects comprised female patients with MBC. S-1 was administered orally daily at 80 mg/m² for 14 days and then discontinued for 7 days. T was given intravenously on day 1, repeated every weekly. The drug levels in the blood of Tegafur (FT), CDHP, and FU, which are the combined components of S-1, were measured at Hours 0, 2, 4, and 6 of day 1.

Results: The PK parameters for 5 registered cases of ST therapy were: FU: Cmax 162.9 ± 37.3 ng/ml, Tmax 3.0 ± 0.4 h, AUC 909.3 ± 232.1 ng h/ml; CDHP: Cmax 352.2 ± 66.9 ng/ml, Tmax 1.5 ± 0.0 h, and AUC 1699.8 ± 452.3 ng h/ml, wherein there were no significant differences in the PK parameters when only S-1 was administered. Out of the 6 cases of S-1 administration subsequent to the prior treatment X, there was 1 case of PR and 1 case of SD, whereas both of the 2 cases of X subsequent to prior treatment with S-1 were PD.

Conclusions: In the ST therapy, there were no severe side-effects and the administration was safely performed with no fluctuations in PK compared to when only S-1 was administered.

Immediate Reconstruction with Extended Latissimus Dorsi Flap with or without Implant after Skin Sparing Mastectomy

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Background/Purpose: We report our experience of extended latissimus dorsi (ELD) flap reconstruction in Korean women immediate after mastectomy with little complication.

Methods: From September 2007 to December 2008, 89 women with breast cancer received ELD flap operation after skin sparing mastectomy. We performed the reconstruction using ELD only in 66 patients and ELD+implant in 23 patients. Mean age was 45.8 years (31-65). Mean body mass index was 23 kg/m². The cup size of breast were 37 cases of A cup, 44 cases of B cup, 8 cases of C cup. Pathologic stage were 77 cases of stage 0, I, II and 12 cases of stage III.

Results: Cosmetic results were fair in 20 cases, good in 49 cases, excellent in 20 cases, and overall cosmetic score was 7.4 out of 10 point scale. There were no flap loss and implant related complication except all minor complication such as only 1 case of wound dehiscence, 1 case of hematoma, 1 case of wound infection, 10 cases of donor site seroma continuing over 1month. There were no radiation induced complication in 10 of irradiated patients. The mean operation time was 3 hours 44 minutes. There were no statistical difference in cosmetic score, complication rate, BMI and operation time between ELD group and ELD+implant group and there was higher tendency of using implant as the size of breast cup increased.

Conclusions: It is possible to reconstruct breast in majority of women using ELD flap with or without implant immediate after skin sparing mastectomy getting good cosmetic results without serious complication.

Surgical Removal of Internal Mammary Lymph Node Recurrence in Breast Cancer Patients

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Background/Purpose: The purpose of this study is to assess the prognosis of surgical removal of recurrent internal mammary lymph nodes (IMLN) in the selected breast cancer patients.

Methods: Patient data were retrieved from Asan Medical Center located in Seoul, Korea, between January 1989 and May 2009. A retrospective review was conducted of 33 breast cancer patients with IMLN recurrence. Recurrent IMLNs were dissected in 17 of the 33 patients. The dissection group was compared with the non-dissection group of 16 patients.

Results: There were no significant differences of stages, ages, ER status, PR status, HER2 status or adjuvant treatment of the initial primary cancer between the two groups. There was no significant difference found in the numbers or extranodal invasion in recurrent IMLNs on imaging studies, although the largest size of the recurrent IMLNs was smaller in the dissection group ($p=0.044$). Axillary LN recurrence and distant organ recurrence were more frequent in the non-dissection group at the time of the IMLN recurrence detection ($p=0.004$, $p=0.0009$), however, axillary LN recurrence did not adversely affect patient survival ($p=0.98$). When analysis was limited to patients without distant organ recurrence at the time of IMLN recurrence, the total was 25 patients and the survival rate of the patients with dissected IMLNs was 100%, while that of the non-dissected patients was 25% ($p=0.0004$).

Conclusions: Our study showed that surgical removal of IMLNs together with types of other adjuvant treatment was effective in selected breast cancer patients with IMLN recurrence. However, this study has several limitations.

Prognostic Factors Affecting Survival of Breast Cancer Patient with Bone Metastasis

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Background/Purpose: Bone is the most common metastatic site of breast cancer. We performed this study to elucidate clinico-pathologic factors affecting survival of breast cancer patients with bone metastasis.

Methods: From January 1991 to December 2006, 2,177 of breast cancer patients were treated at Gangnam Severance hospital. Among them, patients who developed bone metastasis during follow up period after treatment and patients diagnosed as breast cancer with bone metastasis at initial diagnosis were included in this study. We retrospectively collected the clinicopathologic data. We investigated the factors affecting survival after bone metastasis.

Results: One hundred and twenty-two (87.1%) had bone only recurrence after radical surgery and 18 patients (12.9%) showed bone metastasis at initial diagnosis. Mean age of selected patients was 44.5 years-old and mean survival after bone metastasis was 19.6 months. By univariate analysis using Kaplan-Meier method, less number of metastatic lymph node ($p=0.002$), positive hormone receptor ($p=0.008$), radiotherapy ($p=0.005$), chemotherapy ($p=0.001$), bisphosphonate treatment ($p=0.000$), solitary bone metastasis ($p=0.000$), and disease-free interval more than 1 year ($p=0.001$) were significantly associated with good survival after bone metastasis. In multivariate analysis using Cox proportional hazards model, positive hormone receptor ($p=0.000$), chemotherapy ($p=0.011$), bisphosphonate treatment ($p=0.002$), disease-free interval more than 1 year ($p=0.011$), and solitary bone metastasis ($p=0.000$) was statistically proved to be an independent factor for good survival.

Conclusions: These results suggest that chemotherapy and bisphosphonate treatment improve survival of breast cancer patients with bone metastasis. Even in hormone receptor positive patients with bone metastasis, chemotherapy could be considered as initial treatment.

Nation-Wide Survey of Absorbable Mesh on Breast Surgery in Korea

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Background/Purpose: It is known that many physicians have been using mesh on breast surgery recently in Korea but, there is no information for this practice. We investigated the present practice patterns of mesh.

Methods: A structured questionnaire was conducted to the members of the Korean Breast Cancer Society through e-mail, phone and notice in homepage from April 6th, 2009 to April 20th, 2009.

Results: A total of 54 breast surgeons have responded to survey, 74.1% (n=40) of respondents have experience of using mesh and all of them used Vicryl mesh. Ninety two percents (n=36) of respondents using mesh always combined with Interceed. Sixty five percents (n=26) of respondents used mesh when a deformity is expected regardless of T-stage and 80% (n=32) of respondents didn't use mesh on the patients with compromised wound healing process. The experience of infection for inserting area was in 77.5% (n=31) of respondents. There were 39 cases among total number of 843 cases (4.6%) and when it was infected, mesh was removed by 62.5% (n=19) of the respondents. Eighty nine percents (n=33) of the respondents used breast ultrasonography for follow up. Forty seven percents (n=19) of the respondents answered that mesh is absorbed in 6 months so, there was no diagnostic confusion.

Conclusions: Although mesh is somewhat expensive and may be accompanied by complication, there are some merits that it can be lead to keep good breast shape and it can be easily done. If we have good guidelines using mesh, we could maximize the various merits.

Randomized Phase II Trial of Capecitabine/Vinorelbine Followed by Docetaxel Versus Adriamycin/Cyclophosphamide Followed by Docetaxel as Neoadjuvant Chemotherapy for Locally Advanced Breast Cancer: An Interim Analysis

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Background/Purpose: We designed a randomized phase II trial to evaluate the efficacy and safety of capecitabine/vinorelbine (CV) and a standard AC (adriamycin+cyclophosphamide) regimen in patients with locally advanced breast cancer (LABC) and to determine the additional effect of docetaxel (T) after neoadjuvant chemotherapy.

Methods: Previously untreated LABC patients were randomly assigned to AC-T arm (A 60 mg/m² plus C 600 mg/m² [$\times 4$] then T 75 mg/m² [$\times 4$]) or CV-T arm (C 1,000 mg/m² [D1~14] plus V 25 mg/m² [D1, D8; every 3 weeks] [$\times 4$] then T 75 mg/m² [$\times 4$]). Primary end point was clinical response by breast MRI.

Results: Forty patients had been enrolled between July/2005 and June/2008. Median tumor size (6 cm) and other key characteristics were evenly balanced between two arms. The response rate detected by breast MRI was 71% with AC (n=15/21) and 68% with CV (n=13/19). Only two (29%) of 7 patients who showed stable disease to AC or CV showed further response after sequential docetaxel, but, three (43%) showed progressive disease. Among responders for AC or CV, 58% of patients further responded to docetaxel and one patient achieved pCR. Till now, a total of 38 patients underwent surgery, and two patients (10.5%) achieved pCR in each treatment arms.

Conclusions: Both neoadjuvant AC-T and CV-T produced similar clinical and pathologic response rate in patients with LABC. Sequential docetaxel was effective only in patients who had responded to the initial AC or CV chemotherapy. Final efficacy and safety analysis will be performed in October 2009.

Surgical Complication and Oncological Outcome after Breast Reconstruction

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Background/Purpose: Breast reconstruction is a psychological, social, and sexual well-being treatment for the breast cancer patients. The Breast Cancer Treatment and Reconstruction Center (BCTR) was established in our institute in May, 2008 and We perform both immediate and delayed breast reconstruction. We analyzed the complication of these breast reconstructions in BCTR.

Methods: Fifty-one breast cancer patients who underwent breast reconstruction from October 2007 to April 2009, were studied. We analyzed the correlation between complications which required surgical procedures, and operative time, immediate or delayed surgery, reconstruction methods and preoperative chemotherapy or radiotherapy.

Results: All patients belonged to clinical stage 0 to 3C and median age was 46-year-old. No patient showed local recurrence and only one patient showed a distance metastasis. Twenty-four patients (47%) received deep inferior epigastric perforator flap (DIEP), 22 (43%) received latissimus dorsi flap (LD), and 3 (6%) received transverse rectus abdominus myocutaneous flap (TRAM). Thirty-two (63%) and nineteen (37%) patients had immediate and delayed reconstruction, respectively. Average operative time was 7 hours. Ten cases (19%) showed complications; flap necrosis, infections, and thrombosis of anastomotic vessels. Operative time (31% in over 7 h vs. 8% in under 7 h; $p=0.03$) and reconstruction methods (25% in DIEP vs. 4% in LD; $p=0.04$) were significantly affected on complications, though presurgical treatment or operation step did not.

Conclusions: Breast reconstruction is feasible on the aspects of complications and local recurrence. Operative time and reconstruction methods are considered to be predictive factors for occurrence of complications.

Is it Possible to Recommend an Adjuvant Chemotherapy Containing Anthracycline when Ki67 is Positive in HER-2 Positive Breast Cancer?

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Background/Purpose: Ki67 is known as cellular protein of indicating proliferation rate. There is several report that High level of Ki67 is affected to overall survival. The purpose of our report is evaluation of the effect of Ki67 in HER-2 positive breast cancer on DFS and OS at our hospital data.

Methods: 783 patients was operated in our hospital due to breast cancer from Jan 2001 to Dec 2005. 198 patients was diagnosed as HER-2 positive breast cancer due to IHC 3+ or FISH+. HER-2 positive patients were divided by two groups. One group is defined as Ki67 positive, the other group is defined as Ki67 negative. The log-rank test was used to assess the prognostic importance of histopathological characteristics, clinic characteristics and therapeutic modalities. χ^2 test was used to calculate the significance of the relationship between the dichotomous variables. p-values <0.05 were considered to be significant.

Results: There is no age distribution difference between two groups. Tumor size is more bigger in Ki67 positive group (p=0.006). Pathologic N-stage according to AJCC is more advanced in Ki67 group (p=0.0001). The DFS and OS of Ki67 positive group is lower that of Ki67 negative group (p=0.04, p=0.03 respectively). The anthracycline containing adjuvant chemotherapy is not affect to the survival curve in Ki67 positive group.

Conclusions: Ki67 positive is important in HER-2 positive breast cancer's survival rate. Adjuvant chemotherapy containing anthracycline is not important in Ki67 positive groups. The evaluation of adjuvant chemotherapy containing taxol and trastuzumab is needed.

The Effect of Adjuvant Chemotherapy Containing Taxane on Survival Rate when Ki67 is Positive in Triple Negative Breast Cancer

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Background/Purpose: Breast cancer is heterogenous disease. Triple negative breast cancer is known as poor survival rate. As yet, there is no definite treatment guideline about triple negative breast cancer. In recent, there is several reports that High level of Ki67 is affected to overall survival. Our report attempts to evaluate both the effectiveness of Ki67 on DFS, OS and that of adjuvant chemotherapy containing Taxol on Ki67 positive triple negative breast cancer.

Methods: We have evaluated retrospectively medical record of 103 patients who was diagnosed as triple negative breast cancer postoperatively at our hospital from 2001 to Dec 2005. We are divided two groups according to Ki67 status. One group is defined as Ki67 positive, the other group is defined as Ki67 negative. The log-rank test was used to assess the prognostic importance of histopathological characteristics, χ^2 test was used to calculate the significance of the relationship between the dichotomous variables.

Results: Advanced breast cancer is more frequent in Ki67 positive ($p=0.047$). But there is no the other factors' distributional difference between two groups including age, tumor size, AJCC stage, Nuclear grade, p53. The DFS and OS of Ki67 (+) group is lower than Ki67 (-) group ($p=0.0001$, $p=0.006$ respectively) and Stage of AJCC was significant factors on DFS, OS ($p=0.0004$, $p=0.002$ respectively). But adjuvant chemotherapy containing taxol was not significant factors on DFS, OS of Ki67 (+) triple negative breast cancer.

Conclusions: Ki67 (+) triple negative breast cancer is poorer survival rate than Ki67 (-) group. So the evaluation of adjuvant chemotherapy is needed treating Ki67 (+) triple negative breast cancer.

Fulvestrant Use in Clinical Experience of Advanced Breast Cancer in Postmenopausal Women

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Background/Purpose: Endocrine therapy of breast cancer is important after breast cancer surgery operation who is adjuvant endocrine therapy and advance breast cancer. Fulvestrant is a new type of oestrogen receptor (ER) antagonist that down-regulates the ER and has no known agonist effects.

Methods: We performed a retrospective study of 17 postmenopausal Korea women with hormone-sensitive advanced breast cancer. Our study were performed though April 2007 to April 2009. They had progressed on tamoxifen/toremifene following an initial response, received fulvestrant (250 mg; once-monthly intramuscular injection).

Results: In our study 88.2% patients had ER and PR positivity, HER-2 positivity was 33.3%. 23.5% patients had a stable disease (SD) >24 week and 11.7% had Partial Response (PR). Clinical Response, CB)[PR+SD]: 35.2%. TTP: 4 month, with a median follow-up of 10 month. Fulvestrant was tolerable and few side effects.

Conclusions: Fulvestrant 250 mg/month is Activity and the value of fulvestrant were retained in metastatic patients who were hormone responsive.

What is the Influence of Palliative Chemotherapy Containing Taxane on Survival Rate of Breast Cancer with Bone Metastasis?

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Background/Purpose: Bone is the most common site of metastasis of breast cancer. Palliative chemotherapy is one of the treatment. Palliative chemotherapy is usually divided two regimens according to containing taxane in that. The aim of our report is attempt to investigate the effectiveness of regimen containing taxane on survival rate.

Methods: Fifty two breast cancer patients who had presented at early or advanced stage and later developed bone metastases during follow-up period between January 2001 and November 2006 were included in the study. Clinical data including demographics, stage, surgery, pathologic features (ER and PR status, tumor grade, lymph node status, tumor size), date of last follow-up and death, date and site of first recurrence and subsequent metastatic progression, type of systemic results were collected from the patient files, surgical reports, pathology reports and radiotherapy charts. The log-rank test was used to assess the prognostic importance of histopathological characteristics, clinic characteristics and therapeutic modalities. χ^2 test was used to calculate the significance of the relationship between the dichotomous variables. p-values <0.05 were considered to be significant.

Results: The median interval between diagnosis and bone metastasis was 41 months (95% CI, 38-49) in early stage patients. Tumor size, N stage, Ki67 were the factors which significantly affected the early appearance of bone metastasis. The responsiveness of adjuvant chemotherapy was not significant factor in the median survival rate (6 months vs. 4 months, p=0.145).

Conclusions: Response to systemic treatment was not determinative in the development of isolated brain metastases than clinical and pathologic features.

High Resolution Ultrasound Guided Mammotome Biopsy of Suspicious Mammographic Calcifications of the Breast

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Background/Purpose: To evaluate the feasibility of ultrasound guided mammotome biopsy of microcalcifications of the breast.

Methods: Between September 2006 and March 2009 one surgeon performed consecutive 39 procedures in 34 patients presenting with microcalcifications without associated mammographic or ultrasonic or palpable masses. If there is uncertainty in correlating mammographic findings with ultrasound findings, the area is reevaluated after long straight needle localization (6 cases). Specimen mammographs were obtained for each lesions, with success of the procedure based on identifying over 90% of clustered calcifications and over 50% of segmental distributed calcifications. Stereotactic biopsy was carried out when ultrasound guided biopsy was unsuccessful.

Results: Except for only one lesion, 38 lesions were successfully biopsied under sonographic guidance. All procedure could be performed in 30 minutes and there was no major complication.

Conclusions: Ultrasound guided mammotome biopsy of microcalcifications of breast can be successfully performed at experienced hand with high resolution ultrasound device.

Is it Necessary to Perform the Sentinel Lymph Node Biopsy for Breast Cancer Patients with Ductal Carcinoma In Situ (DCIS) Diagnosed by the Stereotactic Vacuum-assisted Breast Biopsy?

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Background/Purpose: The stereotactic vacuum-assisted breast biopsy (ST-MMT[®]) is standard procedure for non-palpable breast lesion with micro calcification in Japan. Furthermore, sentinel lymph node biopsy (SLNB) is also standard technique in clinical node negative breast cancer patients in worldwide. However, pure DCIS is not completely involved axillary lymph node metastasis. It is possible to avoid the SLNB in pure DCIS patients.

Methods: 1104 patients with micro calcification in mammography (MMG) were diagnosed by ST-MMT[®] from January 1999 to December 2008 in our institution. 130 patients were diagnosed as DCIS by ST-MMT[®], and were performed completely resection. The pathological feature of specimens obtained by ST-MMT[®] and surgical resection were compared.

Results: 26 patients (20.0%) were changed the final diagnosis from DCIS to invasive ductal carcinoma according to pathological feature of surgical specimens. Furthermore, axillary lymph node metastasis was involved by SLNB in 2 patients (1.5%) among 130 DCIS patients diagnosed by ST-MMT[®]. One patient was revealed extensive calcification in MMG. The final diagnosis was also widely DCIS without invasive component. The other patient was revealed localized calcification in MMG. The diagnosis by ST-MMT[®] was DCIS defined as three by Van Nuys classification with comedo necrosis. However, the final diagnosis by all serial specimen was invasive ductal carcinoma with small invasive part (9 × 5 mm).

Conclusions: In non palpable patients with micro calcification in MMG, many patients diagnosed as DCIS by ST-MMT[®] were not involved axillary lymph node metastasis and may be avoided SLNB. However, SLNB should be performed in patients with extensive calcification in MMG and high nuclear grade DCIS by ST-MMT[®].

Evaluation of Ultrasonographic-Guided Vacuum-Assisted Breast Biopsy

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Background/Purpose: Recently, vacuum-assisted breast biopsy system (VABB) has been widely used as an alternative to surgical open biopsy, because non-palpable and hypoechoic lesions were often detected by ultrasonography (US). The aim of this study was to evaluate the availability and complications of US-guided VABB, especially for hypoechoic lesions of breast.

Methods: 93 patients were undergone US-guided VABB from 2004 to 2008. US-guided VABB were performed in 647 patients requiring histological diagnosis. Additionally, there were 243 patients of identifying pathological type before neoadjuvant chemotherapy and 3 of fibroadenoma removal. Histological type was evaluated at US-guided VABB and at surgical excision in patients with breast cancer who were detected by US-guided VABB.

Results: 276 (42.6%) patients were malignant and 371 were benign by pathological diagnosis using the US-guided VABB samples in 647 patients. Ultrasound finding was showed the hypoechoic lesion and mass lesion in 208 patients (32.3%) and 393 patients, respectively. 78 of 208 patients with hypoechoic lesion (37.5%) were diagnosed as breast cancer in US-guided VABB samples. Among them, 32 patients (41.0%) were categorized as ductal carcinoma in situ (DCIS). In mass cases, 179 of 393 patients (45.5%) were malignant, and 24 (14.5%) were diagnosed as DCIS. The population of DCIS diagnosed by US-guided VABB for hypoechoic lesion was significantly higher than that for mass lesion.

Conclusions: In regard to diagnosis of breast cancer, US-guided VABB is a useful method for not only mass lesion but also hypoechoic lesion. Especially to perform US-guided VABB in patients with hypoechoic lesion, DCIS is able to be highly detected.

The Utility of ^{18}F FDG-PET/CT for Evaluation of Axillary Lymph Node Status in Invasive Ductal Carcinoma

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Background/Purpose: ^{18}F FDG-PET/CT has been recommended as a preoperative staging modality of advanced breast cancer, but the availability of ^{18}F FDG-PET/CT is still remained controversial. This study was designed to give ideas using ^{18}F FDG-PET/CT for axillary lymph node (ALN) metastasis of invasive ductal carcinoma by comparison positive with negative result group.

Methods: The subjects are consisted of 176 patients with invasive ductal carcinoma who underwent operations on Pusan National University Hospital from Jan. 2007 to Dec. 2008 and preoperative ^{18}F FDG-PET/CT. Among 65 patients with metastatic ALN confirmed on permanent pathologic result, 31 patients with and 34 patients without suspicious ALN metastasis on ^{18}F FDG-PET/CT scan were defined as group A and B.

Results: Group A was related with malignant potential of breast cancer (high histologic grade and score of c-erbB2, p53 expression, presence of necrosis and lymphovascular invasion) and ALN status (higher Nstage). The analysis of group statistic revealed group A had relatively large primary tumor and metastatic LNs, high expression of Ki-67 and many metastatic LNs than group B. In the listed categories, each cut-off values were 1.85 cm, 0.95 cm, 17.5% and 3 by ROS analysis.

Conclusions: The ^{18}F FDG-PET/CT for detecting ALN metastasis in invasive ductal carcinoma was related with high histologic grade of primary tumor. We demonstrated that the accuracy of ^{18}F FDG-PET/CT in detecting ALN metastasis is expected high when the tumor is bigger than 1.85 cm, Ki-67 is higher than 17.5%, number and maximum diameter of metastatic ALN is more than 3 and 0.95 cm. But ^{18}F FDG-PET/CT may not be necessary when ALN is bigger than 0.95 cm, because preoperative confirmation may possible by fine-needle biopsy.

Clinical Study of Lymphatic Drainage Region of Sentinel Lymph Node in Breast Cancer

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Background/Purpose: To validate the hypothesis that the lymphatic drainage of the entire breast, not just of the tumor region, is to the same few sentinel lymph nodes (SLN), through the clinical study of lymphatic drainage region of SLN.

Methods: From Apr. 2004 to Dec. 2008, 103 breast cancer patients were included in this study, who had the indications for sentinel lymph node biopsy (SLNB), but refused to accept the SLNB in stead of axillary node dissection. ^{99m}Tc-labeled filtered sulfur colloid (^{99m}Tc-SC) was injected subdermally directly over the breast tumor in all cases, and dye tracer was injected subdermally into the subareolar location in 73 cases or the diagonal quadrant. All patients received axillary node dissection following SLNB.

Results: With the combination method, ^{99m}Tc-SC, and dye, the SLN identification rate was 100%, 97.1%, and 95.1%, respectively ($p=0.286$), and false negative rate was 7.9%, 8.1%, and 8.1%, respectively ($p=0.999$). In the 95 patients with SLN identified successfully with both ^{99m}Tc-SC and dye, there were at least one SLN that was both blue and nuclide-labeled. The ^{99m}Tc-SC/dye concordance rate was 100% (Spearman coefficient correlation 0.695, $p<0.01$).

Conclusions: Our results showed that the lymphatic drainage of the different location of the breast (the breast tumor site, the subareolar plexus, and the diagonal quadrant) lead to the same SLNs, and validated the hypothesis that the lymphatic drainage of the entire breast, not just of the tumor region, is to the same SLNs. The new concept of SLN conduced to the individualization of the tracer injection site and the enlargement of the SLNB indications.

Feasibility of Sentinel Lymph Node Biopsy after Primary Systemic Chemotherapy in Clinically Node-Positive Patients

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Background/Purpose: This study evaluated the feasibility of sentinel lymph node biopsy according to clinical axillary response after PST in node-positive patients at the initial diagnosis.

Methods: We analyzed 70 operable breast cancer patients with clinically positive lymph node at presentation and receiving PST. Before and after PST, the axillary evaluation was performed with physical examination and ultrasound imaging, and we evaluated the histologic finding of abnormal lymph nodes using ultrasound-guided fine-needle aspiration (FNA) cytology before PST. All patients underwent definitive breast surgery with SLN biopsy and concomitant axillary lymph node dissection.

Results: Twenty-six patients (37.1%) had clinical complete response (cCR), and 18 (31.0%) out of the 58 FNA-positive patients had pathologic complete response (pN0). The overall SLN identification rate was 87.1% (61/70) and the mean number of identified SLN was 2.8 (1-8). There was no significant difference in SLN identification rate according to clinical axillary response (cCR vs non-cCR). In final histology, metastatic axillary lymph nodes were observed in 42.3% of the cCR group and 77.3% of the non-cCR group and, there was a significant difference between two groups. Six patients with negative sentinel nodes had positive non-sentinel nodes after the final pathologic examination (false-negative rate: 15.4%) and the overall accuracy of SLN biopsy were 90.2%. According to clinical axillary response after PST, FN rate was 0% (0/9) in cCR group and 20.0% (6/30) in non-cCR group.

Conclusions: This study suggests that SLN biopsy after primary chemotherapy is feasible in node-positive patients with clinical complete axillary response after PST.

Evaluation of Serum HER2 Extracellular Domain in Breast Cancer Patients: Correlation with Clinicopathological Parameters

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Background/Purpose: We explored the correlation between serum HER2 ECD and tissue HER2 status, their relationship with clinicopathological parameters.

Methods: We included 131 patients with stage 0-4 breast cancer. The serum HER2 ECD level was measured by the use of a chemiluminescence immunoassay (ADVIA centaur[®] system). And tissue HER2 status was analyzed by immunohistochemistry (IHC) and fluorescence in situ (FISH) in all tumors. We reviewed the medical record retrospectively, the included clinicopathological parameters are age, primary tumor size, lymph node involvement, stage, ER, PR, CA 15-3.

Results: High serum HER2 ECD levels (>15 ng/ml) were reported in 19 patients (14.3%). For tissue HER 2 status, 32 patients (24.1%) had a positive FISH and 48 patients (36.1%) had strong positive IHC (3+). The specificity of serum HER2 ECD is 90.9% but the sensitivity is only 31.3%. The concordance between serum HER2 ECD and tissue HER2 status is 25.7%. High serum HER2 ECD levels were significantly associated with tumor size ($p=0.028$), lymph node involvement ($p=0.004$), advanced stage ($p<0.001$), high level of CA 15-3 ($p<0.001$). No statistical relationship was found between HER2 ECD levels and the other clinical factor, such as age, ER, PR.

Conclusions: Serum HER2 ECD test cannot be substituted for tissue HER2 status because of low sensitivity. But high level of serum HER2 is associated with advanced stage and high level of CA15-3. We need to study serum HER2 ECD test as role of tumor marker or prognostic marker.

Limitations of Conventional Contrast-Enhanced MRI in Selecting Sentinel Node Biopsy Candidates among DCIS Patients

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Background/Purpose: A better predictive model for occult invasive disease in ductal carcinoma in situ patients (DCIS) is essential to guide the tailored use of sentinel node biopsies. We hypothesized that recent improvement of contrast-enhanced breast magnetic resonance imaging (MRI) could provide more accurate information on the presence of occult invasion in DCIS patients.

Methods: From a prospectively maintained database, we identified 143 DCIS patients diagnosed with needle biopsies in whom MRI images were available.

Results: Sixty-five patients (45.5%) were upstaged to invasive carcinoma after curative surgery. Ultrasonographic lesion size, mass-appearance on mammography, type of needle used, and the presence of suspicious microinvasive foci were associated with increased likelihood of upstaging. Among the features of MRI, only mass-appearance was significantly associated with presence of invasive disease ($p=0.002$). However, up to 50% of mass on MRI cases had mass-appearance on mammography as well. Other morphologic and pharmacokinetic features of MRI, such as shape, margin, and patterns of enhancement and washout, did not have significant association.

Conclusions: Our results show the limitations of current contrast-enhanced MRI in predicting invasive disease in patients with preoperative diagnoses of DCIS. Further studies on novel imaging or molecular methods are needed to optimize the selective use of sentinel node biopsy in DCIS patients.

Papillary Neoplasm of the Breast Diagnosed with Core-Needle Biopsy-are there Any Predictive Factors to Differentiate Benign from Malignant Lesion before Surgery?

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Background/Purpose: Determining benign from malignant lesion is necessary to avoid unneeded operation for patients who were diagnosed with papillary neoplasm on core needle biopsy. The purpose of this study was to identify predictive factors to differentiate papilloma from papillary cancer of the breast.

Methods: From January 2004 to May 2009, 133 patients who were diagnosed with papillary lesion in Korea University Hospital were reviewed retrospectively. Clinical features, mammographic and sonographic images were compared.

Results: There were 103 patients who received core-needle biopsy and papillary neoplasm was diagnosed in 55 patients. Final pathologic report after surgery reported 7 (12%) patients as papillary cancer and 48(88%) patients as intraductal papilloma. Patients who were over 60 years old were more likely to have papillary cancer (n=3, 42.9%) than papilloma (n= 2, 4.3%) (p=0.001). There were 6 (85.7%) cancer patients who had lesion more than 1cm where 15 (33.3%) had lesion more than 1 cm (p=0.009). On mammographic features, irregular shape was more found in cancer patients (p=0.04) but not on ultrasonogram (p=0.539). As for sonographic features, calcification was the only factor that had statistical significance (p=0.002).

Conclusions: Patients who are more than 60 years old, have lesion more than 1 cm, irregular shape on mammography and calcifications on ultrasonogram should be strongly recommended to have surgery.

Predicting Axillary Lymph Node Involvement in Breast Cancer Patients by Ultrasonography

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Background/Purpose: About 20% of breast cancer patients eligible for sentinel node (SN) biopsy have axillary node metastases. The purpose of this study is to evaluate the sensitivity of preoperative ultrasonography (US) and computed tomography (CT) for SN involvement.

Methods: Between October 2004 and December 2007, a total of 311 breast cancer patients without clinically node involvement were eligible for SN biopsy. The size (length and height) and cortical thickness of lymph nodes (LN) was measured by US before surgery. LN status was also evaluated by enhanced CT.

Results: Sixty-two (20%) of 311 patients had pathologically involved LN (Positive Group), and 249 (80%) were negative for LN metastases (Negative Group). The number of detected LN by US was more in the positive group than the negative group (1.73 vs. 1.49, $p < 0.05$). There was no significant difference in the size of LN by US between the two groups. The cortical layer of LN was thicker in the positive group than the negative group (3.01 vs. 2.07, $p < 0.001$). Eighteen (51.4%) of 35 patients who had a LN with more than 4mm cortical thickness revealed to have a metastatic LN. Twenty-three (67.6%) of 34 patients who had swollen LNs by CT, and seven (87.5%) of eight patients who had a LN with 4 mm of cortical thickness by US and swollen LNs by CT were positive for LN metastasis.

Conclusions: Evaluation of axillary LN by US and CT before surgery is useful for predicting axillary LN involvement. This approach may improve the selection of patients for SN biopsy.

Comparison of Synchrotron Images of Paget's Disease of the Breast with their Pathologic Findings

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Background/Purpose: Synchrotron radiation x-ray imaging have revealed its possibilities to evaluate various breast diseases non-invasively. Using phase contrast technique, we got monochromated synchrotron images of Paget's disease of the breast tissue section. To figure out relation with their optical microscopic features, we compared the synchrotron images of the Paget's disease with their histopathologic findings of the same stained section.

Methods: A x-ray microscope was installed on 1B2 beamline of Pohang Light Source. Zernike phase-shifter was adapted for phase contrast microscopy. Formalin-fixed 5 μ m-thick breast tissue sample was attached onto the Kapton film for imaging. After scanning, we patched these images one and another to show the large area of the tissue section.

Results: The monochromated x-ray microscopic images of Paget's disease of the breast tissue section showed the large lacuna-shaped Paget cells within the epidermis of nipple. The Paget cells revealed large electron-dense nuclei and electron-lucent abundant cytoplasm with distinct cell outlines, and they were seen isolated or in clusters along the basal layer but often permeating the epidermis. The infiltration of inflammatory cells and profuse collagen strands were well recognized even in the low power synchrotron images, but the squamous epithelium of epidermis was not.

Conclusions: The x-ray microscopic images of Paget's disease of breast with synchrotron radiation showed a good correspondence with the histopathologic findings of their stained tissue sections, and revealed the characteristic Paget cells within the epidermis. Therefore the synchrotron imaging of Paget's disease could be applied for the clinical and research purposes in the future.

Can Sentinel Node Biopsy Be Avoided in Some Ductal Carcinoma In Situ with Microinvasion?

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Background/Purpose: The rise in use of screening mammography has led to diagnosis of breast cancer at increasingly earlier stages. SLN biopsies haven't been performed in cases where we performed a conserving operation with small sized DCIS. But sometimes we can find DCIS with micro-invasive breast cancer (MIC) after operation. Should another operation be performed? To determine whether SLNB should be performed.

Methods: Between July 1989 and January 2008, 9,917 patients had operations performed on breast cancers at Asan Medical Center. Among these patients, Between July 1989 and February 2003, ALND was used to surgically stage the axilla. Beginning in May 2003, SLNB has been routinely performed on all patients. Clinical and Pathologic factors investigated included age, multifocality, presence of a palpable tumor, DCIS size, ER status, PR status, and histologic grade.

Results: 265 patients were identified with microinvasive breast cancer. Among these patients, 12 patients didn't have ALN study. 2 patients had bilateral MIC. The research was conducted on the remaining 255 cases. There were 13 cases of ALN metastases identified in this group of patients (5%). Young age ($p=0.006$), multifocal lesion ($p=0.033$) and lymphatic invasion ($p<0.0001$) were predictive factors for ALN metastases.

Conclusions: As the incidence of ALN metastasis in DCIM patients is very low, particularly in those <50 years old, patients with single lesions, and those without lymphatic invasion, conservative treatment may be optional for such patients. The relatively small number of patients examined in the present study indicates a need for validation of our results through extensive prospective research.

Use of Intraoperative Frozen Section Analysis of Sentinel Lymph Node Biopsy in Breast Cancer

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Background/Purpose: To review the accuracy and technical success of intraoperative frozen section of sentinel lymph nodes in a university based institution.

Methods: Between January and December 2008, 57 consecutive patients with biopsy proven stage 0-II breast cancer and a clinically node negative axilla underwent 60 sentinel lymph node biopsies (SLNB). A combination of radioisotope 99mtechnetium (Tc)-albumin sulphur colloid and Patent Blue V dye was used to identify SLN. SLNs were analyzed using standard frozen section procedures. Patients with positive SLN identified underwent axillary dissection during the same surgery. Paraffin sections of SLN were then reviewed. Patients who had false negative (FN) SLN received delayed axillary dissection.

Results: 60 SLNBs were performed during the study period. SLNs were successfully identified in all patients (identification rate 100%). The mean number of SLN identified was 3.7 (range 1-10). Intraoperative FS correctly identified positive SLN in 10 patients (76.9% sensitivity rate), 3 (5%) patients had FN SLN on frozen section and required delayed axillary dissection, with a FN rate of 23.1%. Among the 3 patients, 2 patients had micrometastases. The 2 patients who had micrometastatic disease in SLN did not have residual disease in the remaining axillary content. SLN metastasis was not observed in patients with DCIS. All SLNs found involved in frozen section were confirmed to harbor tumor cells on subsequent paraffin section (100% specificity and positive predictive value). Accuracy rate was 95%.

Conclusions: Sentinel lymph node reliably avoided unnecessary axillary dissection in the majority of patients with early breast cancer.

Alpha B-crystallin as a Novel Marker of Lymph Node Metastasis in Breast Cancer

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Background/Purpose: α B-crystallin, a member of small heat shock protein, is known as an anti-apoptotic protein and is associated with aggressive tumor behavior. In addition, recent study revealed that α B-crystallin was overexpressed in metastatic variant of the GI101A human breast carcinoma cell line. The purpose of this study was to investigate whether expression of α B-crystallin was associated with lymph node metastasis. And also we evaluated the relationship of expression of α B-crystallin and other established prognostic factors.

Methods: Eighty two patients who underwent breast cancer surgery and chemotherapy at Hallym Sacred Heart Hospital were enrolled. Expression of α B-crystallin was determined by immunohistochemical staining using monoclonal antibody (SPA-222, Stressgen Biotech, Victoria, British Columbia, Canada) and graded as negative=0, weakly positive=1, moderately positive=2 and highly positive=3. Estrogen receptor, progesterone receptor, HER-2, lymphatic tumor emboli, histologic grades and other tumor markers were compared with α B-crystallin expression.

Results: Expression of α B-crystallin in breast cancer tissues was associated with lymph node metastasis ($p=0.01$), lymphatic tumor emboli ($p<0.01$), high nuclear grade ($p=0.02$) and triple negative status ($p=0.02$). Five of 6 visceral metastasis cases showed high expression of α B-crystallin.

Conclusions: A strong relationship between lymph node metastasis, visceral metastasis and α B-crystallin expression in breast cancer has been found. And also the expression of α B-crystallin significantly correlated with triple negative breast cancer. We suggest that α B-crystallin could be a novel marker of lymph node metastasis and a good prognostic factor of breast cancer.

Does it Need Further Diagnostic Surgery for Benign Papillary Lesion Diagnosed by Large Volume Vacuum Assisted Biopsy (Mammotome)?

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Background/Purpose: There is ongoing controversy regarding the management of papillary lesions diagnosed by core needle biopsy (CNB). Some authors advocate observation of papillary lesions when the CNB is benign, while others recommend surgical excision of all papillary lesions because of high underestimation rates. Our aim was to evaluate whether papillary lesions diagnosed by vacuum assisted biopsy can be followed up without further diagnostic excision.

Methods: From Jan. 2003 to Feb. 2007, a total of 2751 US-guided mammotome excision were performed in 2226 patients at Kangnam Cha hospital. Among these, 82 lesions which the histologic findings were consistent with benign papillary lesions and followed up more than 2 years without further diagnostic surgical excision were collected and analyzed retrospectively. All lesions were removed by 8 gauge probe without any residual lesion. Ultrasonographic follow-up were made on 3-6 months interval to assess recurrences. Mean follow up period were 49.5 months.

Results: The pathologic diagnoses for the 82 lesions obtained at VABB were benign intraductal papilloma, papillomatosis. Mean patient age was 40.2 years. The average size of lesion was 1.0 cm. 50.0% (41 cases) were palpable. 28 lesions (34.1%) were classified as USG BIRADS category 3, 50 lesions (61.0%) were category 4A, 3 lesions (3.7%) were category 4B, and only 1 lesion (1.2%) was category 5. During follow up period, there had been no local recurrence developed which need surgical re-excision or re-biopsy.

Conclusions: Benign papillary lesions diagnosed and excised by mammotome biopsy system may not need further diagnostic surgical re-excision if surgeons are sure that the targeted lesions were excised completely.

Personal and Social Factors Affecting Mammography Screening in Married Korean Women

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Background/Purpose: The purpose of this study was to identify the personal and social factors affecting mammography screening in married Korean women. The personal factors were breast cancer risk appraisal, perceived susceptibility and the social factors were social network, social support, social influences.

Methods: The data used in this study were collected from 202 married women aged 35 and above using public health centers, health promotion center, cultural centers, obstetrics and gynecology hospital and married women in the community. The interviews were conducted from October 24 to December 4, 2008 using a standard, structured questionnaire. Descriptive statistics, χ^2 test, independent t-test, one-way ANOVA and multiple logistic regression analysis with the SPSS 15.0 program.

Results: 1. Participation rate of mammography screening was 35.8%. 2. The social factors which show statistically significant differences between participating group and non-participating group were; (1) social norms, beliefs about the proportion of age peers who undergo regular mammography screening ($t=-5.07$, $p<0.01$), (2) subjective norms, defined as the extent to which social network members approved of mammography ($t=-4.03$, $p<0.01$). 3. Using multiple logistic regression analysis; the variables which were regular medical-care, breast cancer risk appraisal, social norm and subjective norms were so highly predictive of subsequent mammography, that controlling.

Conclusions: With the result of this study, if we develop and activate the tailored intervention program and socially mediated program which is including all concern about social network, social supporting system, early detecting breast cancer will not be ended as one time event, and with this network structure, regular mammography screening can be operated continuously.

Sentinel Lymph Node Biopsy in Combination with Pathological Tumor Response Predicts Pathological Nodal Status after Neoadjuvant Chemotherapy in Women with Clinically Node Positive Breast Cancer

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Background/Purpose: Sentinel lymph node biopsy (SLNB) is not a standard care in women with clinically node positive breast cancer even if their nodes seem to be negative after neoadjuvant chemotherapy. In this study we determined whether SLNB predicted pathological nodal status after neoadjuvant chemotherapy in women with clinically node positive breast cancer.

Methods: A series of 86 breast cancer cases with clinically positive nodes and no distant metastasis that were treated with neoadjuvant chemotherapy followed by SLNB and completion ALND were included in this study. Clinical tumor size, clinical nodal status, hormone receptors, age and body mass index at baseline, and clinical tumor response, pathological tumor response, chemotherapy regimen, lymphatic vessel invasion (LVI) and SLNB were analyzed for correlation with pathological nodal status.

Results: In 38 cases with a negative SLNB, 33 (86.8%), 4 (10.5%) and 1(2.6%) had pN0, pN1 and pN2 diseases (UICC TNM), respectively. A false-negative (FN) rate of SLNB was 9.4%. In 24 cases with a pathological complete response, 21 (87.5%), 2 (8.3%) and 1 (4.2%) had pN0, pN1 and pN2 diseases, respectively. In 21 cases with a negative SLNB and pathological complete response, all had pN0 disease. LVI and hormone receptors were also correlated with pathological nodal status with less significance than the previous two factors.

Conclusions: SLNB was reported not to be accurate in women with clinically node positive breast cancer who had received neoadjuvant chemotherapy. In this study, however, SLNB in combination with pathological tumor response well predicted pathological nodal status in these patients.

Recent Clinical Features and Treatment of DCIS

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Background/Purpose: Today, DCIS is diagnosed with increasing frequency by screening MMG, and comprises over 15% of all breast cancers. The aim of the present study is to evaluate the recent clinical features and treatment of DCIS.

Methods: We compared the preoperative diagnosis and treatment of 70 DCIS diagnosed and operated at Kitakyushu Municipal Medical Center between 2000 and 2004, with those of 120 DCIS between 2005 and 2007.

Results: Mammographically detected DCIS remarkably increased recently, and microcalcifications on MMG are the most common presentation of DCIS. Ultrasonography reveals more hypoechoic lesions, calcification, and duct ectasia in the latter period. The presence of calcification in MMG is found in 69.1% of cases, and the extent of it tends to be smaller, although it remains large in some DCIS in the latter one. Histological preoperative diagnosis as non-invasive ductal carcinoma becomes 77.5% by increasing use of core needle biopsy or mammotome. Breast conserving surgery for DCIS with calcification increases from 39.5% to 47.9%. Sentinel lymph node biopsy has become an alternative to axillary lymph node dissection.

Conclusions: DCIS is increasing mainly due to MMG screening, and most mammographically detected DCIS shows calcification. It tends to be discovered as a smaller one, and breast conserving surgery is performed more frequently.

Quality of Life among Asian American Breast Cancer Survivors with Limited English Proficiency

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Background/Purpose: Little is known about quality of life (QOL) among Asian American breast cancer survivors with limited English Proficiency. This paper presents the results of a descriptive study evaluating the QOL among Asian American breast cancer survivors.

Methods: Breast cancer patients diagnosed within the previous 5 years participated in face-to-face interviews. Participants were recruited from media, hospitals and cancer supports groups.

Results: The sample was 95 breast cancer survivors with a mean age of 56.6 years. Most were diagnosed with early-stage breast cancer (Stage 0-II). Of the participants, 75.8% of participants received chemotherapy, 53% had received radiation therapy, and 47.9% had undergone a lumpectomy. The mean time since breast cancer diagnosis was 29.8 months. This study is based on our conceptual model of QOL including physical, psychological, social, and spiritual well-being. Based on scoring of 0 (worst outcome) to 10 (best outcome), the overall QOL score was 4.75. Age was significantly and negatively correlated with QOL score ($r=-0.361$, $p<0.0001$). Acculturation was significantly correlated with QOL. Comparison of the four domains indicates greatest needs in the area of physical well-being (3.06) followed by social well-being (4.50), psychological well-being (5.43), and spiritual well-being (6.30).

Conclusions: Results show the need of culturally appropriate programs for Asian American breast cancer survivors with limited English proficiency. The study findings will assist in the development and testing of culturally and linguistically appropriate educational resources that meet the psychosocial need of Asian American breast cancer survivors. The project was funded by a grant from Susan G Komen Foundation.

The Use of External Breast Prosthesis on Korean Breast Cancer Patients

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Background/Purpose: This study was done to evaluate the experiences and preferences regarding breast prosthesis and bras in Korean breast cancer patients.

Methods: With a descriptive design, 61 women with breast cancer who have received a modified radical mastectomy were recruited from a breast clinic in a university hospital in Seoul. A structured questionnaire was developed to measure the experiences of breast prosthesis, and data collection was done twice at the time they had first the fittings and one month after.

Results: Eighty-seven percent patients preferred soft and light products than just light things because those were more natural. The deeper and larger their wound was, the more they preferred asymmetric shapes. Women were not likely to wear prosthesis because it was bothersome, feeling hot or not to make it worn out. Concerning with bras, 8% patients needed additional joint at the end of the bra due to their small breast size. Body shapes of the patients who started wearing the prosthesis after 12 months from surgery were found to be distorted due to the unbalanced vertebra. But if their breast volume was more than 345 ml (size 6), they tended to have distorted vertebra only after 3 months from the surgery.

Conclusions: Fitting breast prosthesis is for therapeutic weight replacement as well as cosmetic purposes. So the nurses should inform the patients that they wear it all day long and be fitted at least within 12 months after the surgery. And bras with smaller cups are needed to be developed.

A Randomized Trial of Simultaneous Stage-Matched Exercise and Diet Interventions for Breast Cancer Survivors

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Background/Purpose: There are only a few randomized controlled trials investigating the effects of a simultaneous exercise and diet intervention for cancer survivors. The purpose of this study was to examine the effectiveness of simultaneous stage-matched exercise and diet interventions (SSED) based on a transtheoretical model (TTM) in breast cancer survivors.

Methods: We randomly assigned 45 women who had been treated for breast cancer 2 years previously to a SSED intervention group (n=23) or a waiting-list control group (n=22). The 12-week individualized intervention promoted regular exercise and a balanced diet through stage-matched telephone counseling and a workbook. We measured stage of change for exercise and diet, physical activity as MET-h/week of aerobic exercise and with the self-administered International Physical Activity Questionnaire; diet quality with the Diet Quality Index; and quality of life variables with EORTC QLQ-C30, the Brief Fatigue Inventory, and the Hospital Anxiety and Depression Scale.

Results: Compared with the control group, the SSED intervention group showed significantly greater improvement in motivational readiness of exercise and diet (p=0.006, and p<0.001, respectively), and emotional functioning (p=0.004) and less pain (p=0.001), insomnia (p=0.057), fatigue (p=0.001), and depression (p=0.035). However, the SSED intervention group did not show significant improvements in physical activity, diet quality, and some QOL outcomes.

Conclusions: Despite small sample size and short follow-up time, our results suggest that culturally-appropriate SSED interventions delivered via telephone are feasible and beneficial for behavioral and QOL outcomes.

Effects of a Psychoeducational Intervention on Successful Transition from Treatment to Survivorship in Breast Cancer Survivors

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Background/Purpose: Quality of life during post-treatment breast cancer survivorship is a relatively new, emerging, and promising area of investigation. The purpose of the study was to examine the effectiveness of psychoeducational intervention on quality of life, symptom experience, and resilience in breast cancer survivors in post-treatment survivorship.

Methods: 42 breast cancer survivors who had completed surgery and adjuvant therapy (chemotherapy or radiation) one month before recruited from a medical center. Subjects were assigned to either the 12-week psychoeducational intervention group or usual care group. The psychoeducational intervention consisted of individual face-to-face education and support session, two weekly telephone and face-to-face education follow-up and 6 weekly support group during 12 weeks. The baseline measurements together with the longitudinal data enable comparison before and after the intervention. Research variables were quality of life and resilience.

Results: No difference in QOL and resilience were reported at baseline between groups. But at 12 weeks later, the experimental group had higher scores (i.e., improved QOL) compared to the control group in QOL. The results were evident in psychological well-being scores between two groups. In resilience, the experimental group reported improved scores at 12 weeks whereas the control group reported no significant difference.

Conclusions: The psychoeducational intervention was an effective intervention in improving QOL and resilience during the first year of breast cancer survivorship. This result supports the need to better prepare women for transition from treatment to survivorship.

Post-Treatment Breast Cancer Surveillance: A Need Assessment for Care Continuity

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Background/Purpose: Care continuity for breast cancer survivors recently obtains public and academic attentions since the number of survivors increases every year by virtue of medical advances. In order to develop an efficient surveillance model for survivors, the need assessment should precede all others. The purpose of this study was to investigate the physical and psychosocial needs of patients who completed medical treatment for breast cancer.

Methods: A mixed method was used for this study. For qualitative inquiry, in-depth individual interviews with fifteen informants were conducted. A survey for quantitative inquiry was conducted with 93 survivors utilizing the MDASI (M.D. Anderson Symptom Inventory) and an investigator-developed questionnaire for symptom management. The interviews and surveys were administered in an urban cancer center out-patient clinic. The interviews were tape-recorded, transcribed, and analyzed using a thematic analysis method. The surveys were analyzed using SPSS program.

Results: The main theme elicited from the qualitative data was 'Feeling alone in the uncertain journey' illustrating the lack of care continuity and struggles with uncertainty of the patients who are out of the intensive medical treatment. The most frequent symptoms experienced were sadness and distress which implies that psychosocial aspect should be the target for the care of the survivors. In addition, symptom management in out-patient setting is reported very poor.

Conclusions: The findings of the study shed light on the lack of care continuity of current medical system for breast cancer survivors. The detailed qualitative and quantitative findings are reported and further implications for research are discussed.

Information about Shanghai Cancer Recovery Club & School

Zhou Pei¹

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Background/Purpose: The face of death changes in disease spectrum. Modern medicine is facing deep changes; we look forward to change the medical concept of starting to rebuild a life in patients with treatment goals for the center.

Methods: Founded in 1989, SCRC is a member of 10,000 cancer patients with self-help mutual aid societies. Of these, 3,000 patients with breast cancer. SCRC founded the school, 15 years have been held 70 terms & 300 groups of activities, set up 8 disease centers. Among them, BCRC group psychotherapy, physical exercise, pleasure therapy, dance therapy sound, other than diet, such as drug treatment.

Results: In means to help patients with awareness and treatment will be combined to broaden the way of rehabilitation. Club formed a team of breast cancer patients, fashion team, dance team, harmonica team, choir, crafts such as weaving interest groups to enhance the quality of life. Of more than 3,000 breast cancer patients with a comprehensive survey: 71.9% think that anti-cancer activities of groups have a strong appeal. 71.8% think that life has always been very happy: 81%.

Conclusions: Social point of research and Traditional Chinese Medicine “seeking medical treatment”, “overall Constant action” concept to the WHO definition of health to consider new anti-cancer groups, the “Shanghai model” meaning treatment. This is not only a form of scientific knowledge, but also a humanistic understanding of life and humanitarian moral practice.

Effect of Taxane-Based Chemotherapy for Early Stage Breast Cancer on Extra-and Intracellular Fluid Volumes

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Background/Purpose: One side effect associated with taxane-based chemotherapy for early breast cancer is peripheral edema. The aim of this study was to describe the time-course of changes in extra- and intracellular fluid (ECF and ICF respectively) in both upper and lower limbs of women treated with taxane-based chemotherapy for breast cancer.

Methods: Twenty women who received 3 cycles of FEC (5-fluorouracil, epirubicin, cyclophosphamide) followed by 3 cycles of docetaxel for node-positive breast cancer were assessed prior to, every 3 weeks during, and at the end of chemotherapy. ECF and ICF in limbs were measured with bioimpedance spectroscopy (BIS) on each occasion.

Results: Six women showed increased ECF in their affected arm compared to the unaffected arm at the end of docetaxel but not during or at the end of FEC. Four of these women had an impedance index above the cut-off indicative of lymphedema at the end of docetaxel. Notably, those women with increased ECF in their affected arm also had increased ICF in the same arm. ECF and ICF of the unaffected arm and the legs showed slight fluctuation during and at the end of docetaxel but remained within the normal range. ECF and ICF were also in the normal range in all limbs of the remaining 14 women.

Conclusions: Taxane-based chemotherapy for breast cancer treatment may increase extra- and intracellular fluid in the arm on the affected side and at risk of lymphedema but not in their other limbs.

Illness Experience of Women with Breast Cancer in Korea: Using Feminist Perspective

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Background/Purpose: Breast cancer is the most prevalent cancer among women in Korea. However, the illness experience of women with breast cancer is not well known in Korean society where breast cancer is highly stigmatized. The purpose of this study was to explore the illness experience of Korean women with breast cancer using a feminist perspective.

Methods: Qualitative research. Data were collected by individual in-depth interviews from six women with total mastectomy with audio-taping. The data were analyzed using thematic analysis with feminist perspective to reveal implicit socio-cultural norms that oppress women with breast cancer in a patriarchal society.

Results: Seven major themes emerged: (1) unfairness of having breast cancer; (2) getting stuck into the “illness-world”; (3) struggling to keep on being a good mother; (4) hardness of being a daughter-in-law; (5) recognizing self as a precious wife; (6) social disgrace; and (7) awakening of true self. All women felt it was very unfair to get breast cancer, because they had done their best to carry their weight in roles of a mother, a wife, and a daughter-in-law. They could not continue to carry out these roles once they were in the “illness-world”, where death is close. By awakening their true self, they could manage balance between other-oriented life and self-oriented life, thus feeling more fairness.

Conclusions: Oncology professionals need to support women with breast cancer in finding their true self in a traditional patriarchal culture where the family and society oppress women.

The Effects of Lavender Foot Bath on Psychological Suffering, Sleep, and Fatigue in the Breast Cancer Patients after Surgery

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Background/Purpose: The purpose of the study is to examine the effects of lavender foot bath (LFB) on sleep, perceived psychological suffering (PPS), and fatigue of the breast cancer patients after surgery.

Methods: In a time series design, 4 observations (before LFB, before 3rd, before 5th, and one week after) were made from the 14 breast cancer patients not receiving pain medications with a convenience method. 5 time LFBs from 4th post op. to 12th post op day were made every other day. The subjects bathed their feet in the 5 drop essential oil added 40°C water foot bath tub for 15 min in the afternoon. The night sleep times (ST), awakening episodes (AE), and the PPS and fatigue on 100 mm VAS over 2 days before each observation were measured. None-parametric and descriptive statistics were used.

Results: The means of ST at each observations showed increase tendency (13.9 hr, 13.8 hr, 14.7 hr, and 15.2) while the means of AE showed somewhat decrease tendency (5.2, 3.3, 3.8, and 2.8). There were significant differences in PPS among the sequential data except that between the 3rd and the 4th. The differences between the 2nd and the 3rd and between the 2nd and the 4th in fatigue showed statistical significances. The mean of PPSs and fatigues showed decrease tendency from the 1st to the 3rd but a little increase between the 3rd and the 4th.

Conclusions: The results implies LFB could decrease PPS and sleep disturbances and fatigues of the breast cancer patients after surgery.

The Distress and Quality of Life of Breast Cancer Survivors in Korea

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Background/Purpose: The number of breast cancer survivors has increased over the past several years due to increased incidence and survival rates in Korea. The purpose of this study was to explore the distress and quality of life of Korean breast cancer survivors.

Methods: The data were collected by survey interviews from 122 breast cancer survivors who were in between 6 months and 2 years after the completion of cancer treatments without recurrence. The ‘distress thermometer and problem list’ and ‘functional assessment cancer therapy-breast’ were used to measure the distress and quality of life respectively. The subjects were instructed to identify on the distress thermometer a number from 0 (no distress) to 10 (extreme distress) and to select “yes” or “no” on the problem checklist.

Results: The mean score of distress was 4.77 (± 2.35). The number of subjects having moderate to severe distress which ranked level 4 or greater on the thermometer was 77 (63.11%). The mean score of the quality of life was 88.22 (± 18.41), indicating 6.13 in terms of 10. The correlation between the distress and quality of life was negative ($r = -0.37810$, $p < 0.0001$).

Conclusions: The results of the study indicate that the distress is prevalent and the level of quality of life is relatively low among Korean breast cancer survivors. Thus oncology professionals need to pay attention to breast cancer survivors, by regularly assessing their distress and by providing appropriate psychosocial interventions to improve their quality of life.

Effects of Mother and Daughter Breast Health Program on Breast Cancer Screening Promotion

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Background/Purpose: The purpose of this study was to explore the effects of breast cancer screening education program for college students on their mother's breast cancer screening promotion.

Methods: This study was a one-group pretest and posttest design. Data were collected from September to November, 2007 from a sample of 80 college students and 80 their mothers using a survey questionnaire. The survey included measures of demographic variables, knowledge, concerns, and communication related to breast cancer, stage of change attitude (pros and cons) for mammography screening, and confidence for breast self-examination. College students who received the education about breast cancer for 50 minutes, educated their mothers about breast cancer. Data were analyzed with descriptive statistics and paired t-test.

Results: The mean age of college students was 22.01 years. Mothers ranged in age from 43 to 58 years, with a mean of 49.36 years. After receiving education on breast cancer, there were significant changes in mean scores of knowledge, concerns, and communication about breast cancer for college students and their mothers. Also, there were significant changes in mean scores of pros in mammography and confidence in practicing breast self-examination for mothers.

Conclusions: This study indicated that education on breast cancer to mothers through their college-age daughters are effective and could be utilized to promote the breast cancer screening behavior.

Psychosocial Needs of Low-Income Cancer Patients Receiving Home Care Services in Korea

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Background/Purpose: With an increasing number of cancer patients, oncology professionals have begun to pay attention to psychosocial problems. However, very few researchers have investigated the psychosocial needs of cancer patients in Korea, not to mention those of low-income cancer patients. The purpose of this study was to identify these needs of low-income cancer patients receiving home care services in Korea.

Methods: In the cross-sectional survey, 11 community health centers nationwide participated with a total of 238 subjects who were approached by home visiting nurses. The questionnaire consisted of 48 items across six domains on a scale of 1-5, indicating the importance for them. Cronbach's α for the study was 0.95.

Results: Thirty of the 48 items were important for more than 50% of the subjects. Among the six domains, 'health professionals' had the highest score (3.86) followed by 'information' (3.49), and 'support network' (3.45). The lowest domain was 'emotional and spiritual domain' (2.71) followed by 'daily activity' and 'identity'. In 'health professional', all items were demanded by over 50% of the subjects and the 'information' category all but only one item.

Conclusions: Unmet needs of low-income cancer patients were high although they had received home care services. They especially were in need of oncology professionals treating them with more empathy and respect, as well as various kinds of information. The results of the study would help oncology professionals develop more effective psychosocial interventions for low-income cancer patients in Korea.

Focus Group Study on the Psychosocial Distress of Cancer Patients in Korea

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Background/Purpose: Although health professionals recognize the negative impact of distress on the quality of life of cancer patients, the nature of distress is not yet well understood. The purpose of the study was to explore all aspects of cancer experiences, that is, the distress experienced by cancer patients in Korea.

Methods: Three focus group interviews were conducted to collect the data from 19 outpatients with cancer. All interviews were audio-recorded and transcribed verbatim. The data were analyzed using grounded theory method.

Results: Seven major categories emerged from the analysis. 'Physical symptoms', 'damaged self-identity', and 'emotional problems' were identified as major distresses in individual dimension. 'Family problems', 'inefficient communication', and 'lack of information' were identified in the dimensions of family and health care setting. 'Stigma and misunderstanding of lay people' was identified as a major distress in the dimension of society. To overcome these problems, the participants relied heavily on family support and individual endeavor such as having a positive mental attitude, in the absence of appropriate support from oncology professionals.

Conclusions: The result of the study indicate that to relieve the distress of cancer patients, changes are needed in the health care setting dimension, with more concentration on communication and information-giving to the patients. The result would help start up development of effective psychosocial interventions and distress tools that reflect the cultural and social context of Korea.

A Subjectivity Study on the Meaning of the Life of Breast Cancer Survivors: Focused on the Participation of the Support Groups

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Background/Purpose: This study basically aims to identify the types of meaning of life of breast cancer survivors applying Q-method based on the participation of support groups, and to develop efficient and personalized nursing strategies.

Methods: Q-statements are selected from the literature and interviews of 10 breast cancer survivors. Total number of 136 statements were collected and 35 Q-samples were finally selected. 60 breast cancer survivors were sampled to be divided equally into 3 groups depending on the degree of their participation in the support group (non-participants, recent participants, long participants). Q-sorting by each subject were coded and analyzed using the PC Quanl program.

Results: Four types of breast cancer survivors were derived from the Q-method. TypeI: 'self-centered life' TypeII: 'life of despair' TypeIII: 'life with receptive mind' TypeIV: 'life joining in a self-supporting group'.

Conclusions: This study has a significant contribution that this is the first trial to identify the usefulness of breast cancer survivors' access to the support group program empirically and to analyse its meanings. The group participating in the support group felt positive for the meaning of their lives. And it was confirmed that the participants in the support group for a shorter period of time were more reliant on the group, which suggests that the support group was more influential over their lives. This study also suggested nursing interventions depending on the types of the subjects. Finally, this study should be followed by the future studies to develop more effective nursing strategies as well as sustainable measures for each type of the breast cancer survivors.

Development of a Program for Anger Management Based on Self-Efficacy in Patients with Breast Cancer

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Background/Purpose: The purpose of this study was to develop a program for anger management based on self-efficacy.

Methods: In this study, four types of approaches to enhance anger control were developed: 1) a role play for vicarious experiences; 2) an assertive training for anger expression; 3) a 30-minute long education program & a 20-minute long telephone call coaching for verbal persuasion; and 4) a booklet for anger management and self care behaviors. One group pretest-post test design was used for evaluating the program. Study subjects were 6 cancer patients undergoing chemotherapy. The group were received a 4-week intervention, 60-90 minutes a day weekly, and measured the variables at baseline, 4 weeks later. Anger-in, anger-out, and anger-control were measured by STAXI-K. Data was analysed by Wilcoxon using SPSS 12.0 program. Anger situation was analysed into primary anger-thoughts and secondary anger-thoughts based on cognitive theories of anger.

Results: The program for anger management consisted of a role play, an assertive training, education, telephone call coaching and a booklet. The program revealed significantly less Anger-in ($Z=-1.997$, $p=0.046$), anger-out ($Z=-2.207$, $p=0.027$). No difference, however, was found in anger control ($Z=-1.826$, $p=0.068$).

Conclusions: This evaluation suggested that more assertive training and longer intervention may need to the anger control.

Choice of Chemotherapy for Metastatic Breast Cancer According to Intrinsic Subtypes

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Background/Purpose: According to the progress of translational research, we have to design the strategy of breast cancer treatment based on the prediction of medical efficacy in recent years. It is reported that the intrinsic subtypes distinguished by the expression of hormone receptor and HER2 are important predictive and prognostic factor. In this study we evaluated the efficacy of chemotherapy for metastatic breast cancer (MBC) according to intrinsic subtypes.

Methods: Eighty MBC patients who treated Okayama University Hospital (OUH) from 1998 to 2006 were enrolled. We evaluated time to recurrence (TTP), overall survival (OS), the number of chemotherapy regimens and duration of administration (DA) according to four subtypes (luminal A [A], luminal B [B], HER2 positive [H] and Triple negative [T]) retrospectively.

Results: The median age was 56 (range, 26-83). The sites of metastases were visceral, 68 (85%) and bone metastases, 12 (15%). A, B, H and T type were 36 (45%), 10 (13%), 18 (23%) and 16 (20%). The median TTR was significantly long in A type (59 months) ($p=0.006$), and OS was significantly short in T type (19 months) ($p=0.042$). The number of chemotherapy regimen for B and H type was more than A and T type. The DA of taxane for A type was significantly shorter than for T type (4.8 vs. 10.2, $p=0.018$). DA of anthracycline and oral Fu were similarly between four subtypes.

Conclusions: The number of chemotherapy regimen for patients with HER2 negative breast cancer was small. A type received hormone therapy. However T type received only chemotherapy and worse prognosis.

Expression of PTEN and its Correlation with Clinicopathological Parameters in Breast Cancer

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Background/Purpose: Phosphatase and tensin homologue (PTEN) on the chromosome 10q23 has been identified as one of the major tumor suppressor genes in human cancers. In breast cancer, mutations at the PTEN locus have been frequently reported but the relation of PTEN expression with clinical outcome remains to be controversial. The aim of this study was to analyze PTEN expression and to correlate it with clinicopathological parameters of breast cancer.

Methods: From September 2005 to December 2008, 397 consecutive patients with breast cancer, including 323 cases of invasive ductal carcinoma and 36 cases of ductal carcinoma in situ (DCIS), were evaluated for PTEN expression by immunohistochemical methods. The results were compared with the following clinicopathological parameters: age, menopausal status, size of primary tumor, multiplicity, histologic grade, nuclear grade, vascular invasion, axillary lymph node status, TNM stage, hormone receptor status, p53 and HER2 expression.

Results: All DCIS cases expressed PTEN, but 35 (9.7%) of the 361 invasive cases did not express PTEN. The PTEN expression was associated with tumor size ($p=0.021$), vascular invasion ($p=0.002$), ER ($p=0.001$), PR ($p=0.015$), HER2 ($p=0.033$), but not with age, menopausal status, multiplicity, histologic grade, nuclear grade, axillary lymph node status, TNM stage, and p53.

Conclusions: The loss of PTEN expression was found in 8.8% of all breast cancers and PTEN expression correlated with tumor size, vascular invasion, hormone receptor status, and HER2 expression. Our results suggest that PTEN expression may be an independent prognostic indicator in patients with breast cancer.

Clinicopathologic Factors Affecting to Actual 5-Year Survival Rate in Invasive Ductal Carcinoma of Breast: A Single-Center Experience with 365 Patients

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Background/Purpose: The aim of study was to figure out clinicopathologic factors of invasive ductal carcinoma affecting to actual 5-year survival rate (5-YSR).

Methods: A retrospective study was carried out with 365 invasive ductal carcinoma patients who underwent operation from Jan. 1999 to Dec. 2003 in Pusan National University Hospital breast clinic. The uni- (log rank test) and multivariant (Cox regression test) analysis were performed with clinicopathologic factors with actual 5-YSR.

Results: The mean age was 47.6 years and median follow-up period was 63 months. Thirty-nine of the 365 patients had expired within 5 years and an actual 5-YSR was 89.3%. The variables affecting to actual 5-YSR in univariant analysis were preoperative CA15-3 level ($p=0.0211$), T stage ($p<0.0000$), N stage ($p<0.0000$), lymphovascular ($p=0.0004$) and perineural invasion ($p=0.0192$) of primary tumor, more than 2 and 3 grade of progesterone receptor ($p=0.0457$) and c-erb B2 ($p=0.0179$), pathologic stage ($p<0.0000$), tumor recurrence ($p<0.0000$) in tumor-related factors and breast-conserving surgery ($p<0.0000$), perioperative period transfusion ($p=0.0002$), neo- and adjuvant chemotherapy (both $p<0.0000$), treatment with tamoxifen ($p=0.0380$) in treatment-related factors. In multivariant analysis of actual 5-YSR, the important factors with significance were pathologic stage ($p=0.001$) and adjuvant chemotherapy ($p=0.010$).

Conclusions: The most significant factors related with actual 5-YSR were pathologic stage and adjuvant chemotherapy throughout overall uni- and multivariant analysis. Between two factors, pathologic tumor stage is difficult to change, but adjuvant chemotherapy may have many regimens according to physicians. That means adjuvant chemotherapy should be selected with caution considering by patient's clinicopathologic state.

The Relationship between the Expression of Cytokeratin 5/6 and Clinicopathologic Factors in Invasive Breast Carcinoma

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Background/Purpose: Analysis of gene expression profiling data on breast cancers has revealed “molecular subclasses” that may have prognostic significance. The basal-like subtype is associated with poor clinical outcomes. We have investigated the relationship between the expression of basal-like subtype and clinicopathologic factors and defined the clinical implications of this class in invasive breast carcinoma.

Methods: An immunohistochemical study was performed on tissue microarrays constructed with 91 invasive carcinoma samples. Immunohistochemistry for estrogen receptor (ER), progesterone receptor (PR), HER2/neu and cytokeratin (CK) 5/6 was performed.

Results: Of total 179 invasive breast carcinomas from 2005 to 2008, 91 cases (50.8 %) were tested CK5/6. The basal-like tumors were 13.2% (12/91). Clinicopathologic factors significantly associated with this subtype included ER, PR and histologic grade ($p=0.001$, 0.001 and 0.004 , respectively). While the other variables, like patient age, tumor size, lymph node involvement, stage, or HER2/neu expression, were non-significant ($p>0.05$).

Conclusions: The present study demonstrated that the expression of CK5/6 is more likely to ER (-) and high histologic grade status. These are important observations as these tumors are limiting the range of relevant adjuvant therapies. But these findings should be further assisted by adding more basal-like carcinomas in clinical specimens and finally help to facilitate treatment and constant studies of this tumor subtype. Furthermore, we will try to find out the relationship CK5/6 expression and breast cancer stem cells, known as CD44+, CD24- cells.

Young Age as a Prognostic Factor for Operable Breast Cancer: Significance of Molecular Subtype in Recurrence-Free Survival

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Background/Purpose: We investigated the clinicopathological characteristics and outcomes of younger breast cancer patients (≤ 35 years of age), and assessed the prognostic significance of young age according to molecular subtype.

Methods: We analyzed 2,474 primary invasive breast cancer patients who underwent surgery between 2000 and 2005. The younger age group consisted of patients aged ≤ 35 years. Subtypes were defined by expression of hormone receptor (HR) and HER2: luminal (HR⁺ irrespective of HER2 status), triple-negative (HR⁻ and HER2⁻) and HER2 (HR⁻ and HER2⁺).

Results: A total of 229 (9.3%) patients were aged ≤ 35 years. Breast cancers in this age group were associated with larger size, higher lymph node positivity, higher nuclear and histological grades, and elevated Ki-67 index, compared with tumors in older patients. Younger patients had a greater probability of recurrence than older patients ($p < 0.001$). By multivariate analysis, young age remained a significant predictor of recurrence (hazard ratio, 1.54; 95% confidence interval, 1.15-2.06; $p = 0.004$). When the cancer subtypes were considered, young age was a significant predictor of recurrence in patients with both luminal and HER2 subtypes. In patients with the triple-negative subtype, however, young age was not a predictor of recurrence.

Conclusions: Young age (≤ 35 years) was an independent predictor of recurrence for operable breast cancer patients with the luminal and HER2 subtypes, but not for those with the triple-negative subtype.

Chronological Spectrum of Fibroepithelial Neoplasm of the Breast

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Background/Purpose: This study was conducted to find clinical evidence that phyllodes tumor is a chronological spectrum of fibroadenoma, and to find a new factor that can predict malignancy in phyllodes tumor.

Methods: The authors retrospectively analyzed 105 histologically proven phyllodes tumor in surgical specimen, of which were 74 benign, 24 borderline, and 7 malignant tumors. The proportion of concurrent fibroadenoma in phyllodes tumor was assessed. The specimen from core-needle biopsy was compared with surgical specimen in 46 cases of which surgeries were conducted within 6 months after core-needle biopsy. The correlation between the proportion of concurrent fibroadenoma and the biologic characteristics of phyllodes tumor was tested.

Results: The mean age of the patients was 34.2 years. The average size was 24.8 mm in benign, 33.8 mm in borderline, and 50.0 mm in malign tumor, respectively ($p < 0.001$). 73 cases (69.5%) were the mixture of phyllodes tumor and fibroadenoma. The proportion of concurrent fibroadenoma was largest in the malignant, followed by the borderline ($p < 0.001$). The pathologic report of biopsy specimen was significantly concordance with that of surgical specimen only in the case without concurrent fibroadenoma. Local recurrence developed in 2 borderline and 2 malignant tumors, all of which had undergone wide excision. None of these showed concurrent fibroadenoma.

Conclusions: Decrement in the proportion of concurrent fibroadenoma is chronological metamorphosis of malignant change in phyllodes tumor. The proportion of concurrent fibroadenoma has affect on the diagnostic accuracy of biopsy with limited material. Absence of concurrent fibroadenoma in phyllodes tumor can be a predictor of local recurrence.

The Factors Influencing Axillary Lymph Node Metastasis in Patients with T1 Invasive Ductal Carcinoma

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Background/Purpose: The aim of the study is to identify the state of axillary lymph node invasion and factors that influence the lymph node metastasis among the patients with T1 invasive ductal carcinoma.

Methods: Between January 2003 and August 2008, 205 patients diagnosed as T1 invasive ductal carcinoma after the breast cancer resection at Gachon University Gil Hospital were enrolled in this study. Each patient's age, size and location of cancer, number of tumor, tissue and nucleus grade, infiltration of lymph vessels, immunohistochemistry test result (ER, PR, p53, Ki67, HER2 etc.), and state of axillary lymph node metastasis were compared.

Results: For the rate of axillary lymph node metastasis, in the group of cancer size smaller than 1 cm (T1a, T1b), 3/32 (9.4%) patients showed axillary lymph node metastasis, and in the group of cancer size larger than 1 cm (T1c), 55/173 (31.8%) patients showed axillary lymph node metastasis. The result distinguished by the size of the cancer was statistically significant ($p=0.015$). The rate of axillary lymph node metastasis according to the number of tumor was 49/180 (27.2%) with 1 tumor, 5/17 (29.4%) with 2 tumors, and 3/5 (50%) with more than 3 tumors. This result distinguished by the number of tumor was statistically significant ($p=0.038$). Also, Lymphovascular invasion was statistically significant ($p=0.000$).

Conclusions: It is considered that the size and the number of tumor, and lymph vessel infiltration are the significant factors that influencing axillary lymph node metastasis of the T1 invasive ductal carcinoma.

Patterns of Relapse and Metastatic Spread in HER2-over-expressing Breast Cancer According to Estrogen Receptor (ER) Status

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Background/Purpose: The primary aim of this study was to compare the relapse patterns of estrogen receptor (ER)-positive and ER-negative patients with HER2-overexpressing breast cancer. A secondary aim was to distinguish the preferential primary site of metastases in HER2-overexpressing breast cancer.

Methods: Out of 886 patients treated for metastatic breast cancer (MBC) between January 1995 and December 2006, 269 patients with HER2-positive tumors were identified. Of these, 198 patients with relapsed breast cancer following surgery were included in this study. Rates and patterns of relapse and pattern of metastatic spread of HER2+/ER+ and HER2+/ER- patients were analyzed.

Results: Median disease-free survival (DFS) was longer in the HER2+/ER+group than in the HER2+/ER-group (32.0 vs. 21.0 months, $p=0.0022$). The peak of recurrence occurred at 12 months after surgery in HER2+/ER- patients. The peak of relapse was later and the level was lower in HER2+/ER+patients (66 and 78 months following surgery) than in HER2+/ER- patients (33 and 39 months following surgery). Young age (hazard ratio (HR) 1.59, $p=0.002$), TNM stage 3 (HR 1.51, $p=0.005$), and ER-negativity (HR 1.68, $p<0.0001$) were identified as independent risk factors for relapse. Severe bone metastasis (HR 4.48, $p=0.028$) and massive hepatic metastasis (HR 5.24, $p=0.043$) were identified as independent predictive factors on early relapse within 24 months.

Conclusions: Our study shows that HER2-overexpressing breast cancer displays characteristic patterns of relapse and metastatic spread depending on ER status. Large prospective study for evaluating the influence of ER on HER2-overexpressing breast cancer is warranted to understand the clinical course of HER2-positive breast cancer.

Biomarkers for Prediction of Neoadjuvant Chemotherapy

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Background/Purpose: Neoadjuvant chemotherapy is an essential part of the management of locally advanced breast cancer. But we cannot predict the response before therapy. So many efforts have been performed for discovering the biomarkers of neoadjuvant chemotherapy. However there is no effective and predictive biomarker for prediction of neoadjuvant chemotherapy. This study was performed to discover the biomarker for that situation by using proteomic methods which have been improved recently.

Methods: For discovering of protein-candidates, proteomic method (ICAT) was used for finding differently expressed proteins between the tissues of response groups and the tissues of resistant groups for chemotherapy as neoadjuvant regimen. After that, we verified the candidates by western blot. And then some candidates were selected, which were verified by small-sized immunohistochemistry on some core-needle biopsed tissue samples.

Results: Totally 39 proteins were expressed differently over 1.78 folds between tissues of two groups. In these proteins, we selected 12 proteins, which were verified through the ROC curve by western blot. After that process, 3 proteins were identified as candidates for biomarkers on neoadjuvant chemotherapy. IHC were performed for 3 candidates by using 15 core-needle biopsed tissue samples. Through verification, we found significant candidate, protein X, showing the more decreasing rate of tumor size in MRI before and after chemotherapy if core needle biopsed tissue sample were protein X-positive result on IHC.

Conclusions: Protein X seems to be predictive biomarker on neoadjuvant chemotherapy. For that, the large-sized tissue validation will be needed.

Analysis of Predicting Factors for Time to Death in Deceased Breast Cancer Patients

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Background/Purpose: To identify predicting factors for time to death in deceased breast cancer patients who were treated with multimodality therapy.

Methods: From June 1994 to June 2008, 3,835 patients with stage I-III breast cancer received surgery, radiation therapy, and chemotherapy at Samsung comprehensive cancer center. In these patients, 224 patients had died, and among them, 173 patients had follow-ups within 6 months before dying. Nineteen patients died of disease other than breast cancer, and 154 patients died of breast cancer. We retrospectively reviewed medical records of these 154 patients. Mann-Whitney test was used to compare the median time to death between different groups.

Results: The median time to death was 37 months (range, 6-120 months), and third-quarter of patients died within 5 years after treatment. The median time to death in patients who developed brain, liver, lung, and bone metastasis were 5 months, 6 months, 10 months, and 12 months, respectively. In univariate analysis, factors affecting on the shorter time to death were triple negativity of tumor, advanced pathologic stage (pI-IIIa vs. IIIB-IIIC), and visceral organ (liver or brain) metastasis as first treatment failure.

Conclusions: Triple negativity of tumor, advanced pathologic stage and visceral organ metastasis as first treatment failure were related to shorter life expectancy in deceased patients with breast cancer.

Prognostic Effect of Serum 25-Hydroxy Vitamin D Levels in Breast Cancer Patients

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Background/Purpose: There is increasing evidence that vitamin D has been linked to breast cancer risk, but prognosis effects are unknown. We investigated the possible association between vitamin D and breast cancer prognosis by comparing serum vitamin D level.

Methods: From June to December 2006, serum 25 (OH) vitamin D levels were measured in 310 Korean women with breast cancer at the Asan Medical Center. Clinical, Pathologic, and dietary data were accessed to examine prognostic effects of serum 25 (OH) vitamin D.

Results: Mean age was 48.7 years, mean serum 25 (OH) vitamin D level was 31.4 ± 16.1 ng/ml. 25 (OH) vitamin D levels were deficient (<20 ng/ml) in 24.2%, insufficient (20-29 ng/ml) in 30.6%, and sufficient (30-150 ng/ml) in 24.0%. Mean follow up was 30 months, and 31 patients had recurrences. Women with deficient 25 (OH) vitamin D levels had an increased risk of recurrence (HR=2.93; 95% CI=1.27 to 6.77) compared with those with sufficient levels. 25 (OH) vitamin D levels were inversely associated with prognosis of hormone receptor positive tumors, but not with hormone receptor negative tumors (HR=5.73, 95% CI=1.82 to 18.06 for hormone receptor positive tumor, HR=1.142, 95% CI=0.33 to 3.92 for hormone receptor negative tumor). The association remained after individual adjustment for age, tumor size, nodal status, and estrogen receptor status (HR=4.13, 95% CI=1.77 to 9.61).

Conclusions: Vitamin D deficiency may be associated with poorer outcomes in hormone receptor positive breast cancer patients.

Clinical Features and Course of Brain Metastases in Triple-Negative Breast Cancer: Comparison with HER2+ and Other Type

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Background/Purpose: Incidences and clinical aggressiveness of intracranial metastasis in triple-negative (TN) breast cancer have not been well delineated compared to HER2+ subtype.

Methods: Patients (pts) who were diagnosed with primary breast cancer at Asan Medical Center from January 1990 to July 2006 were screened. All pts with brain metastases, identified by CT/MRI, were included and classified into three subtypes (TN/HER2+/other). The clinical features and course of brain metastases with TN breast cancer, defined according to immunohistochemical staining and HER2 FISH analysis, were reanalyzed and compared.

Results: 198 pts (of 7,872 pts screened) developed brain metastases and 61pts with unknown ER/PR/HER2 status were excluded. Of 137 pts, incidences of TN, HER2+ and other group were 32% (44), 50% (69) and 18% (24), respectively. Clinical parameters such as performance status, previous adjuvant chemotherapy or radiotherapy, was similarly distributed among groups except pts with earlier stage (I, II) were more prevalent in TN group compared to other two groups (59%/36%/38%, p=0.01). With a median follow-up duration of 99 months (m), the median time from initial diagnosis to brain metastases was significantly shorter in TN group, compared with other two groups [TN/HER2/other; 20 m/32 m/45 m, p=0.01] and the one from diagnosis of primary cancer to the first distant metastases at any sites was also shorter [16 m/23 m/23 m, p=0.005]. The median OS from diagnosis of primary cancer was significantly shorter in TN group [31 m/39 m/57 m, p=0.02] and however, the one after brain metastases was not different among 3 groups [5.9 m/5.2 m/8.8 m, p=0.31].

Conclusions: TN breast cancer showed earlier brain metastases, earlier distant metastases at any sites and shorter OS despite high proportion of early stages, compared with other phenotypes.

Development and Evaluation of Self-Efficacy Scale for Breast Cancer

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Background/Purpose: The purpose of this study was to develop and validate a Self-efficacy Scale for Patients with Breast Cancer (SE-Br).

Methods: The SE-Br was developed and validated as follows: item generation, pilot study, and test of validity and reliability. Twenty-one items were developed through evaluation by 10 experts and 18 items were finally confirmed through item analysis. Psychometric testing was performed with a convenient sample of 303 women with breast cancer from one cancer center. The data were analyzed using factor analysis, Pearson's correlation coefficients, and Cronbach's alpha.

Results: Five factors evolved by factor analysis, which explained 59.3% of the total variance. The first factor 'Coping with psychosocial demand' explained 29.4%, 2nd factor 'Maintenance of healthy lifestyle' 8.5%. 3rd factor 'Management of side-effects' 8.2%, 4th factor 'Sexual life' 6.8%, and 5th factor 'Therapeutic compliance' 6.3%. Among 18 items, two items were excluded; one item showed a low factor loading, and the other was not matched to conceptual framework. Thus, final SE-Br consisted of 14 items. Furthermore, SE-Br demonstrated a good concurrent validity with Mishel's Uncertainty of Illness Scale, and health-related quality of life scale, EORTC QLQ-C30 & BR23. The internal consistency, Cronbach's alpha was 0.803, and subscale's reliability ranged from 0.661 to 0.788.

Conclusions: SE-BR identified as a tool with high degree of reliability and validity. The tool can therefore be effectively utilized to assess the level of self-efficacy for patients with breast cancer.

Thalidomide Associated Gynecomastia: Case Report

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Background/Purpose: Thalidomide has become a novel agent in the treatment of multiple myeloma and many other hematological and solid malignancies. Thalidomide has various adverse effects including neurologic, hematologic, cardiovascular, gastrointestinal, dermatologic, and endocrine toxicities. We experienced gynecomastia, rare side effect of thalidomide and report of our experience.

Results: A 42-year-old man visited our institution due to both breast engorgement 1 year ago and complained of mild tenderness (Fig. 1). 6 years ago, he had been diagnosed malignant histiocytosis by skin punch biopsy at left palpable axillary mass lesion. He was treated with 10 courses of prednisolone, vinblastine, and etoposide. But, 6 months later, the response of chemotherapy was refractory result and then, he has been received thalidomide salvage therapy (25 mg-100 mg/day) for 5 years. Mammography and ultrasonography revealed a diffuse ductolobular hyperplasia involving both breast (Fig. 2). Laboratory findings disclosed normal values of estradiol, testosterone and β -HCG. Serum prolactin was slightly increased to 25.2 ng/ml (normal ranges: 1.8-15.9 ng/ml). We have treated him with bromocriptine. With a follow up of 1 year, gynecomastia remained stable but, both breast discomforts was improved.

Conclusions: Thalidomide is now commonly used as an anticancer agent. Given the increasing clinical use of thalidomide, it becomes important to study the side effects of this agent. There has been only 1 report of thalidomide associated gynecomastia in multiple myeloma similarly. We report here the first case of thalidomide associated gynecomastia in treatment of malignant histiocytosis.



Fig. 1.

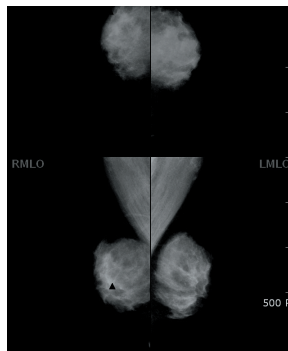


Fig. 2.

Radiation Therapy for Brain Metastasis of Breast Angiosarcoma

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Methods: Case report

Results: Breast angiosarcoma is a rare malignant tumor, accounting for about 0.05 % of all primary breast malignancy. There is a few reports dealing with radiotherapy for brain metastasis of breast angiosarcoma. Furthermore the utility of such treatment has not been fully established. We report the case of a patient who was able to keep good performance status (PS) treated with whole brain radiation for brain metastasis. 32-year-old pregnant women (22 weeks gestation) had an 18 cm tumor in her left breast and a 4 cm tumor in her right breast. The diagnosis of angiosarcoma has been proved by needle biopsy. Left simple mastectomy and right lumpectomy were performed. One month later, local recurrence of right breast, multiple lung metastasis and meningeal dissemination appeared. After cesarean section right mastectomy was done. As a systemic therapy, we underwent paclitaxel treatment, but after 2nd course pulmonary lesion became progressive disease. After switching to adriamycin and ifosfamide therapy, Long stable disease was obtained. Nine months after the operation, headache, nausea and clouding of consciousness occurred. MRI (magnetic resonance imaging) revealed multiple brain metastasis and invasion of frontal lobe from meningeal dissemination. The symptoms were clearly improved (PS3 → 1) after radiation therapy of 30 Gy and the patient could discharge. We underwent Adriamycin up to full dose and changed Docetaxel and Gemzar. Sixteen months later from first therapy and 5 months from brain metastasis diagnosis, the patient died. Indeed the fetal issue, the radiotherapy was effective and helped the patient to maintain good Activities of Daily Living.

Solitary Renal Metastasis from Breast Cancer: A Case Report

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Background/Purpose: We report a case of metastatic renal tumor secondary to a breast cancer 5 years after conserving surgery. A 52-year-old woman underwent breast conserving surgery and 6 cycles of CMF chemotherapy (Cyclophosphamide, MTX, Fluorouracil) for the left breast cancer. On a routine follow-up CT examination after 5 years of breast cancer treatment, an about 1.5 cm sized renal mass limited in the cortex was detected. No local recurrence or metastases to other organ were found through physical, laboratory and radiological examination including a radionuclide bone scan and a PET-CT scan. She did not complain any clinical symptom. MR was used for additional imaging work-up, but there are no definite differentiation between the solitary renal metastases and primary renal cell carcinoma. A laparoscopic partial nephrectomy was performed for the renal tumor, and histopathological diagnosis was metastatic invasive ductal carcinoma. There are no evidence of recurrence or metastases on routine follow-up examination 1 year post-partial nephrectomy.

Treatment Related Acute Myeloid Leukemia in Breast Cancer: A Single Institute Experience in Korea

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Background/Purpose: Treatment-related acute myeloid leukemia (t-AML) is a rare and lethal iatrogenic complication of chemotherapy and radiation therapy in breast cancer and accounts for 10-15% of all cases of AML. This study was performed to review the clinical characteristics of t-AML including recently experienced 2 cases in our hospital.

Methods: We collected total 6 cases of t-AML and analyzed retrospectively by review of medical records in St. Mary's Hospital, The Catholic University of Korea.

Results: Total 6 cases of t-AML were enrolled. At diagnosis of breast cancer, mean age of patients was 44 years (39-49 years) and stages of disease were as follows; 1 in stage I, 1 in IIA, 3 in IIB, 1 unknown. Mean latency period to development of t-AML was 34.8 months (25-41 months) and all of them were treated with adjuvant chemotherapy with standard dose including alkylating agents and anthracyclines; CMF in 2 cases, and CAF in 1, CAF in 1, FAC in 1, CEF in 1, and EC in 1. Radiation therapy was performed in 3 cases. Prognosis was very poor, 4 cases out of 6 were expired with 1 year (1-11 month) after diagnosis of t-AML.

Conclusions: Our data confirmed that t-AML was associated with chemotherapy including alkylating agent and anthracyclines and the prognosis of t-AML was very poor. Therefore, despite of rare incidence, the risk of tAML should be considered in choosing chemotherapy regimens for breast cancer, especially with younger age.

The Risk Factors of Infectious Complications of the Implantable Venous Access System in Cancer Patients

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Background/Purpose: It is necessary for cancer patients to access safe and comfortable intravenous system. Total implantable port systems are widely used for cancer chemotherapy. The long term complications, particularly infectious complications, have not been carefully evaluated. The purpose of this study was to investigate factors associated with infection complication of total implantable venous access ports (TIAP) system.

Methods: We reviewed 569 patients who underwent TIAP placement between January 2006 and December 2006 were followed until TIAPs removal (or the last known recorded documentation), death or until June 31 2008. Indications and circumstances of placement, patient diagnosis, patient demographics, as well as technical and microbiologic device related infection complication from medical records.

Results: 572 TIAPs were placed in 569 patients. There were 30 infectious complications (5.2%, 0.14 per 1,000 catheter days). A total of 213,169 catheter days were analyzed (median 325.5; range, 1-910). The major pathogen was *Staphylococcus aureus* (24.1%). A multivariate analysis with Cox regression, showed that outpatients department patients ($p<0.05$; OR=3.4), duration of hospitalization ($p<0.05$; OR=1.7) significantly influence catheter infection. The risk of infection decreases over time from catheterization ($p<0.05$; OR=0.88 per month).

Conclusions: Total implantable venous access ports (TIAP) in cancer patients are safe and well tolerated. However, short term infection complications were significantly associated with outpatient department based insertion and long term infection complications were mainly associated with duration of hospitalization. This study result will be useful data for developing infection prevention strategy.

Surveillance, Chemoprevention and Prophylactic Surgery in BRCA1/2 Mutation Carrier

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Background/Purpose: Options for affected BRCA carrier included surveillance, chemoprevention, and prophylactic mastectomy. It has been reported that prevalence and penetrance of BRCA1/2 mutation in Korean women is similar to the Western data, but chemoprevention and prophylactic mastectomy for cancer prevention does not seem to be actively performed. The aim of this study was to investigate the patterns of the usage of surveillance of the breast/ovarian cancer, chemoprevention and risk-reducing surgery of breast and ovary in Korean BRCA mutation carrier.

Methods: We retrospectively reviewed medical record of 40 patients with BRCA mutation carrier who had prospective follow-up between January 2005 and May 2009 at Seoul National University Bundang Hospital.

Results: During a mean follow-up of 16.4 months, the mean age of patients was 45 years (27-74). The numbers of proband and family member were 31 (77.5%) and 9 (22.5%), affected/unaffected carrier 34 (85%) and 6 (15%). Of these 40 patients, the numbers of surveillance only group was 21 (52.5%)/23 (57.5%), prophylactic mastectomy/oophorectomy group 2 (5%)/9 (22.5%). There were 2 cases of chemoprevention (5%). There were 2 cases of contralateral prophylactic mastectomy and risk-reducing salphingo-oophorectomy at the same time, 7 cases of prophylactic salphingo-oophorectomy only. The mean follow-up period from post-test counseling to prophylactic surgery was 4 months for mastectomy and 8.6 months for oophorectomy.

Conclusions: The usage of chemoprevention and risk-reducing surgery were relatively lower than that of Western report. Adequate genetic counseling about the actual risk of breast/ovarian cancers and risk and benefits of preventive intervention should be done for BRCA mutation carriers. Nationwide study of usage patterns of preventive intervention is needed.

The Comparison of Perceived Nursing Educational Needs for Discharge between Stomach Cancer Patients with Gastrectomy and Nurses

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Background/Purpose: To compare the nursing educational needs for discharge between patients with gastrectomy and nurse and to use this research results for making the nursing educational program for stomach cancer patient's needs.

Methods: This research was a comparative survey.

Results: There was no statistically significant differences in total perceived nursing educational needs for discharge between stomach cancer patients with gastrectomy and the nurses. In comparison of the degree of the nursing educational needs for discharge according to areas: Patient's degree was higher than nurses in areas of 'treatment direction and time of activity after surgery', 'health assisted activities', and nurses' degree was higher than patients in areas of 'follow-up management after discharge'. In comparison of ranking of the nursing educational needs for discharge: the first ranking area was 'diet management after surgery' for both groups and other areas were ranked similar. But, 'follow-up management after discharge' area was the fifth ranking for patients, the second ranking for nurses.

Conclusions: In comparison of areas, the first ranking area was 'diet management after surgery' for both groups and in comparison of items, patient's concern is more positive about their health and is focus how to control best health condition but nurses's concern is how to control the bad result from inadequate self care by patients after discharge. So, the nurses who are taking care of the patients with gastrectomy, have to teach more about diet management after surgery and to remember about their awareness need for their good healthy life for the discharge education.

Intake of Fiber and Nuts During Adolescence and Incidence of Proliferative Benign Breast Disease

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Background/Purpose: Evidence has shown that high fiber intake reduces mammary tumor incidence and exposures during childhood and adolescence may be important in breast carcinogenesis. However, the role of adolescent fiber intake in early stage of breast cancer development is largely unknown. We examined the association between adolescent intake of fiber and sources of fiber and proliferative BBD, a marker of increased breast cancer risk, in the Nurses' Health Study II.

Methods: Among 29,480 women who completed a high school diet questionnaire in 1998, 682 proliferative BBD cases were identified and confirmed by centralized pathology review between 1991 and 2001. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusted for potential risk factors for BBD.

Results: Women in the highest quintile of adolescent fiber intake had a 25% lower risk (multivariate HR [95% CI]: 0.75 [0.59, 0.96], p-trend=0.01) than women in the lowest quintile. Intake of nuts and apples was also related to significantly reduced BBD risk. Women consuming 2 servings of nuts/week had a 35% lower risk (multivariate HR [95% CI]: 0.64 [0.48, 0.85], p-trend<0.01) than women consuming <1 serving/month. Results were essentially the same when the analysis was restricted to prospective cases (n=142) diagnosed after return of the high school diet questionnaire.

Conclusions: Adolescent fiber intake was inversely associated with proliferative BBD risk. The apparent effect of fiber may mainly come from nuts and apples. These findings may suggest a viable means for breast cancer prevention.

Dietary Patterns and Breast Cancer Risk

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Background/Purpose: The association of breast cancer risk with dietary pattern has not been adequately studied in Asian women. We identified major dietary patterns among Korean women, and evaluated their associations with breast cancer risk according to menopausal and hormone receptor status.

Methods: Dietary patterns were derived via principle component analysis using FFQ in a hospital-based case-control study, with 357 cases and 357 age-matched controls. The relation between dietary pattern and breast cancer risk was assessed by using multivariate logistic regression.

Results: Two dietary patterns (vegetable-seafood and meat-starch) were identified in Korean women. The vegetable-seafood pattern was inversely associated with breast cancer risk (OR for the highest vs. the lowest quartile: 0.07; 95% CI: 0.04, 0.14; p for trend <0.001). However, among premenopausal women, the effect was observed only in women with both estrogen and progesterone receptor positive tumors. No association between the meat-starch pattern and breast cancer risk was found. In a combined index of the 2 patterns, women who were high consumers of the meat-starch and low consumers of the vegetable-seafood diet showed an increased risk of breast cancer compared with women who were low consumers of meat-starch and high consumers of vegetable-seafood diet (OR: 3.30; 95% CI: 1.97, 5.52; p for trend <0.001).

Conclusions: This finding indicates that a diet rich in vegetables and seafood and low in meat and starch is associated with a decreased breast cancer risk in Korean women, and the effect of dietary patterns on breast cancer risk may vary by menopausal and hormone receptor status.

EGF-Induced MMP-9 Expression is Mediated by the JAK3/ERK Pathway, but not by the JAK3/STAT-3 Pathway in a SKBR3 Breast Cancer Cell Line

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Background/Purpose: Epidermal growth factor receptors (EGFRs) and their ligands are highly expressed in malignant tumor cells. The EGF signaling pathway is also activated in up to one third of patients with breast cancer. Here, we investigated the novel function of the WHI-P131, JNK3 inhibitor, on EGF-induced MMP-9 expression and the regulatory mechanism of EGF-induced MMP-9 expression.

Methods: MMP-9 mRNA and protein levels were analyzed by RT-PCR and zymography, respectively. Using the adenovirus system, STAT-3 and constitutively active-MEK were overexpressed in SKBR3 cells.

Results: EGF increased MMP-9 mRNA and protein expression in a dose-dependent manner. JAK3 inhibitor, WHI-P131, as well as JAK3 siRNA transfection, but not the JAK1 and JAK2 inhibitors, significantly decreased EGF-induced MMP-9 expression. In addition, EGF-induced STAT-3 phosphorylation was inhibited only by WHI-P131. EGF-induced MMP-9 expression was decreased by Ad-STAT-3 overexpression in a dose-dependent manner, while it was significantly increased by STAT-3 siRNA transfection. Basal levels of MMP-9 expression were significantly increased by constitutive active-MEK (CA-MEK) overexpression. EGF-induced ERK phosphorylation was prevented by WHI-P131, but not by JAK1 and JAK2 inhibitors. On the other hand, EGF-induced MMP-9 expression was decreased by the MEK1/2 inhibitor, UO126.

Conclusions: Therefore, we suggest that the WHI-P131 inhibits EGF-induced STAT-3 phosphorylation as well as ERK phosphorylation. The JAK3/ERK pathway may play an important role in EGF-induced MMP-9 expression in SKBR3 cells.

MMP-1 Expression can be Up-regulated by ER-A through Both Genomic and Non-genomic ER Pathways under the Influence of HER2

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Background/Purpose: In our previous work, Ets-1 upregulates HER2-induced MMP-1 expression. On the basis of the above knowledge and result, we hypothesized that ER and its signaling pathway may affect MMP-1 expression under the condition of HER2 transfection. Also, we investigated how HER pathway cross-talk with ER signaling pathway in genomic and non-genomic action of ER, especially in the nucleus.

Methods: After transfection of HER2 into MCF7 breast cancer cell line, MMP1 expression was analyzed using RT-PCR, Western blot analysis and ELISA assay. Then, MMP-1 expression was reanalyzed after ER- α siRNA transfection. In addition, Akt/MAPK down-stream pathway was evaluated with their blocking agents. EMSA was performed with nuclear protein extracts to exam DNA binding activity.

Results: HER2-induced MMP-1 expression was up-regulated by ER- α . Interestingly, this up-regulatory effect was mediated by both ER classical genomic (ERE) and non-classical genomic (AP-1) pathways. In addition, this up-regulatory effect was found to be mediated by Akt/MAPK signaling pathways in breast cancer MCF-7 cells and to be blocked by Akt/MAPK-specific inhibitors via ER non-genomic pathway. Importantly, the DNA binding activity of estrogen response elements (ERE) was activated by HER2 and reversed by siER. ERE binding activity was suppressed by Akt/MAPK specific inhibitors as well as AP-1 binding activity together with MMP-1 AP-1.

Conclusions: Our results indicate that ER can upregulate MMP-1 expression under the influence of HER2 in MCF-7 cells through both ER genomic and non-genomic pathways.

A Microfluidic Platform for Multiple Immunohistochemistry

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Background/Purpose: A microfluidic multiple immunohistochemistry (MIHC) platform was proposed for quantitative pathological diagnosis. Multilayer soft lithography and two-step lithography technologies were used for various solutions control and regular IHC staining. By using reversible sealing method between the device and a cellblock sample, not only perfect fluid control for various solutions was exhibited without any leakage, bubble formation and cross-contamination, but also stable sample preservation was guaranteed such as conventional paraffin storage manner. In addition, image analysis was conducted and quantified with Matlab software to overcome the subjective decision for immunohistochemistry results.

Methods: Four biomarkers, ER, HER2, PR and Ki-67, were examined on cellblocks of various breast cancer cell lines; SK-BR-3, MCF-7, AU 565 and HCC 70. We also checked the expression of these biomarkers on tissue slides of human breast cancers using with MIHC platform.

Results: The results were concordant with scores from histopathologist. The MIHC platform saved not only biomarker consumption by enhancing reaction efficiency and volumetric effect but incubation time as well. This phenomenon could be explained by convective diffusion mass transport and corresponded to continuous fluidic dynamics (CFD) simulation result.

Conclusions: The MIHC platform could provide more precise biopsy diagnostics by applying various predictive and prognostic biomarkers.

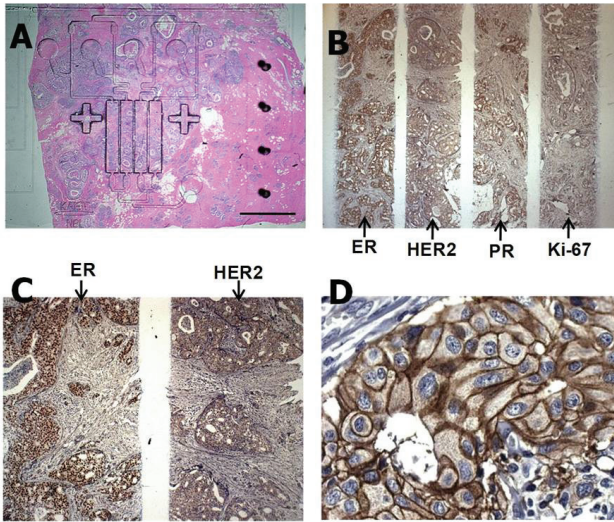


Fig. 1. MHC on a tissue sample.

		MHC platform							
		ER	-	+	++	+++	Total	k	p
Conventional method	-	1					1	1	0
	+		0				0	NA	NA
	++			2			2	1	0
	+++					20	20	1	0
	Total	1	0	2	20	23	1	<0.00001	
		PR	-	+	++	+++	Total	k	p
	-	2		1			3	0.78	0.0001
	+		0	1			1	0	NA
	++			2	1		3	0.50	0.0079
	+++					16	16	0.89	0
	Total	2	0	4	17	23	0.71	<0.00001	

		HER2	0	1	2	3	Total	k	p
	0	15					15	0.68	0.0003
	1+	3	2				5	0.51	0.0025
	2+			0			2	1	0
	3+				1		1	1	0
	Total	18	2	0	1	23	0.72	<0.00001	

		Ki-67	-	+	++	+++	Total	k	p
	-	11					11	1	0
	+		9	1			10	0.82	0
	++		1	1			2	0.45	0.015
	+++					0	0	NA	NA
	Total	11	10	2	0	23	0.85	<0.00001	

Fig. 2. Verification accuracy.

Genetic Tumor Heterogeneity in Breast Cancer Begins as Early as DCIS Level

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Background/Purpose: Tumor heterogeneity is a well known, yet, controversial concept in cancers. Elucidating the nature and the mechanism of tumor heterogeneity will improve our understanding of how cancers originate and how they evolve or progress.

Methods: To investigate the tumor heterogeneity at the genetic level, whole genome LOH and DNA copy number alterations were examined using 250K SNP microarray from Affymetrix and dChip analyzer in 40 samples of 15 patients with diffuse DCIS, invasive breast cancer with DCIS, and synchronous multifocal breast cancers, including 2 bilateral cases.

Results: Two out of 4 diffuse DCIS cases showed substantial genetic heterogeneity within the same breast. In 3 multifocal invasive carcinomas, the DCIS components were genetically more related to their adjacent invasive foci than to distant separate invasive tumors. All 11 synchronous multifocal breast cancers were genetically similar, but 4 cases showed additional unique genetic alterations in each tumor mass, suggesting they originated from the same clone but evolved along a different pathway accumulating different genetic alterations. The most frequent genetic alterations were LOH on 8p, 11q, 16q, and 17p and copy number gain on 1q, 8q, and 16p. Amplification at 8p11-12 was not shared between all synchronous tumor foci, indicating it is often a late event. 8q21-24 gain and 16q LOH were shared in multifocal IDCs or DCIS with invasive foci, suggesting it is an early event in tumor development.

Conclusions: At least some tumors from the same patient showed substantial genetic heterogeneity in addition to core changes, suggesting genetic divergence in tumor development.

The Clinicopathologic Characteristics and Clinical Outcomes of Estrogen Receptor-negative and Progesterone Receptor-positive Breast Cancer

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Background/Purpose: The aims of this study were to evaluate the clinicopathologic characteristics and the prognosis of patients with ER-PR+ breast cancer.

Methods: 1,570 patients were stratified according to ER/PR phenotype and our study focused on the ER-PR+ phenotype. The clinicopathologic characteristics and the prognosis of patients with the ER-PR+ phenotype were compared with those of patients with ER+ (ER+PR- or ER+PR+) breast cancer.

Results: The mean age at diagnosis was 47.1 years (range 20-88) and the mean follow-up was 65.2 months. The hormone receptor phenotype was “ER-PR+” in 75 cases (4.8%) and “ER+” (ER+PR+ or ER+PR-) in 917 cases (58.4%). A patient age <35 ($p=0.002$), a high histologic grade ($p=0.004$) and C-erbB2 over-expression ($p=0.006$) were more frequent for the patients with the ER-PR+ tumors. There was a significant difference between the two groups for the mean age ($p<0.001$). The 5 year and 10 year disease-free survival (DFS) rates of the ER-PR+ group were 67.2% and 55.3%, respectively, and those of the ER+ group were 84.9% and 73.1%, respectively ($p<0.001$). The 5 year and 10 year overall survival (OS) of the ER-PR+ group were 82.4% and 62.6%, respectively, and those of ER+ group were 93.4% and 83.3%, respectively ($p=0.001$).

Conclusions: ER-PR+ tumors have more aggressive clinicopathologic features than ER+ tumors. Furthermore ER-PR+ tumors showed a worse prognosis than did the ER+ tumors. Consequently, treatment modality and the prognosis of the patients with ER-PR+ tumors probably need to be altered from those of the patients with ER+ tumors.

Changes and Prognosis of Estrogen Receptor, Progesterone Receptor, and HER-2 Expression in the Primary and Recurrent Breast Cancer

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Background/Purpose: This study was aimed at evaluating the changes of estrogen receptor (ER), progesterone receptor (PR), and HER-2 expression in primary and recurrent breast cancer.

Methods: Between 1991 and 2005, we analyzed the pattern of changes of ER, PR, and HER-2 immunohistochemical expression and predictive factors for the changes in 153 patients with primary and recurrent breast cancer.

Results: There was significant decrease in the positivity rate of ER (50.3% to 38.6%, $p < 0.001$), PR (43.8% to 26.8%, $p = 0.01$), and HER-2 (40.3% to 36.3%, $p < 0.001$) expression between primary and recurrent breast cancer. Triple negativity (ER/PR/HER2: all negative) was increased from 25.8% to 43.5% ($p < 0.001$). Among 44 (28.6%) patients with the change of ER, the change from positive to negative was occurred in 31 patients (20.3%), and vice versa in 13 patients (8.3%) ($p = 0.0067$), and 42 patients (27.5%) and 16 patients (10.4%) ($p = 0.0006$) for 58 patients (37.9%) with the change of PR, and 21 patients (16.9%) and 9 patients (7.3%) ($p = 0.029$) for 30 patients (24.2%) with the change of HER-2. In multivariate analysis, adjuvant hormonal therapy was significant factor that could influence on ER (OR: 4.4) and PR (OR: 2.6) change. There was no significant difference of survival rate according to the changes of ER, PR, and HER-2 expression.

Conclusions: Especially, the more common changes from positive to negative of ER, PR, and HER-2 indicated a poor tumor biology of recurrent tumor. Therefore, the assessment of ER, PR, and HER-2 is important for effective treatment in recurrent breast cancer, although survival benefit did not observe in this study.

Phosphorylation Level of P90RSK as a Predictive Biomarker of Response to Induction Neoadjuvant Chemotherapy

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Background/Purpose: Doxorubicin is an effective breast cancer drug but is hampered by a severe, dose-dependent toxicity. The resistance mechanisms responsible for doxorubicin-resistance of breast cancer have been the subject of numerous investigations. Identification of proteins that is associated with doxorubicin resistance is a first step toward better response prediction and tailored treatment of patients.

Methods: In this study, we compared the expression of core proteins and their phosphorylated forms of several canonical pathways (MAPK signaling, Apoptosis, PI3K/Akt Signaling, Cell Cycle/Checkpoint and TGF- β /Smad signaling) in breast cancer tissues which were divided into two classes based on the type of response to doxorubicin therapy by immunoblotting. As a result, we found that the phosphorylated form of ribosomal protein S6 kinase (RSK) was low in doxorubicin-resistant breast cancer tissues compared with doxorubicin-sensitive breast cancer tissues.

Results: We investigated RSK's phosphorylation rate and doxorubicin sensitivity of various breast cancer cell lines including MCF-7, MCF-7s (sphere form), MDA-MB-231, MDA-MB-231s, MDA-MB-436, MDA-MB-453, MDA-MB-468, ZR75-1, BT474, Hs578T, T47D and MCF-10A to determine the phosphorylation rate of RSK in relation to the drug sensitivity of the breast cancer cell lines. Expectedly, the phosphorylation of RSK was low in doxorubicin resistant breast cancer cell line such as MDA-MB-453, ZR75-1 and Hs578T. Additionally, MCF-7s and MDA-MB-231s showed decreased phosphorylation rates compared with MCF-7 and MDA-MB-231.

Conclusions: In conclusion, decreased phosphorylation of RSK may predict response and further clinical studies should evaluate for molecular function of phosphorylated RSK during doxorubicin therapy.

15-Deoxy- Δ 12,14-Prostaglandin J2 Upregulates the Expression of Heme Oxygenase-1 and Subsequently Matrix Metalloproteinase-1 in Human Breast Cancer Cells

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Background/Purpose: Heme oxygenase-1 (HO-1) has recently been found to be involved in angiogenesis and metastasis. In this study, we investigated whether HO-1 could potentiate the metastatic potential of human breast cancer cells.

Methods: MCF-7 and MDA-MB-231 cells were treated with 30 nM of 15-deoxy- Δ 12,14-prostaglandin J2 (15d-PGJ2). Western blot analysis, real time PCR, and luciferase assay were conducted to detect the expression and transcriptional activity of matrix metalloproteinases (MMP-1) and HO-1. The effect of 15d-PGJ2 treatment on level of labile iron was determined by analysis of calcein fluorescence. To monitor the intracellular accumulation of ROS, the fluorescent probe DCF-DA was used. To determine whether 15-PGJ2-induced MMP-1 expression is associated with HO-1 expression, the cells were transfected with HO-1 siRNA or Nrf2 siRNA. Wound migration and invasion assay were conducted to monitor the invasiveness of the cells treated with 15d-PGJ2.

Results: Treatment of MCF-7 and MDA-MB-231 cells with 15d-PGJ2 increased the expression and the activity of HO-1, which preceded the induction of MMP-1. The 15d-PGJ2 induced up-regulation of MMP-1 was abrogated by the HO-1 inhibitor zinc protoporphyrin IX (ZnPP) as well as introduction of HO-1 siRNA. In addition, HO-1 inducers, such as cobalt protoporphyrin IX and hemin, up-regulated the expression of MMP-1. Overexpression of HO-1 in the MCF-7 cells caused the induction of MMP-1 expression. Treatment with the HO-1 inhibitor ZnPP abolished the migrative phenotype of 15d-PGJ2-treated MCF-7 cells. MCF-7 cells treated with 15d-PGJ2 exhibited intracellular accumulation of reactive oxygen species (ROS) which was abolished by ZnPP. We hypothesize that excess iron, released as a consequence HO-1 activity induced by 15d-PGJ2, is transiently available for the stimulation of intracellular ROS generation and subsequently MMP-1 expression. 15d-PGJ2-mediated upregulation of MMP-1 expression was blocked by the iron chelator desferrioxamine and the Fe²⁺-specific chelator phenanthroline. The iron chela-

tors as well as the antioxidant NAC abrogated ROS formation by 15d-PGJ2.

Conclusions: 15d-PGJ2 up-regulates MMP-1 expression via through induction of HO-1 and subsequent production of iron capable of generating ROS, which may contribute to increased metastasis and invasiveness of the human breast cancer cells.

Emodin Reverses Multi-drug Resistance and Affects ERCC1 Protein Expression in Breast Cancer Cells

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Background/Purpose: To study the effects of emodin on reversing the multi-drug resistance and ERCC1 protein expression in breast cancer cell line MCF-7/Adr, and explore the relationship between reversal of multi-drug resistance and ERCC1 protein expression.

Methods: MTT assay was conducted to test the cytotoxicity of adriamycin and cisplatin to MCF-7/Adr cells with and without emodin pretreatment, and ERCC1 protein expression was determined by Western blotting.

Results: MCF-7/Adr cells have 21-fold and 11-fold baseline resistances to adriamycin and cisplatin, respectively. When emodin is added to the cell culture at the concentration of 10 $\mu\text{g/ml}$, the drug resistance has been reduced from 21 folds to 2.86 folds for adriamycin, and from 11 folds to 1.79 folds for cisplatin. When MCF-7/Adr cells are exposed to 10 and 20 $\mu\text{g/ml}$ of emodin for 2, 4, 6 and 10 days, there have been dose-dependent and progressive decreases in ERCC1 protein expression, with greater inhibition effect in 20 $\mu\text{g/ml}$ of emodin.

Conclusions: Emodin could reverse the multi-drug resistance in MCF-7/Adr cells, down-regulate ECRR1 protein expression, in a time- and dosage-dependent fashion.

A Molecular Signature of MCF10A Human Breast Epithelial Cell Invasion Induced by H-Ras: S100A8/A9 as Candidate Markers

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Background/Purpose: The goal of the present study is to unveil the gene expression profile specific to the biological processes of human breast epithelial cell invasion and migration using an MCF10A model genetically engineered to constitutively activate the H-ras or N-ras signaling pathway.

Methods: We previously showed that H-Ras, but not N-Ras, induces MCF10A cell invasion/migration, while both H-Ras and N-Ras induce cell proliferation and phenotypic transformation. Thus, these cell lines provide an experimental system to separate the gene expression profile associated with cell invasion apart from cell proliferation/transformation.

Results: Analysis of whole human genome microarray revealed that 412 genes were differentially expressed among MCF10A, N-Ras MCF10A and H-Ras MCF10A cells and hierarchical clustering separated 412 genes into 4 clusters. We then tested whether S100A8 and S100A9, two of the genes which are most highly upregulated in an H-Ras-specific manner, play a causative role for H-Ras-mediated MCF10A cell invasion and migration. Importantly, siRNA-mediated knockdown of S100A8/A9 expression significantly reduced H-Ras-induced invasion/migration. Conversely, the induction of S100A8/A9 expression conferred the invasive/migratory phenotype to parental MCF10A cells. Furthermore, we provided evidence of signaling cross-talk between S100A8/A9 and the MAPK signaling pathways essential for H-Ras-mediated cell invasion and migration.

Conclusions: This study revealed S100A8/A9 genes as candidate markers for metastatic potential of breast epithelial cells. Our gene profile data provide useful information which may lead to identification of additional potential targets for prognosis and/ortherapy of metastatic breast cancer.

The G12 Family Proteins Upregulate Matrix Metalloproteinase-2 VIA P53 Leading to Human Breast Cell Invasion

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Background/Purpose: Although mounting evidence suggests a role for G12 proteins, G α 12 and G α 13, in tumor progression, a direct role of G12 proteins has not been determined. This study aims to elucidate the molecular mechanism for tumorigenic and invasive potential of G α 12/13 in MCF10A human breast epithelial cells.

Methods: Invasive/migratory abilities and expression of matrix metalloproteinase (MMP)-2/9 were assessed in MCF10A cells stably transfected with GTPase-deficient active G α 12 (G α 12QL) and G α 13 (G α 13QL) through in vitro invasion/migration assays, siRNA knockdown, promoter assay, EMSA and chromatin immunoprecipitation assay. To support clinical relevance, human breast tissues from 26 breast cancer patients were analyzed for expression of G α 12 and MMP-2 by RT-PCR.

Results: Here we report, for the first time, that G α 12/13 upregulate MMP-2 by transcriptional activation, allowing MCF10A cells to acquire invasive/migratory phenotypes. We further show that a transcription factor p53 is involved in the MMP-2 transcriptional activation by G α 12/13. G α 12/13-induced MMP-2 upregulation and the resultant changes in invasion/migration were the outcomes of sequential activation of Ras, Rac1, MKK3/6, p38 and Akt. Moreover, in human breast cancer samples, the levels of expression of G α 12 and MMP-2 are strongly correlated with the pathogenically diagnosed cancer ($p < 0.0001$) and also the level of expression of G α 12 shows strong correlation with that of MMP-2, identifying the tumorigenic potential of G α 12 in human breast cells.

Conclusions: This study suggests the role of G α 12/13-induced expression of MMP-2 in invasion/migration of breast cells in vitro and in vivo, elucidating a molecular basis for human breast cell invasion and tumor progression induced by G α 12/13.

Comparison of 6 Cycles Versus 4 Cycles of Neoadjuvant Epirubicin Plus Docetaxel Chemotherapy in Stages II and III Breast Cancer

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Background/Purpose: This phase III clinical study was designed to investigate whether 6 cycles of epirubicin plus docetaxel (ED) is more effective than 4 cycles of ED as neoadjuvant chemotherapy (NC) in patients with stage II or III breast cancer.

Methods: Women with breast cancer that had tumors larger than 3 cm were prospectively randomized to receive 4 or 6 cycles of epirubicin 75 mg/m² and docetaxel 75 mg/m² every 3 weeks. The primary end point was the clinical response to NC.

Results: A total of 176 patients were randomly assigned, and 150 patients were assessable for efficacy and toxicity. Groups were well balanced for clinicopathologic parameters. The median age was 42 years (range 30-58). Overall clinical response was observed in 72% with ED4 and 82% with ED6. pCR was observed in 11% with ED4 and in 24% with ED6 (p=0.047). 47% of the ED4 group underwent breast conserving surgery (BCS) whereas 58% of ED6 group underwent BCS (Table 1). Grade 3/4 neutropenia was observed in 27% in ED4 and 31% in ED6. Febrile neutropenia occurred in 17% with ED4 and 19% with ED6. Grade 3 mucositis was observed in 8% with ED4 and in 6% with ED6 (Table 2).

Conclusions: 6 cycles of ED enhanced the rates of pCR and BCS compared with 4 cycles without increasing treatment-related toxicities.

Response rates to ED #4 or ED #6.			
	ED #4 n = 66; n (%)	ED #6 n = 84; n (%)	p value
Pathologic complete response	7 (11)	20 (24)	0.047
ypT0	6 (9)	15 (18)	0.21
ypDCIS	1 (2)	5 (6)	
Partial response	40 (61)	49 (58)	0.78
Stable disease	18 (27)	21 (25)	0.68
Breast conservation	31 (47)	49 (58)	0.17

Abbreviations: ED, epirubicin + docetaxel; ypT0, no tumor after neoadjuvant chemotherapy; ypDCIS, ductal carcinoma in situ only after neoadjuvant chemotherapy.

Fig. 1. Table 1.

Severe toxicities according to NCI CTC v2.0.		
	ED #4 n = 66; n (%)	ED #6 n = 84; n (%)
Neutropenia (G 3/4)	18 (27)	26 (31)
Febrile neutropenia	11 (17)	16 (19)
Mucositis (G 3)	5 (8)	5 (6)
Abdominal pain (G 3)	2 (3)	3 (4)

Abbreviations: ED, epirubicin + docetaxel; G, grade.

Fig. 2. Table 2.

Impact of Surgical Resection on Survival in Stage IV Breast Cancer

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Background/Purpose: Currently, primary treatments for stage IV breast cancer are radiation and systemic therapy which include chemotherapy, endocrine therapy and targeted therapy. Surgical resection of primary tumor is usually done for tumor-related complications. A recent review suggested that surgery may improve long-term survival in stage IV breast cancer patients. We evaluated the impact of primary site surgical resection on survival in such patients.

Methods: We reviewed the records of stage IV breast cancer patients treated at Seoul National University Hospital between 1992 and 2008. Clinical and tumor characteristics, systemic and local treatments were compared for the surgically versus nonsurgically treated patients.

Results: Of 199 patients identified, 111 (55.8%) received surgical excision of their primary tumor and 88 (44.2%) did not. The mean survival of surgically treated patients was 67 months versus 52 months for patients those who did not ($p=0.0276$). In multivariate analysis, after adjustment for ER status, visceral metastasis, number of metastatic sites and herceptin treatment, surgery remained an independent factor associated with improved survival (HR 0.547 [95%CI 0.359-0.971] $p=0.001$).

Conclusions: Surgical resection of the primary tumor in stage IV breast cancer patient was independently associated with improved survival, even after adjustment for other factors associated with survival. Randomized prospective trials are needed to validate these findings.

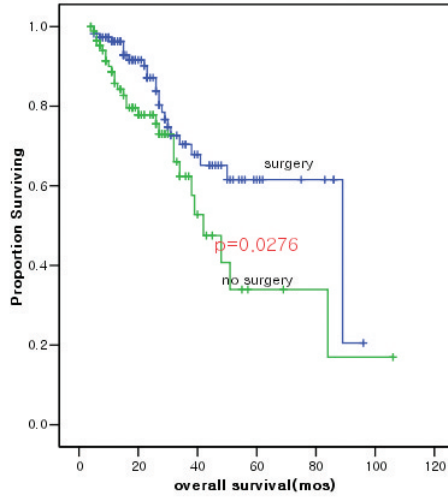


Fig. 1. Overall survival by surgery status.

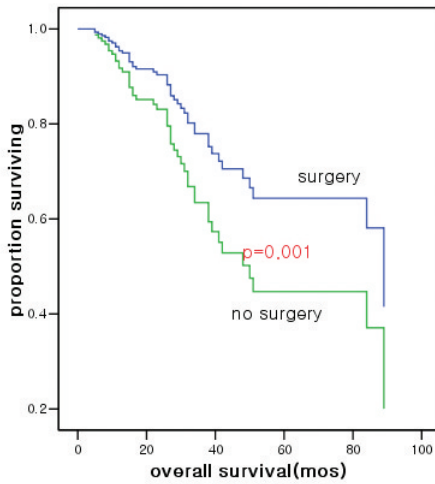


Fig. 2. Adjusted overall survival by surgery status.

Triple Negativity is not Related to Loco-regional Recurrence in Patients Undergoing Breast Conservative Therapy

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Background/Purpose: To evaluate the prognostic significance of triple negative (TN) phenotype in patients treated with breast conservative therapy.

Methods: One hundred and nine patients whose immunohistochemical staining for HER-2, ER, and PR was available among 125 patients who underwent breast conservative therapy were enrolled into this study. All patients underwent breast conserving surgery and adjuvant radiotherapy. Forth patients also received adjuvant chemotherapy and/or hormonal therapy.

Results: There were 19 TN tumors and 90 non-TN tumors. There was no difference in age, T stage and N stage between TN and non-TN tumors. The 5-year locoregional relapse-free survival (LRRFS) and distant metastasis-free survival (DMFS) rates were 92.2% and 91.6%, respectively. On univariate analysis, TN phenotype was associated with inferior DMFS (5-year rate, 78.6% vs. 94.4%, $p=0.0690$), but not with LRRFS ($p=0.5479$). In addition, age <40 yrs and tumors >2 cm were also adverse prognostic factors for DMFS ($p=0.0441$ and 0.0028 , respectively). When incorporating TN phenotype, age, T stage, and N stage into Cox proportional hazard model, T stage ($p=0.0526$) and age ($p=0.0732$) were associated with DMFS with a borderline significance, while only trend for inferior DMFS in TN phenotype ($p=0.1236$). As for LRRFS, age was the only significant prognostic factor on univariate analysis ($p=0.0377$).

Conclusions: Triple negative phenotype was not associated with loco-regional recurrence in patients treated with breast conservative therapy, and therefore it should not be considered a contraindication for breast conservative therapy.

The Effects of a Brief Psychosocial Intervention Using CD-ROM in Cancer Patients Receiving Adjuvant Therapy

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Background/Purpose: To test the effects of a brief psychosocial intervention using CD-ROM (BPIC) on psychosocial (fighting spirit, helplessness/hopelessness, anxiety, and depression) and behavioral (self-care behaviors) outcomes in cancer patients receiving adjuvant therapy. Design: Quasi-experimental design. Setting: A comprehensive cancer center in Seoul, Korea Sample: Seventy-one patients undergoing adjuvant therapy.

Methods: The study participants were assigned to either BPIC or control group. The experimental group underwent a 2-week psychosocial intervention via CD-ROM, booklet, and telephone counseling.

Results: After BPIC intervention the experimental group showed significantly higher scores than the control group for fighting spirit ($p=0.005$) and self-care behaviors ($p<0.001$). However, the two groups showed no significant differences in helplessness/hopelessness ($p=0.420$), anxiety ($p=0.279$), and depression ($p=0.068$).

Conclusions: The results partially supported the effectiveness of BPIC for adaptation among cancer patients receiving adjuvant therapy. A brief psychosocial intervention using CD-ROM improved fighting spirit and self-care behaviors. A brief psychosocial intervention using multimedia can be used effectively in clinical oncology settings to accelerate adaptation among cancer patients in the adjuvant phase.

Breast Reconstruction Using Inframammary Adipofascial (Anterior Rectus Sheath) Flap

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Background/Purpose: There have been many advanced procedures of immediate reconstruction after breast cancer surgery. In case of the tumor located lower portion of the breast, it has been shown difficulties to make a good shape, and there is no procedure of choice. Especially, the size of breast of Asian women is relatively small, then it is sometimes difficult to use local flap, including local adipose tissue or breast tissue. Using inframammary adipofascial (anterior rectus sheath) flap instead of TRAM or LD flap, we performed several cases of them.

Methods: Patients have Size <2 cm and lower located (4 h-8 h) tumor, small breast were included. Before surgery, tumor, inframammary fold, extent of flap (about 7 cm from the inframammary fold) were designed. After sentinel lymph node biopsy, the incision was made on inframammary fold line, and tumor was excised. and then dissection was performed in depth of 3-4 mm, making a flap including anterior rectus sheath, taking care of injury to perforating branches from the pectoralis major muscle. And then reflect it superiorly, fixing them to remnant breast tissue.

Results: we experienced 3 cases, there were no fat necrosis or seroma on them. Good cosmetic outcomes were achieved postoperatively and after radiotherapy.

Conclusions: Breast reconstruction using inframammary adipofascial (anterior rectus sheath) flap is useful in small breast and tumor located in lower part of the breast, easier than reconstruction using TRAM or LD flap, and it does not required another incision, does not make a skin or muscle defects.

Oncoplastic Techniques for Treatment of Superiorly Located Breast Cancers

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Background/Purpose: In case of larger lesions or small-size breasts, the removal of adequate volumes for breast conserving surgery (BCS) may compromise the cosmetic outcome, causing unpleasant results. In order to address this issue, oncoplastic techniques have been introduced in recent years. This article discusses the use of oncoplastic technique for superiorly located breast cancers in the BCS.

Methods: From January of 2007 to May of 2009, 34 women (mean age, 46 years) were treated for superiorly located breast cancers. We divided into 3 groups according to the distance from nipple-areolar complex (NAC); near, intermediate, far. Oncoplastic techniques after lumpectomy included 'Round Block' Technique, 'Batwing Mastopexy' for near lesions and 'Tennis Racket' Method, 'Rotational Flap' for intermediate lesion, 'Parallelogram mastopexy lumpectomy' for far lesion from NAC.

Results: The mean age was 46 and the average follow up interval was 10 months. The various surgical techniques included lumpectomy with the 'Round Block' technique (n=5), 'Batwing Mastopexy' (n=2) and 'Tennis Racket' method (n=18) (Fig. 1), 'Rotational Flap' (n=6) (Fig. 2), 'Parallelogram mastopexy lumpectomy' (n=3). There were two complications (NAC partial necrosis, radiation burn) during the follow up periods. There were no local recurrences in the remaining breast or axilla. The overall cosmetic result was evaluated at 6 months. The majority of patients were satisfied to the cosmetic result.

Conclusions: Oncoplastic techniques for superiorly located breast cancers can be safely treated oncologically by breast conserving therapy. This various oncoplastic techniques yield a satisfactory aesthetic results.



Fig. 1. Tennis Racket' method.

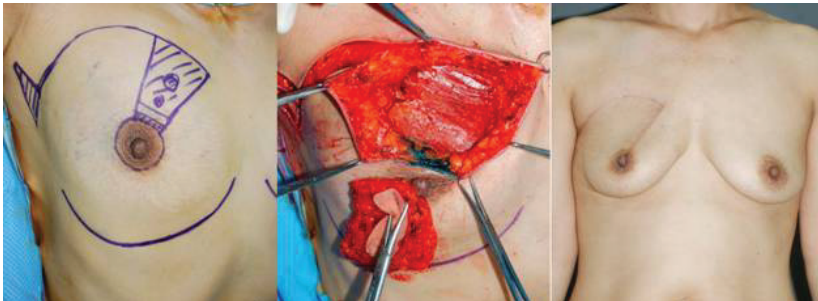


Fig. 2. Rotational Flap.

An Observational Study of Docetaxel-Based Adjuvant Chemotherapy in Breast Cancer Patients at High Risk of Recurrence in Asia-Pacific

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Background/Purpose: This observational study (registry) aims to assess patient profile and pattern of care in operable BC patients at high risk of recurrence treated with docetaxel-based adjuvant chemotherapy in Asia-Pacific countries.

Methods: Newly diagnosed female BC patients aged >18 years were enrolled from December 2006. Post-enrollment assessments included: demographics, medical history, BC stage and biologic characteristics, curative surgery and chemotherapy plan, and adverse events (AEs). No experimental intervention was imposed; treatment was determined by the treating physician. Data presented reflect the second interim analysis at 3 years. Further follow-up will be at 5 years post-enrollment.

Results: 1,537 patients were enrolled in 10 countries: Taiwan (n=432); Korea (n=417); China (n=327); Hong Kong (n=147); Vietnam (n=69); Philippines/Singapore (n=64); Pakistan (n=39); Bangladesh/India (n=42). Mean age was 47.7 years (range: 23-83); 52.4% (n=804) were premenopausal, and 38.8% (n=595) postmenopausal. Most patients (97.4%, n=1495) had high or intermediate risk of recurrence. 59.3% (n=910) were ER positive; 43.1% (n=662) were HER2 positive. Total mastectomy was the most common surgical intervention (72.6%, n=1116) and sequential docetaxel therapy the most frequently administered adjuvant chemotherapy (56.5%, n=860), followed by combination therapy (38.2%, n=581) and other regimen (13.5%, n=68). 8.0% of patients received concomitant granulocyte-colony stimu-

lating factor (mean 3.6 cycles). Incidences of AEs are shown in Figure 1.

Conclusions: Interim findings of this observational study suggest that sequential docetaxel-based adjuvant chemotherapy is a core component of care for Asia-Pacific BC patients at high risk of recurrence.

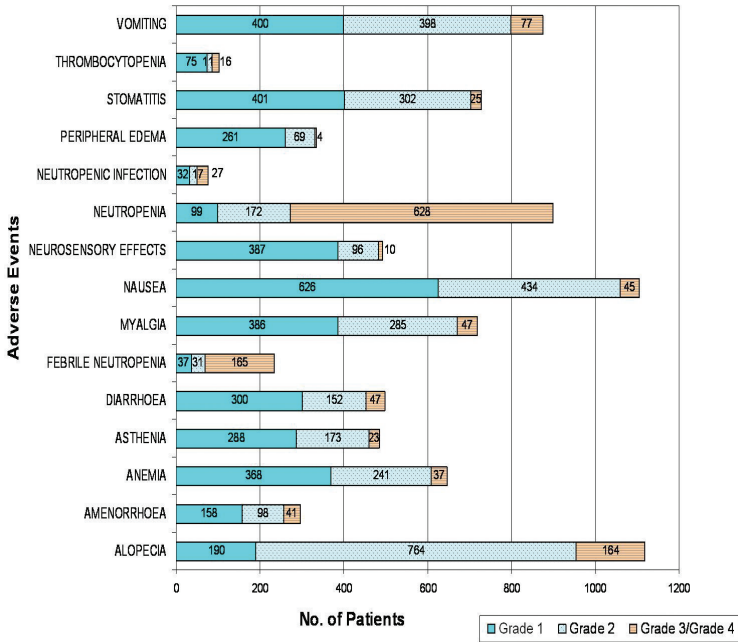


Fig. 1. Incidence and grade of adverse events (n=1522, safety population).

Oncoplastic Technique for Breast Malignancy with Nipple Discharge: A Case Report

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Background/Purpose: Nipple discharge that accompanies a breast malignancy has traditionally been an indication for mastectomy. But oncoplastic approaches is emerged, the lesions presenting with nipple discharge may be treated by central wide excision.

Methods : A 54-year-old woman presented with abnormal mammographic finding. Breast USG showed about 2.0 cm sized mass with tiny microcalcification in left subareolar area. She was taken core needle biopsy at outside local clinic. The result showed low grade ductal carcinoma in situ. During physical examination, we found a bloody nipple discharge. We performed central wide excision with oncoplastic reconstruction preserving nipple projection and sentinel node biopsy. Frozen biopsy for nipple margin was reported as no tumor cell. Final pathologic report showed 0.2 cm sized invasive ductal carcinoma within 1.2 cm sized ductal carcinoma in situ and the margin status was free from tumor. The sentinel node biopsy showed no tumor cell. The patient was taking radiotherapy and hormonal treatment.

Conclusions: This operation method could be a good impact on patients satisfaction but there is no data relating to directly surgical approaches that preserve the nipple for cancer with nipple discharge. We need to study the long term result.



Fig. 1. Left nipple discharge with subareolar mass, preoperative state.



Fig. 2. Postoperative state.

Mindfulness, Positive Cancer Coping Styles, and Posttraumatic Growth in Breast Cancer Survivor

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Background/Purpose: Mindfulness is receptive attention and awareness of present experiences and it is known to be associated with coping in cancer patients. Mindful cancer survivors are more likely to do positive coping and adopt themselves to post-treatment lives. The purpose of this study is to examine structural relationships among mindfulness, positive cancer coping styles, and posttraumatic growth in breast cancer survivors.

Methods: Breast cancer patients who finished treatment (except hormone therapy) at least one year ago were included in the study. Patients were recruited at a tertiary cancer center in Seoul. Mindfulness, positive cancer coping styles, and post-traumatic growth were defined theoretical latent variables and measured using self-respondent questionnaires. Hypothetical models drawn from different theories were tested, and the data were analyzed using SPSS 15.0 and AMOS 7.0.

Results: Total 170 breast cancer survivors answered questionnaires whose mean age is 50.9 and mean month of diagnosis is 44.3. There were significant correlations among mindfulness, positive cancer coping styles, posttraumatic growth. Mindfulness was positively correlated to positive cancer coping styles and both of them are positively related to posttraumatic growth. It was not significantly related with post-traumatic growth when we control the positive cancer coping styles. Yet, mindfulness seemed to affect posttraumatic growth and positive cancer coping styles seemed to mediate its effect.

Conclusions: The result supports important roles of mindfulness on adaptive coping process and its positive outcomes such as positive cancer coping styles and posttraumatic growth.

Which of Neoadjuvant Chemotherapy Regimes is Higher Response Rate in Advanced Breast Cancer between TA and FAC?

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Background/Purpose: Neoadjuvant chemotherapy can expand the number of breast cancer patients who can be treated with breast-conserving surgery and can predict benefit from adjuvant chemotherapy. Because there is several kinds of neoadjuvant chemotherapy, we need of response rate according to neoadjuvant chemotherapy regimens. So we have investigated the response rate of neoadjuvant chemotherapy, and compared of response rate according to TA or FACq.

Methods: 43 patients was injected neoadjuvant chemotherapy in our hospital due to breast cancer from Jan 2001 to Dec 2005. 25 patients was injected neoadjuvant chemotherapy using TA. 18 patients was injected that using FAC. we used Cross table as analyzing methods in clinicopathologic factors distributions between two groups.

Results: The mean age at diagnosis was 48.9 yr old (range 29-63 yr). The tumoral response to neoadjuvant chemotherapy using TA was, 3 patients (12%) showed a complete response (CR), 17 patients (68%) showed a partial response (PR), and the response to that using FAC was, 2 patients (11.1%) showed a complete response (CR), 12 patients (66.6%) showed a partial response (PR). The overall response rate to neoadjuvant chemotherapy was 80.0%, 77.7% respectively.

Conclusions: There is no difference in response rate between TA and FAC. In our study that pathological response is not a favorable prognostic factor following neoadjuvant chemotherapy.

Outcomes in Breast Conserving Surgery (BCS) with Immediate Vicryl Mesh Insertion

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Background/Purpose: Although BCS has become standard therapy in breast cancer surgery with improved cosmetic outcome, many attempts to achieve superior result have been introduced. One of the oncoplastic surgery, Vicryl mesh insertion is frequently used methods. Therefore, we tried to analyze aesthetic outcomes and patient's satisfaction, as well as technical issues and complications of Vicryl mesh.

Methods : From May 2007, until March 2009, 65 patients who had BCS and completed questionnaire were enrolled. 34 patients received BCS with Vicryl mesh insertion and other 31 patients had only BCS. Retrospective analysis of patient record and oral interview was performed. Patients were graded in the 5 score system overall satisfaction, shape and pain.

Results : 15 of 34 patients (44.1%) who had BCS with mesh insertion were satisfied with their outcome. 9 of 31 patients (29.1%) who had BCS were satisfied with their outcome. But there was no meaning statistical difference ($p=0.140$). 21 patient underwent aspiration at follow up visit. (mean aspiration frequency and amount: 1.02 ± 1.21 , 99.9 ± 76.39 ml) Four cases of complication have been observed, 2 patients who had removed Vicryl mesh at POD #30 and #34 due to infection. One patient had wound dehiscence and the other patient suffered from recurrent infection.

Conclusions: In this study, BCS with immediate Vicryl mesh insertion showed acceptable results of patient satisfaction and failure rate. Considering the side effects and no difference in satisfaction between two-groups as a better cosmetic method we must reconsider the mesh insertion and need to make further investigation into the risk factors of complication and failure.

TAC (Docetaxel-Doxorubicin-Cyclophosphamide) Combination in Adjuvant Chemotherapy of Breast Cancer (BC) with G-CSF Primary Prophylaxis? Results of Russian Observational Multicenter Study

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Background/Purpose: Adjuvant TAC is highly effective in breast cancer (BC) but is associated with febrile neutropenia (FN) rate over 20%. Primary endpoint of this observational study was FN rate of adjuvant TAC with G-CSF primary prophylaxis.

Methods: From 23.10.2006 to 30.09.2008 patients with stage T1-3N1M0 BC, 18-69 years, ECOG PS 0-2, with no prior therapy except surgery received Taxotere 75 mg/m², Doxorubicin 50 mg/m², Cyclophosphamide 500 mg/m² q3w, 6 cycles. G-CSF in standard doses started from cycle 1 on day 2-5 for minimum 5-7 days at each cycle. All toxicities including FN were defined according to NCICTC.

Results: Median age of 101 enrolled patients was 47.5 years (range 25-67). Median interval between surgery and chemotherapy was 0.9 months. Total number of cycles was 585, mean 5.8 ± 0.7 , median 6.0 (range 1-6.0) per patient. 91 patients (90.1%) completed 6 cycles. Lenograstim and filgrastim use: 71 patients (5.9 ± 1.2 days/cycle) and 30 patients (5.6 ± 1.4 days/cycle), correspondingly. FN occurred in 9 (8.9%) patients at 19 (3.2%) cycles, median duration 4 days (range 2-18). Neutropenic infection occurred in 3 (3%) patients at 4 (0.78%) cycles. Treatment was delayed at 6 cycles and Taxotere dose was reduced in 1 pt (1%) at 2nd cycle due to hematological toxicity. There were no grade 3-4 non-hematological toxicities, SAEs and deaths.

Conclusions: Adjuvant TAC with G-CSF primary prophylaxis was well tolerated, had low FN rate allowing 90% patients to receive complete treatment.

Parameter	% of patients
Stage IIa	18,8%
Stage IIb	27,7%
Stage IIIa	48,5%
ECOG PS 0-1	94%
ECOG PS 2	5.9%

Fig. 1. Patients' characteristics.

Grade	1-2	3	4
Leucopenia (per pt/per cycle, %)	26,7 / 18	6,9 / 4,3	3,0 / 0,5
Neutropenia (per pt/per cycle, %)	20,8 / 12,9	5,0 / 3,6	5,0 / 1,0
Thrombocytopenia (per pt/per cycle, %)	31,4 / 12,5	1,0 / 0,2	0
Anemia (per pt/per cycle, %)	41,5 / 17,8	0	0

Fig. 2. Hematological toxicity.

Comparison between Nipple-Areola Saving Subcutaneous Mastectomy and Conventional Subcutaneous Mastectomy in Local Relapse and Prognosis: 5 Year Follow-Up Results

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Background/Purpose: There is no report of long term result of skin-sparing mastectomy (SSM) and nipple-areola-skin sparing mastectomy (NASSM) in Korea.

Methods: 202 patients who underwent SSM (N=67) or NASSM (N=135) for breast cancer were included in analysis. Local recurrence (LR) rate and disease free survival (DFS) was analyzed and compared the result between NASSM and SSM.

Results: The mean follow-up month of NASSM was 70.9 months and 60.5 months in SSM. 60 NACs (29.7%) of the all objective NACs were involved by cancer cell. Neoplastic NAC involvement was more common in invasive carcinoma with extensive intraductal component ($p<0.001$) or ductal carcinoma in situ component ($p=0.048$). But tumor size, vascular invasion and nodal status did not affect to NAC involvement. LRs occurred in 8.9% (NASSM) and 6.0% (SSM) of all patients ($p>0.05$). LRs occurred at NAC (8 cases), skin flap (3 cases) and chest wall (1 cases) in NASSM group, and 4 skin flaps in SSM group. All NAC recurrences were treated by wide excision of NAC. After treatment of LR, only one case of SSM group proceeded to distant metastasis. 5 year DFS rate was 88.2% in NASSM and 88.4% in SSM group ($p>0.05$).

Conclusions: Our long term follow-up study shows that NASSM is oncologically safe procedure for breast cancer in patients who are candidates for mastectomy. Even if relapse is occurred in the NAC, this recurrence cannot affect to the progression of relapse after adequate local treatment. Thus, NASSM is alternative method for SSM with oncological safety and better cosmetic outcome.

Lapatinib Plus Capecitabine for HER2-positive Advanced Breast Cancer in Patients with or without Prior Exposure to Capecitabine: A Single Institutional Experience of Lapatinib Early Access Program

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Background/Purpose: The combination chemotherapy of lapatinib and capecitabine has shown activity in women with HER2-positive advanced breast cancer that has progressed after use of anthracycline, taxane, and trastuzumab. We investigated the activity of lapatinib plus capecitabine in a single institution and evaluated whether prior capecitabine exposure affect the outcome.

Methods: Women with HER2-positive locally advanced or metastatic breast cancer that had progressed after chemotherapy including anthracyclines, taxanes, trastuzumab with or without capecitabine received lapatinib and capecitabine combination therapy. The primary end point was time to progression and the secondary end points were overall response, clinical benefit, and overall survival.

Results: Between February 2007 and April 2008, 39 women with locally advanced or metastatic breast cancer received a total of 386 cycles of lapatinib and capecitabine combination therapy. Of those, 13 patients had previously received capecitabine. The median follow-up was 12.4 months and time to progression was 6.3 months (95% CI, 2.0-10.6). Overall response was 38.5% and clinical benefit was 92.3% and median overall survival was 16.1 months. These clinical outcomes were comparable with previous studies. There were no significant differences in median time to progression (8.2 vs. 4.2 p=0.3), overall response (85.7% vs. 23.0%, p=0.16), clinical benefit (96.1% vs. 8.4%, p=0.2), and overall survival (19.5 vs. 12.5, p=0.2) between capecitabine-naïve and capecitabine previously treated patients.

Conclusions: We confirmed the acceptable clinical activity of combined lapatinib and capecitabine even in previously anthracycline, taxane and trastuzumab pre-treated HER2-positive metastatic breast cancer and treatment outcomes did not seem to be affected by prior capecitabine exposure.

Low Axillary Recurrence after Sentinel Lymph Node Biopsy Alone after Median Follow-Up of 6 Years

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Background/Purpose: The aim of this prospective study was to determine the frequency, pattern of recurrence and survival rate after sentinel lymph node biopsy (SLNB) alone in early breast cancer patients with negative sentinel lymph node (SLN).

Methods: Between August 1999 and May 2004 at Gangnam severance hospital, 314 patients with T1 or T2 and clinical node negative breast cancer patients who underwent SLNB with subareolar intradermal injection technique using Tc-99m antimony trisulfide colloid. Of the 199 patients with negative SLN in frozen sections, 133 patients received SLNB alone and 63 patients underwent further axillary lymph node dissection.

Results: The mean tumor size was 1.6 cm and the mean number of removed SLNs was 1.8. Of 123 patients had negative SLN in permanent pathology, 6 patients showed sub-micrometastasis and 4 patients had micrometastasis. After median follow-up of 72 months, 3 patients had systemic recurrence (2.3%), 3 patients had breast recurrence (2.3%) after breast conserving treatment and only one patient developed ipsilateral axillary recurrence (0.8%). Ipsilateral axillary recurrence was found 101 months after SLNB alone. During follow up period systemic or local recurrence was not show in patients with sub-micometastatic or micrometastatic SLN following SLNB alone. 5 year overall survival rates and 5-year disease free survival rates were 97.5% and 95.5% respectively.

Conclusions: The rate of axillary recurrence and systemic recurrence were low in SLN negative early breast cancer patients who received SLNB alone, but further long term follow up data with large number of patients are required.

The Early Assessment of Response to Chemotherapy by Using ^{18}F -FDG PET in Breast Cancer

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Background/Purpose: Until now preoperative chemotherapy has the role for the more patients to undergo breast conserving surgery in advanced breast cancer. Even though some useful methods developed for prediction of response to chemotherapy, it is still difficult to apply in clinic. This study aimed to evaluate the possibility of early prediction of response to chemotherapy by using ^{18}F -FDG PET in breast cancer.

Methods: Women (N=12) who were received preoperative chemotherapy in 9 patients and palliative chemotherapy in 3 patients for breast cancer were evaluated the response to treatment by using ^{18}F -FDG PET after one or 2 cycle chemotherapy. The ^{18}F -FDG PET taken baseline before treatment and after one or two cycle chemotherapy was measured semi-quantitatively using maximum standardized uptake values (maxSUVs). And then we analyzed the correlation between response to chemotherapy and maxSUVs of ^{18}F -FDG PET in individual patients.

Results: Two of 12 were pathologic complete response and one was radiological complete response in patients taken preoperative chemotherapy. Their maxSUV 60minutes delayed (60 md) were all less than 2.0 and indicated the more decrease of maxSUV 120 minutes delayed (120 md) than maxSUV 60 md in ^{18}F -FDG PET after one or two cycle chemotherapy. The maxSUV 60 md of 3 partial response cases were between 2.0 and 2.5 and maxSUV 60 md of 6 stable cases were more than 2.5.

Conclusions: The sequential ^{18}F -FDG PET from baseline to the early cycle of chemotherapy showed the possibility of the prediction of response to chemotherapy as early as the first cycle of chemotherapy in breast cancer.

Breast Cancer Patients' Distress due to Alopecia and its Relationship with Body Image

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Background/Purpose: Women are generally concerned with their appearance including weight and body. Such premorbid concerns are often deeply ingrained and can contribute to psychological distress of breast cancer patients. Breast cancer patients experience various altered appearance including loss of breast and darkening skin, and alopecia is the most often and stressful event. This study aims to examine breast cancer patients' distress due to alopecia and its relationship with body image.

Methods: Of total 344 women with breast cancer participated in this study, and their mean age was 49.9 (SD 0.42). Participants were recruited at public events that provided beauty education to women with cancer at 16 different locations in Korea. We measured specific distress (0-3, 0=not at all 3=very much) due to alopecia using a tool developed for this study. The tool includes 27 questionnaires related to physical symptoms, emotion, daily activities, and social relationship. Body image was measured using EORTC-BR23.

Results: More than 80% patients (255) reported distress due to alopecia. Patients reported higher distress related to their emotion (Mean=1.08, SE=0.9) compared to daily activities (Mean=0.75, SE=0.77) and social relationship (Mean=0.74, SE=0.76). Distress due to alopecia was negatively associated with body image and it was statistically significant (coefficient=-12.68, p=0.000). Patient who reported higher distress reported lower body image.

Conclusions: Most of breast cancer patients experienced distress due to alopecia, and it was strongly correlated with lower body image. Alopecia is a side effect that breast cancer patients cannot avoid. It is necessary to provide proper education and emotional support by clinicians.

Vacuum-Assisted Biopsy for Single Duct Nipple Discharge

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Background/Purpose: To identify the feasibility of vacuum-assisted biopsy applied for diagnosis and treatment in patient with nipple discharge.

Methods: From March 2006 to March 2009, 50 vacuum-assisted biopsies in 45 patients were performed under sonographic guidance for diagnosis and treatment of single nipple discharge which was bloody, serous, or watery. A portion of the dilated duct or suspicious lesion was excised including just that of under the nipple.

Results: Histopathological results showed 34 papillomas, 12 fibrocystic changes, and 1 fibroadenoma. 3 cases were confirmed to DCIS and treated appropriately. Among 47 cases except three DCIS cases, recurrence of nipple discharge was identified in 3 cases (6.4%). In them, two were recommended microdocheotomy, one observation.

Conclusions: Our results showed 6.4% of recurrence of nipple discharge when diagnosed and treated with vacuum-assisted biopsy. More experiences and data are needed to classify the appropriate case to be treated with vacuum assisted biopsy in patient with nipple discharge.

Perceived Body Change and Distress due to Surgery in Women with Breast Cancer

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Background/Purpose: A large proportion of women with breast cancer experience distress due to cancer treatment induced altered appearance. However, few studies examined women's perceived body change and its distress. The goal of this study was to examine perceived body change and distress of women with breast cancer.

Methods: Participants were recruited at public events that provided beauty education to women with cancer at 16 different locations in Korea. Patients were asked about their attitude on appearance, perceived body change due to surgery. In addition distress due to altered appearance and quality of life were measured in this study.

Results: Of total 352 women with breast cancer participated in this study, and their mean age was 49.9 (SD 0.42). About half of the participants (116, 47.4%) were currently receiving treatment and more than 75% of patients (185) were stage I and II when they were diagnosed. More than 45% of patients reported severe changes of their breast, and there was no difference between patient who had lumpectomy and mastectomy ($p=0.09$). Patients who were 5 years more survivors still experienced distress due to change of their breast, and it was not different from patient either how are during the treatment or who just finished the treatment ($p=0.496$).

Conclusions: Patients equally perceived body changes regardless of surgical treatments or survivor period. In addition, they keep experiencing distress due to surgery induced body change, even 5 years after the surgery. Further investigation is necessary for exploring factors associated distress due to perceived physical change.

Clinical Significance of Ki-67 in Neoadjuvant Chemotherapy for Primary Breast Cancer as a Predictor for Chemosensitivity and for Prognosis

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Background/Purpose: Neoadjuvant chemotherapy (NAC) is one of the main strategies for patients with locally advanced breast cancer. In this retrospective study, we focused on Ki-67 as a biological marker and examined the correlation between Ki-67 and chemosensitivity, and the prognosis after the start of treatment.

Methods: Between July 1996 and March 2008, 148 patients with tumors ≥ 3 cm in diameter or lymph node metastases received NAC and surgery. The variables investigated were ER/PgR, HER2 and Ki-67 from core needle biopsy. NAC consisted of 3 different regimens (EC, ET, FEC-DOC).

Results: Clinical response was 79.7% and pCR was 14.2%. Multivariate analysis revealed that Ki-67 was significantly related to pCR. Moreover, there was no pathological responder in cases with Ki-67 $< 25\%$. The Ki-67 values significantly decreased after NAC (from 45.0% to 17.5% in the median value). Patients with cCR had significantly lower Ki-67 values after NAC. There was a significant difference in the Ki-67 value in terms of the presence and the absence of recurrence (median value: 26.0% with recurrence vs. 12% without recurrence). The DFS was significantly lower in the patients with Ki-67 $< 12\%$ after NAC than those with Ki-67 $\geq 12\%$.

Conclusions: The Ki-67 value before NAC was a significant predictive factor for the effectiveness of NAC. The Ki-67 values after NAC significantly decreased and correlated with clinical response and DFS. Therefore, the higher Ki-67 values ($\geq 25\%$) before NAC as well as the lower values ($< 12\%$) after NAC, might be clinically significant for treating patients.

The Assessment of Breast Cancer Response and the Prediction of Pathologic Complete Response to Neoadjuvant Chemotherapy: Comparison of MRI and PET

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Background/Purpose: To retrospectively compare dynamic contrast enhanced MRI and 18F-fluorodeoxyglucose PET/CT in the assessment of tumor response to neoadjuvant chemotherapy.

Methods: This retrospective study was approved by our institutional review board and informed consent was waived. Between August 2006 and May 2008, 32 women (mean age: 46.4 years old) with breast cancer underwent concurrent MRI and PET/CT before and after neoadjuvant chemotherapy. The response evaluation criteria in solid tumors (RECIST) were used for the response assessment in MRI with the measurement of the maximum dimension of the tumor (Dmax). The assessment criteria of PET/CT were defined as follows; complete response (CR) as no hypermetabolic activity, partial response (PR) as 50% or more reduction of standard uptake values (SUV), non-response (NR) for the others. The correspondence rates and the degree of agreements between each imaging and pathologic assessment were calculated. The sensitivity, specificity, positive and negative predictive values (PPV, NPV) in the prediction of pathologic complete response (pCR) were evaluated. Statistical analysis was performed by using Pearson correlation and McNemar test with the statistical significant $p < 0.05$.

Results: The pathologic assessment of tumor response to neoadjuvant chemotherapy identified 8 pCR (25.0%), 10 PR (31.2%), and 14 NR (43.8%). The correspondence rate of response assessment was 75.0% (24/32) between MRI and pathology, 53.1% (17/32) between PET/CT and pathology, and 53.1% (17/32) between MRI and PET/CT. In the prediction of pCR, specificity (95.8% vs. 62.5%) and PPV (83.3% vs. 47.1%) were statistically higher in MRI than PET/CT ($p < 0.05$), while sensitivity (100% vs. 62.5%) and NPV (100% vs. 88.5%) of PET/CT tended to be higher than MRI.

Conclusions: Before and after neoadjuvant chemotherapy for breast cancer, Δ Dmax in MRI moderately correlates with Δ SUV in PET/CT. For the prediction of pCR, MRI was a more specific method than PET/CT.

Axillary Recurrence and Systemic Metastasis after a Negative Sentinel Lymph Node Biopsy for Breast Cancer

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Background/Purpose : Sentinel lymph node biopsy (SLNB) is standard procedure to assess axillary lymph node status and to avoid axillary lymph node dissection (ALND). The aim of this study is to evaluate rate of axillary recurrence and systemic metastasis in early breast cancer with a negative sentinel lymph node.

Methods: Between May 2000 and Dec 2006, among 1,074 patients underwent SLNB with breast cancer and clinically negative axilla, 142 patients (13.2%) with ductal carcinoma in situ and 263 patients (24.5%) performed additional ALND with axillary metastasis or micrometastasis were excluded, 669 patients (62.3%) with a negative SLNB and without additional ALND were enrolled to this study.

Results: With a median follow up of 43.6 months (range 1-103.6), axillary recurrences and synchronous systemic metastasis was detected in 1 patient (stage I, ER/PR/HER-2 +/-/3+, chemotherapy, radiation, tamoxifen) 31 months after SLNB, 1 patient (stage IIa, ER/PR/HER-2 -/-/-, chemotherapy, radiation) was diagnosed with axillary recurrence followed by systemic metastasis 20 and 29 months after SLNB. The incidence of false negative SLNB is 0.29% (2/669). In 14 patients (2.10%) systemic metastases were detected with a 28.3 months (range, 9.2-46.4) median follow up. Only 1 patient expired due to multiple metastases 45.7 months after SLNB.

Conclusions: The false negative rate was 0.37%, systemic metastasis was 2.42% with 43.6 months median follow-up after SLNB in T1-2 invasive breast cancer with clinically negative axilla. Our results suggest that SLNB in invasive breast cancer without ALND is reliable and safe procedure.

The Role of Lymphangiogenesis in Lymph Node Metastasis of the Microinvasive Breast Cancer

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Background/Purpose: The presence of axillary lymph node metastasis in ductal carcinoma in situ (DCISM) is variable (0-14%). To ascertain the role of lymphangiogenesis to predict the lymph node metastasis in DCISM, we compared the lymphangiogenesis and angiogenesis by the presence of lymph node metastasis in the group which did axillary dissection with breast surgery due to DCISM.

Methods: We identified the 47 patients who underwent breast surgery with axillary dissection to evaluate the LN status with a diagnosis DCISM from June 1996 to March 2008. With two markers, D2-40, specific for lymphatic vessels to study lymphangiogenesis and CD34 for angiogenesis, breast pathologist and one observer counted the number the blood and lymphatic vessel density. Among these 47 patients, 9 patients had a axillary lymph node metastasis.

Results: Lymph vessel density (LVD) was lower than blood vessel density (BVD) in both groups. In the patients with lymph node metastasis, LVD was higher than that of the patients without lymph node metastasis, however, there was no statistical significance. And we also compared with that of other factors, such as size and type of underlying DCIS, nuclear grade, presence of lymphovascular invasion, estrogen receptor (ER), progesterone receptor (PR) and c-erbB2. Of these factors, presence of LN metastasis with nuclear grade and total score of PR showed statistical relation.

Conclusions: There was increasing tendency of LVD and BVD in the group of LN metastasis, but there was no statistical significance. Further studies will be needed.

Which DCIS Patients Should be Performed Sentinel Node Biopsy?

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Background/Purpose: Currently, sentinel node biopsy is a standard method to evaluate axillary metastasis in breast cancer. However, in ductal carcinoma in situ patients, axillary lymph node metastasis is rare and at present there is no indication to determine which patients should be considered from sentinel node biopsy. In this paper, we would like to assess the necessity of sentinel biopsy when core biopsy is diagnosed as DCIS.

Methods: We chose 169 patients, who were diagnosed as DCIS by core-needle biopsy at Seoul National University Hospital between 1996 and 2006, as our sample population. We examined the cases of positive lymph node and then analyzed characteristics of them.

Results: 169 patients were diagnosed as DCIS by core-needle biopsy in preoperative time. 27 patients had no axillary staging. Of these 142 patients who had axillary staging, 7 patients (4.9%) were found that they had axillary metastasis. Sonographic mass size greater than 1.6 cm was significantly associated with lymph node metastasis ($p=0.018$). Another risk factor associated with metastasis were mass on mammography ($p=0.021$) and multifocal lesion ($p=0.015$). Preoperative MRI size did not have correlation ($p=0.078$).

Conclusions: The statistical analysis shows that sentinel node biopsy should be performed when patients with core-needle-biopsy diagnosed DCIS have mass on mammography, mass greater than 1.6 cm and multifocal lesions.

Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy for Breast Cancer

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Background/Purpose: Neoadjuvant chemotherapy (NAC) has been evolved and increasingly used in the management of patients with various stage of breast cancer instead of postoperative adjuvant chemotherapy. However, it remains controversial whether sentinel lymph node biopsy (SLNB) is suitable for patients after neoadjuvant chemotherapy. In this study, we attempted to assess the feasibility and accuracy of SLNB after NAC.

Methods: We reviewed the chart of a total of 89 patients who are previously treated by NAC between January 2006 and December 2008. The patients underwent SLNB followed by axillary lymph node dissection (ALND). The sentinel lymph node(SLN) was mapped by radioactive colloid alone or blue dye alone or combination.

Results: The patients' median age was 43 years. Sixty eight of these patients were premenopausal. At the beginning of treatment, 78 women had clinically positive axillary nodes. The mean tumor size was 3.7 cm at the initial evaluation. The mean tumor size reduced from 3.7 cm to 1.6 cm, and 19 of 89 patients (21%) showed a pathologic complete response(pCR) after neoadjuvant chemotherapy. The 61 patients underwent breast conserving surgery. The rate of SLN identification was 92.1% (82/89), and the false negative rate was 13.0% (6/46).

Conclusions: The SLN identification and false-negative rates were similar to rates in non-neoadjuvant studies. Sentinel lymph node biopsy after NAC is therefore considered to be a feasible and accurate method to predict the AXLN status. Even in the case of clinically suspicious axilla metastasis and the case of pathologically proven, the false negative rate remains acceptable.

The Effects of Preoperative ^{18}F -FDG-PET/CT in Breast Cancer Patients in Compare of Conventional Imaging Study

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Background/Purpose: Recent years, ^{18}F -FDG-PET/CT has been studied in diverse cancer including breast cancer for diagnosis, staging and for follow up. In this study, we have investigated the potential effects of ^{18}F -FDG-PET/CT in the initial assessment of patients with primary breast cancer.

Methods: Sixty consecutive biopsy proven invasive breast cancer patients enrolled in this study. Patients underwent conventional imaging studies including mammography, Breast USG and Breast MRI for local assessment and Chest PA, Abdomen USG, Bone scan for rule out distant metastasis. All sixty patients underwent ^{18}F -FDG-PET/CT in initial assessment.

Results: The median age was 51 (30-75) years. Breast USG and MRI detect all sixty primary breast lesions. But in 4 patients (6.7%), ^{18}F -FDG-PET/CT showed no evidence of primary breast lesion. Axillary LN metastases were found in 26 out of 60 patients. The sensitivity and specificity of ^{18}F -FDG-PET/CT to detect axillary LN metastasis were 91% and 57%, whereas the sensitivity and specificity of conventional imaging were 88% and 54%, respectively. Extra-axillary LN metastases were found in 6 out of 60 patients. ^{18}F -FDG-PET/CT detected all extra-axillary LN metastasis, but conventional imaging detected only one extraaxillary LN metastasis. The sensitivity and specificity of ^{18}F -FDG-PET/CT in detecting distant metastasis were 100% and 87.5%, whereas the sensitivity and specificity of conventional imaging were 94% and 62%, respectively.

Conclusions: ^{18}F -FDG-PET/CT had no advantage in detecting primary breast lesion and axillary LN metastasis in compare of conventional imaging studies. Rather, ^{18}F -FDG-PET/CT is a valuable tool in detecting unsuspected extra-axillary LN metastasis and distant metastasis in compare of conventional imaging studies.

The Role of Telemammography Using Soft-Copy CR in Japan

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Background/Purpose: Despite the increase of licensed mammographers and radiologists who can participate in screening in Japan, distribution of them is uneven especially in rural. Digital Mammography is spreading and it enables teleradiology; however, the majority of them in Japan are CR (computed radiography) mammography. We elucidated the advantage and problems of telemammography using soft-copy of CR.

Methods: We interpret the soft-copy CR mammograms transferred from a screening facility to our institute via the optic fiber using 5 M pixels monitor.

Results: Between July 2005 and March 2008, we interpreted 15,805 screeners. The recall rate was 6.15%, the cancer detection rate 0.32%, and the positive predictive value 5.2%. This result was almost equivalent to those of conventional film screen mammograms in Japan.

Conclusions: Digital mammography enables image optimization through the control of window level and width, reduction of storage space, easy access to the previous mammograms; moreover, teleradiology can reduce the time and costs of data transfer. However, there still remain some problems concerning interpretation and network management. Especially interpretation of two or more kinds of soft-copy CR using one viewing system is difficult without soft-copy standardization.

The Axillary Recurrence after SLN Biopsy Alone in SLN Negative Breast Cancer Patients

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Background/Purpose: Sentinel lymph node (SLN) biopsy has become routine practice in the surgical therapy for clinically axillary lymph node (ALN) negative breast cancer patients. However, SLNB has a false-negative rate of 0-22%. In addition, axillary recurrence is a major concern after a SLNB alone in patients with breast cancer. In this study, we investigated rate of axillary recurrence after SLNB.

Methods: 318 patients with clinically ALN negative breast cancer who underwent SLNB between Jan. 2003 and Dec. 2007 at Dongsan Medical Center. SLNs were identified using the combined method. SLNs were examined by frozen sections and standard HE stain. We retrospectively reviewed the medical records of 216 patients who had negative SLNs. All patients who had negative SLNs received SLNB only.

Results: The SLN identification rate was 99% (315/318). A Mean tumor size was 1.7 cm and a mean of 1.5 SLNs were removed per patients. All 216 patients received adjuvant therapy according to standard treatment guideline. At a median follow-up of 41 months (range 14-76), 91% (196/216) of patients were re-assessable and axillary recurrence was observed in only one patient (0.5%, 1/196). At 52 months after operation, axillary recurrence was developed. Postoperative stage and hormone receptor status of recurred patient were T2 (2.2 cm), N0 (0/1) and positive.

Conclusions: The axillary recurrence rate after SLNB alone in SLN negative breast cancer patients was very low (0.5%, 1/196). According to our result, omitting ALN dissection is concluded to be safe in patients who received adequate SLNB and had negative SLN. This low axillary recurrence rate supports wider use of SLNB for breast cancer staging.

Comparative Studies in Breast Cancer: Breast-Specific Gamma Imaging (BSGI) and MRI in the Detection of Malignant Lesion, BSGI and USG in the Diagnosis of Axillary Lymph Node Metastasis

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Background/Purpose: We aimed to assess the correspondence of malignant lesion with BSGI and MRI, and to identify the sensitivity and specificity of BSGI for the detection of axillary lymph node (ALN) metastasis comparing with USG.

Methods: From April to May, 2009, a retrospective review of prospectively collected 144 patients diagnosed breast cancer by biopsy was performed. Patients underwent BSGI with intravenous injection of 30 mCi of ^{99m}Tc-Sestamibi through contralateral antecubital vein. Within 10 minutes, images were obtained in the craniocaudal (CC) and mediolateral oblique (MLO) view. All patients underwent surgical resection. All imaging findings (BSGI, MRI and USG) were correlated with pathologic diagnosis.

Results: The mean age of the patients is 49.7 ± 9.4 years (range of 27 to 77). In 144 patients, 167 malignant lesions identified by pathologic results (invasive cancer: 137 (82%), DCIS: 15 (9%), invasive cancer with carcinoma in situ 15 (9%)). MRI found 167 malignant lesions, and BSGI found 156 malignant lesions. The corresponding rate was 93.4% between BSGI and MRI. There were 8 false positive findings and 11 false negative findings in BSGI. In the diagnosis of axillary lymph node metastasis, the sensitivity, specificity, and accuracy were 32.7%, 92.1%, and 69.4% for BSGI, and 49.1%, 77.5%, and 66.7% for USG.

Conclusions: There was a high correspondence (93.4%) between BSGI and MRI on malignant lesions in breast but, BSGI may have low diagnostic value in assessment of ALN metastasis comparing with USG.

Anatomical Susceptibility to Arm Lymphedema after Breast Surgery with Axillary Lymphnode Dissection (ALND)? What we Learned from Mapping of Arm Lymphatic Flow

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Background/Purpose: Is susceptibility to arm lymphedema after ALND explained by anatomical variation of individual arm lymphatic flow?

Methods: 42 arms of 21 postoperative cases with unilateral ALND and 10 arms of 5 healthy volunteers were subjected to LINF (Lymphatic Imaging with Non-radioactive Fluorescent tracer). A fluorescent dye, indocyanine green was injected intradermally near the wrists. The fluorescent image was observed under near infrared light illumination through CCD camera. Lymphatic flow patterns to the axilla of healthy arms without ALND were categorized and the relation to severity of lymphedema of contra-lateral arms with ALND was studied.

Results: LINF for healthy arms showed following three lymphatic flow patterns or their combination, (1) a single flow to the axilla, (2) multiple flows to the axilla, (3) accessory flow which does not reach axilla but drains deeply into deep lymphatic network halfway. LINF for healthy volunteers showed that arm lymphatic flow pattern is almost identical in both arms. In cases with flow pattern (1) alone (n=6), 2 cases (33%) showed clinically evident lymphedema in their contra-lateral arm with ALND. 3 cases (50%) showed lymphedema of subclinical level. In the other cases (n=15), no one showed clinically evident lymphedema and 7 cases (47%) showed lymphedema of subclinical level.

Conclusions: In this study, we showed that patients who have only a single lymphatic flow to the axilla have higher risk to develop arm lymphedema after ALND. Mapping of arm lymphatic flow by LINF may be a useful tool to predict individual susceptibility to arm lymphedema after ALND.

Breast-Specific Gamma Imaging with ^{99m}Tc-Sestamibi in the Diagnosis of Breast Cancer

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Background/Purpose: Breast ultrasonography (US) is the most widely used diagnostic method for detecting breast cancer. Recently, Breast-Specific Gamma Imaging (BSGI) has been introduced as an alternative screening tool in breast cancer. However, there are only few studies concerning BSGI. Therefore, we planned to analyze the diagnostic performance of BSGI and compared its result with that of breast US in this study.

Methods: From February 2009, until June 2009, 47 patients underwent BSGI alone and 183 patients underwent breast US and BSGI simultaneously at Ewha Womans University Mok-dong hospital. 9 patients who underwent breast US were excluded from this study because of incomplete evaluation or already proven malignancy. Prospective analysis was performed.

Results: Mean age was 45 ± 10.29 (Range 21 to 78). BSGI was positive for 65 (28.3%) of the patients and negative for 165 (71.7%) Sensitivity and specificity of BSGI was estimated 94.1% and 91.0% respectively. A positive predictive value (PPV) of 75.4% with a negative predictive value (NPV) of 98.2% were calculated. And sensitivity and specificity of breast US was 95.8% and 85.9%. A PPV and NPV of breast US was 70.8% and 98.3% respectively.

Conclusions: In this study, BSGI showed good result in the detection of breast cancer. Although further investigation with larger population may be necessary, we may suggest BSGI as an alternative in screening breast cancer.

Necessity of Surveillance Mammography in Patients with Postoperative Breast Cancer: A Retrospective Study

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Background/Purpose: Current guidelines recommend surveillance mammography of the contralateral breast for all breast cancer patients. To evaluate surveillance mammography in detecting contralateral breast cancer after the operation of unilateral breast cancer by retrospective study.

Methods: We treated with 3,216 breast cancer patients from 1 August 1972 to 28 February 2009 in Gunma Prefectural Cancer Center, and 75 asynchronous contralateral breast cancer patients were included. Sixty patients were operated unilateral breast cancer and contralateral one in our hospital, Fifteen patients were operated unilateral breast cancer in other hospital and contralateral one in our hospital.

Results: We classified asynchronous contralateral breast cancer patients to three groups. Group A: No continuous follow-up: 40 cases. Group B: Continuous follow-up without surveillance mammography: 24 cases. Group C: Continuous follow-up with surveillance mammography: 11 cases. Rate of Clinical tumor size under 2.1 cm was 47.5% in the Group A, 45.8% in the Group B, 90.9% in the Group C. Mean pathological tumor size was 2.21 cm in the Group A, 2.25 cm in the Group B, 0.78 cm in the Group C. Rate of DCIS (ductal carcinoma in situ) was 7.5% (3/40) in the Group A, 4.2% (1/24) in the Group B, 36.4% (4/11) in the Group C. In these three items, although the difference was not in A and B, the significant difference was in A and C ($p < 0.05$).

Conclusions: In order to detect contralateral breast cancer early, we confirmed that surveillance mammography is needed for the patients after the operation of unilateral breast cancer.

Initial Experience of Breast Specific Gamma Imaging (BSGI)

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Background/Purpose: The purpose of this study is to evaluate the impact of Breast-specific gamma imaging (BSGI) for the diagnostic tools at our breast center.

Methods: We performed a retrospective review of the initial data of patients underwent BSGI performed as part of the imaging work-up between November 2008 and June 2009. BSGI were classified according to focal uptake as normal (score of 1), with no focal or diffuse uptake; benign (score of 2), with minimal patchy uptake; probably benign (score of 3), with scattered patchy uptake; probably abnormal (score of 4), with mild focal uptake; and abnormal (score of 5), with marked focal uptake. Mammography and ultrasonography were categorized according to BI-RADS criteria. Patients with abnormal BSGI or ultrasonography were underwent biopsy.

Results: A total of 715 patients underwent BSGI because of suspicious imaging, abnormal physical examination, foreign body implant, multiple lesions or high risk patient. Positive result in BSGI with 30.6% was evaluated. Seven patients with a new diagnosis of cancer obtained BSGI for further work-up. False-positive results included fibroadenoma, intraductal papilloma, phyllodes tumor, atypical ductal hyperplasia, atypical lobular hyperplasia.

Conclusions: Breast-specific gamma imaging can be a useful additional diagnostic tool and detect the occult cancer in negative conventional studies. But some limitation of this study was exposed. Multiple heterogeneous patchy uptake was complicated to evaluate of the breast lesion and high proliferative benign lesion could be revealed in false positive. Furthermore, pathologic confirmation in BSGI only positive lesion was difficult. We need further studies will be needed to continue to define the role of BSGI.

The Role of Sentinel Lymph Node Biopsy in Ductal Carcinoma In Situ of Breast Diagnosed by Preoperative Biopsy

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Background/Purpose: The aim of the study is to investigate the role of sentinel lymph node biopsy (SLNB) for the patients with ductal carcinoma in situ (DCIS) diagnosed by preoperative biopsy.

Methods: Three hundred eleven patients preoperatively diagnosed with DCIS were enrolled in the study. We reviewed final pathology of primary tumor and lymph nodes status, and evaluated positive rate of SLNB, DCIS underestimation rate of core needle biopsy (CNB), and survival rate.

Results: Among 311 patients, 110 (35.4%) cases turned out invasive components of the tumor at the final pathology. Preoperative CNB and incision biopsies were performed in 254 and 57 patients, respectively. The underestimation rate of CNB was much higher than that of incision biopsy (107/254 [42.1%] vs. 3/57 [5.3%], $p < 0.001$). The positive rate of SLNB in cases that turned microinvasive or invasive cancer at the final pathology were 9.1% (10 out of 110 patients). Five years recurrence free survival (RFS) rate of the postoperative DCIS cases was higher than that of the microinvasive or invasive cancer cases which were confirmed by the final diagnosis, however, there was no statistically significant difference between them (5 years RFS rate; 100% vs. 93.0%, $p = 0.117$).

Conclusions: Because the rate of DCIS underestimation with preoperative CNB was about up to 40%, and about 9% of DCIS underestimation cases showed sentinel node metastasis, it is necessary to perform SLNB for the patients with DCIS diagnosed by preoperative CNB. The SLNB may contribute to reducing the risk of missing metastatic axillary lymph nodes in this group of patients.

Outcomes of Incidentally Detected Breast Lesions by Chest CT Scan, Based on Histopathologic Correlation

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Background/Purpose: To analyze of the histopathologic findings of incidentally detected breast lesion by chest CT scan and to predict the imaging findings of suggesting malignancy.

Methods: We retrospectively reviewed the medical records of 41 cases of breast abnormalities, detected by chest CT scan for screening and diagnostic CT scan (total 198 chest CT scans). Most of the patients were women (M:F=3:38). According to the CT scan, follow up evaluation were done by breast US and mammography. Histopathologic correlation was done if there's any finding, suggesting malignancy and over category 4a lesions and follow up breast US were done for cat, 3 lesions.

Results: Of 41 patients, 13 cases (31%) were confirmed as malignancy (8 invasive ductal carcinoma, 2 ductal carcinoma in situ, 1 mucinous carcinoma, 1 small cell carcinoma, 1 lymphoma). Remaining 28 cases were benign lesion, (19 were fibrocystic disease, 7 were fibroadenomas, 2 were intramammary lymph nodes). The CT features, suggesting malignancy were speculated margin (8/13), peripheral rim enhancement (5/13), axillary node enlargements (4/13), central low attenuation area (3/13), perilesional infiltrations (3/13). Associated calcifications, size and multifocal nodular enhancement were also shown in malignant lesions.. Conversely, smooth well defined margin of the mass was more common in benign lesions (17/28 cases).

Conclusions: Based on our study, significant rates of malignancy were found in incidentally detected breast malignancies by chest CT scan. The CT findings of spiculated margin and peripheral enhancement with axillary lymphadenopathy were reliable findings in predicting malignancy.

Follow-Up CT for PET-CT Detected Hypermetabolic foci in Breast Cancer Patients

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Background/Purpose: To evaluate the outcomes of the PET hypermetabolic foci in the lungs of breast cancer patients, correlated with follow up CT findings.

Methods: For recent 4 years, we retrospectively analyzed the PET-CT and follow up chest CT findings of breast cancer, who received operation. Total 61 patients were included (age range from 34 to 69 years old). The mean interval between PET- CT and chest CT was less than 51 days (from 3 to 102 days). In 9 patients, pathologic correlation was done for the nodule or consolidative lesions (percutaneous needle biopsy in 7, excision in 2), detected in CT scan. Remaining 52 patients, follow-up CT scans were done.

Results: In 9 cases, three were granulomas, four cases were metastatic lesions from breast cancer, two cases were primary lung cancers (adenocarcinomas). Remaining 52 patient, 37 lesions were decreased (26 lesions) or disappeared (9) on follow up CT scan. In fifteen patients, the nodular lesions were stable over 2 years follow up.

Conclusions: The hypermetabolic foci, detected in follow up PET of breast cancer patients, follow up CT is essential and pathologic correlation and correlation with laboratory findings are important to exclude metastatic and new malignant lesions.

Usefulness of an Ultrasound-Guided Mammotome Biopsy Device for Excision of Bilateral Multiple Benign Breast Lesions in Patients Younger than 35-Years Old

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Background/Purpose: Percutaneous vacuum-assisted breast biopsy (Mammotome, Fa. Ethicon Endo-Surgery Breast Care) is commonly performed as the initial approach to diagnose and treat benign breast lesions. Its indication is more wider recently, Mammotome biopsy is applied not only a single tumor but bilateral multiple lesions. The purpose of this study was to report our experience of Mammotome biopsy to bilateral multiple breast lesions in patients younger than 35 years old.

Methods: We performed 197 cases of Mammotome biopsy (total 76 patients) to excise bilateral multiple benign breast lesions in younger than 35 years old, between January 2003 and December 2008 in Chosun University Hospital. They were followed up for more than 6 months, and then ultrasonographic follow-up examinations were performed. We analyzed clinical and pathologic results retrospectively.

Results: The mean patient age was 26.7 (range: 17-35) years. The average number of lesions was 2.5. 62 patients (81.6%) had one-stage procedure, and the others underwent 2-stage procedure. 179 lesions (90.9%) were completely removed, 18 cases (9.1%) of residual lesion was reported. Ultrasonographic follow-up after 6 months of procedure revealed that 12 patients had a newly demonstrated mass. Among them, 5 patients underwent additional Mammotome or excisional biopsy, and other 7 patients are under observation.

Conclusions: Mammotome biopsy is an effective management of bilateral multiple benign breast lesions with high accuracy and patients' comfort.

False Negative Sentinel Nodes Biopsy after Operation

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Background/Purpose: Sentinel nodes (SLN) biopsy is common in many hospitals. Some problems are rising. One is the management of false negative SLN biopsy by permanent section diagnosis. The necessity of additional axillary lymph nodes dissection is unknown. We analyzed the false negative SLN biopsy cases in our hospital retrospectively.

Methods: From May 2004 to July 2008, 295 cases were performed SLN biopsy by the combination of RI (99mTc-tin colloid) and dye (Indocyanine Green). SLN were sliced 2 mm thin and examined by HE stain during operation. Permanent section were examined by HE and immunohistochemistry (cytokeratin).

Results: 295 of 298 cases were identified SLN and 246 cases were diagnosed node negative. Eight of 246 were converted to node positive (3%). The size of metastatic lesion was 2.5 mm, 1.0 mm, under 0.4 mm (five cases) and ITC. Three cases were confirmed by reexamination of frozen sections, however five cases could not be confirmed metastatic lesion. All patients were treated adjuvant therapy as lymph node positive except refused and aged patients. At that time, there is no recurrence in 8 patients.

Conclusions: False negative SLN biopsy after operation is 3% and the size of metastatic lesion is small (under 0.4 mm) in 6/8 cases.

Evaluation of GeneSearch™ System on Stored Frozen Sentinel Lymph Node Samples from Chinese Breast Cancer Patients

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Background/Purpose: GeneSearch™ System is a technique using real time RT-PCR to detect the mRNA of cytokeratin 19 (CK19) and mammaglobin (MG) as markers of metastasis in sentinel lymph node (SLN) of breast cancer. We carried out a retrospective study using this system on stored frozen SLN samples from Chinese breast cancer patients for verification.

Methods: Previously, a series of SLN samples had been gathered and cut along long axis into two equal parts: one half stored in -80°C tissue bank and the other sent for routine pathological examination. GeneSearch™ system (from Veridex) was used to detect mRNA of CK19 and MG in these frozen samples. Positive node was defined as either one or both of MG and CK19 detected. Results were compared to pathological reports.

Results: 59 SLNs were assayed to yield 20 positive nodes and 39 negative nodes. Of the 20 positive nodes, 16 were pathologically positive and 4 were negative. Of the 39 negative nodes, 1 node was pathologically positive and 38 were negative. Sensitivity was 94.1% (16 of 17) and specificity was 90.5% (38 of 42). Overall concordance was 91.5% (54 of 59), positive predictive value was 80% (16 of 20) and negative predictive value was 97.4% (38 of 39).

Conclusions: Our data showed that the sensitivity, specificity, concordance, and positive and negative predictive values are all comparable to those obtained in the prospective trials using fresh nodal tissues. Our study in Chinese patients has confirmed the reliability of GeneSearch™ Breast Lymph Node Test Kit even in stored frozen samples.

Clinical Implementation of OSNA (One-Step Nucleic Acid Amplification) Assay for Intraoperative Diagnosis of SLN Metastasis in Breast Cancer Patients

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Background/Purpose: Histopathological method to examine breast cancer metastasis in sentinel lymph node (SN) varies among institutions. In addition to the issues of cumbersome specimen preparation, variable quality of specimen and inconstant diagnosis accuracy, histopathological methods can inherently examine only a part of SN. Furthermore, no standardized method is available for quantitative diagnosis of cancer cells in metastasis foci. To solve these issues, OSNA method, which amplifies CK19mRNA rapidly and directly from SN homogenate, has been introduced to our institution since last November. We report the results from clinical use of OSNA in our institution.

Methods: Dissected SN was divided at 1 or 2 mm intervals. All slices were submitted to OSNA after examination of every cutting surface by imprint cytology (IC). OSNA reported the result of SN metastasis detection in 3 different classifications (2+, 1+, and [-]) according to the detected CK19mRNA concentration. Concordance between IC and OSNA as well as the turnaround time of OSNA were evaluated.

Results: Concordance rate between IC and OSNA was 90.4% (103/114). Six of 7 discordant results were IC negative but OSNA positive by 1+. Only 1 SN resulted in cytology positive but OSNA negative with low CK19mRNA concentration, which suggests the possible existence of ITC. The average turnaround time of OSNA was 40 minutes per patient.

Conclusions: OSNA helped us avoid 6 second surgeries and 1 over-surgery. OSNA can be applied in an intra-operative clinical setting, and contribute to standardizing the breast cancer treatment by minimizing the variability in the method and accuracy of SN diagnosis.

Comparison of the Self Care Behavior According to Mental Adjustment to Cancer

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Background/Purpose: This study was to compare the differences in self care behavior between fighting spirit group and helplessness group.

Methods: This study utilized a cross-sectional descriptive design. A total of 97 ambulatory cancer patients completed the Mental Adjustment to Cancer (MAC) scale by Watson et al. (1988), and Self Care Behavior Scale by Oh et al. (1997). The data was analyzed using frequency, percentage, t-test, ANOVA, Pearson's correlation and stepwise multiple regression.

Results: Fighting spirit group were found to conduct self care behavior more comparing to the helplessness group ($t=3.346$, $p=0.000$). The score of the self care behavior in fighting spirit group was 4.42 out of a total score of 7 and that of helplessness group was 3.85. There was a significant difference ($p=0.000$) in self care behavior according to the level of faith and performance status. Fighting spirit ($R^2=0.120$, $p=0.000$), performance status ($R^2=0.078$, $p=0.001$) were predictive of a self care behavior.

Conclusions: Cancer patients' mental adjustment is correlated with the degree of the self care behavior. Fighting spirit is one of the most adaptive adjustment to cancer.

From the Eyes of American Teenagers: Images of Breast Cancer Awareness

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Background/Purpose: Many teenagers have experienced the impact of breast cancer through family, school friends and neighbors. There is no other long term health concern that has had so great an influence on cancer awareness among teens or created more opportunity for participation in advocacy and support activities. Since its first use in 1991, the pink ribbon has become the universal symbol of Breast Cancer Awareness, seeming to appear everywhere. A Google search produced 799,000 website listings of pink ribbon products ranging from t-shirts and day planners to toaster ovens and BMWs. Along with its popularity, the breast cancer symbol has also stirred controversy; critics argue that “pinkwashing”, the widespread use of the symbol to boost sales, does not contribute to the fight against breast cancer in a meaningful way. This study asks what teenagers think about pink ribbon products and the extent to which they are aware of how product purchase helps the cause.

Methods: A photo voice approach is used to combine photos of high school students using pink products and brief interviews to produce a conference poster.

Results: Teens go out of their way to buy pink ribbon products but do not know how much money goes to the cause, what organizations and kinds of programs benefit, or if a product is associated with reduced disease risk.

Conclusions: Teens are supportive of the breast cancer cause but are ill informed about how product endorsements can or should help. Teen ideas for direct advocacy and fund raising are discussed.

A Study on the Relationship of Upper Extremities Function, Pain and Anxiety in the Breast Cancer Survivors

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Background/Purpose: The purpose of this study was to identify the degree of upper extremities function, pain, and anxiety in the breast cancer survivors and to clarify the relationship among these variables.

Methods: Participants of this study were 122 breast cancer survivors who had lumpectomy or mastectomy and other adjuvant treatments. Data were collected from November 1 to December 25, 2006 using measurement of upper extremities function, face pain rating scale and state-trait anxiety inventory. Data were analyzed by descriptive statistics, t-test, ANOVA and Pearson correlation using the SPSS Win 11.5.

Results: Among the survivors of the breast cancer, Mean upper extremities function was 3.56, pain was 2.02, anxiety was 2.23. The group who didn't have religions experienced more pain in comparison to those who had religions. The group who didn't have religions were more anxious than those who had religions. Also, the group with lower socioeconomic status rated higher in anxiety level than those with higher status. The upper extremities function showed lower rate with the group who were treated by radiation. The anxiety rated higher in the group who were treated by radiation. There were significant negative correlation of upper extremities function and anxiety, and positive correlation of pain and anxiety.

Conclusions: Findings suggested that the breast cancer survivors have experienced upper extremities function disorder, pain and anxiety. To promote their health, nursing interventions to manage pain, anxiety, upper extremities function are needed.

The Relationship between Stress and Quality of Life in Mothers of Children with Cancer

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Background/Purpose: The purpose of this study was to identify the levels of stress and quality of life and their relationship in mothers of children with cancer and to provide basic data for developing nursing intervention programs for them.

Methods: The participants in this study were 138 mothers whose children have been treated for cancer in seven university hospital located in Busan and Ulsan, Dageu. The data were collected by structured questionnaire from March 2 to 31, 2009. Data analysis was done using SPSS Win/12.0 program.

Results: 1. The mean score for the stress level in the mothers of the children with cancer was 2.93 ± 0.60 (tool range; 1~4). 2. The mean score for the level of quality of life in the mothers of the children with cancer was 2.95 ± 0.42 (tool range; 1~5). 3. There were significant difference level of stress according to presence of spouse, financial status, medical benefits. 4. There were significant difference in level of quality of life according to mother's perceived financial status, child's schooling status. 5. There was a moderately negative correlation ($r=-0.41$, $p=0.000$).

6. Among the factors influencing mothers' quality of life, perceived health status, family relationship and personal role, mothers' perceived child's school life adaptation, marriage satisfaction explained 56.1% of quality of life of mothers.

Conclusions: This study might help in developing nursing intervention programs to reduce stress and improve quality of life in mothers of children with cancer, and it is necessary to consider above mentioned relating factors for planing of nursing intervention programs.

Effects of Behas Exercise Program on Health Related Physical Strength, Stress, Self-Esteem and Quality of Life in Breast Cancer Survivors

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Background/Purpose: The purpose of this study were to identify effectiveness of a BeHaS program that consists of exercise, education, and cognitive supports to improve health related physical strength, stress, self-esteem, quality of life in breast cancer survivors.

Methods: The research design was non-synchronized research design with non-equivalent control group. The effects of the BeHaS program was tested at two points; before and 10 weeks after the intervention. The subjects of breast cancer survivors participating in this research were selected from Chungnam National University Hospital located in Deajeon city, consisting of 30 experimental group and 31 control group. BeHaS (Be Happy and Strong) program for patients with breast cancer consisted of exercise, education, encouranging of self-esteem. Data collection were performed during the period from February to June 2008. The effects of BeHaS program is measured based on shoulder flexibility, a grip strength, perceived stress, cortisol, self-esteem, quality of life.

Results: The scores of grip strength, shoulder flexibility, self-esteem and quality of life of the experimental group were significantly higher than those of the control group. The perceived stress of the experimental group was significantly lower than that of the control group.

Conclusions: In conclusion, this study suggested that BeHaS program plays a useful role in improving breast survivors physical, psychological problem and quality of life.

Relationship of Quality of Life, Fatigue and Perceived Family Support in Korean Cancer Patients

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Background/Purpose: Quality of life is not only very important in the process of treatment but also prognosis of breast cancer. Family can support especially for cancer patients to overcome cancer and cancer treatment in Korean society. The purpose of this descriptive study was to explore quality of life, fatigue and perceived family support in Korean cancer patients.

Methods: The subjects of the study were 81 cancer patients who were admitted in three general hospitals around in Kyungpook province from January 8th to April 10th, 2007. The research instruments utilized in this study were quality of life (FACT-G), fatigue (FACT-F) in Korean version 4 and Tae's family support scale (1985). Data were analyzed using Pearson correlation, t-test and ANOVA with SPSS/WIN 12.0.

Results: Score of quality of life in cancer patients showed a significant difference in purpose of treatment, change in weight, performance status, exercise, and state of sleep. Fatigue of cancer patients showed a significant difference in performance status, change in weight change, exercise, and state of sleep, type of treatment. Family support of cancer patients showed a significant difference in the marital status, education level, income, living together, helper, type of treatment, and change in weight. The mean score of quality of life in cancer patients was 53.04. The mean score of fatigue of cancer patients was 22.53. The mean score of family support in cancer patients was 30.48. Quality of life in cancer patients showed a negative correlation to fatigue significantly ($r=-0.710$, $p<0.000$). Quality of life in cancer patients showed a positive correlation to family support significantly ($r=0.499$, $p<0.000$).

Conclusions: The results demonstrate the need for intervention to improve quality of life, to reduce fatigue and to increase in family support for cancer patients according to the physical state and general characteristics of each patients. It is necessary that the development of nursing education program for family which help to support the cancer patient in improving the quality of life and for reducing fatigue.

Evaluating the Benefits of a Two-Week Community-Based Breast Cancer Training Program in Shanghai, China

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Background/Purpose: A two-week intensive training program was offered by the Cancer Club in Shanghai, China to improve the quality of life among breast cancer survivors. The training program included three main aspects: understanding treatment options, building relationships among members for support, and coping with stress. Participants checked into the dormitory at the Cancer Club and spent two weeks living together as a group during the training. Although the Cancer Club has been offering cancer support groups as well as training programs for the past fifteen years, this evaluation project is the first one conducted with a community participatory approach.

Methods: Two focus groups were conducted before and after the intensive training to assess the reasons for participating in this training program and how they view their quality of life before and after the training. A total of thirty participants were included. All the participants were female and diagnosed with different stages of breast cancer. The contents of the focus group discussion were recorded in Chinese and the PI of the project analyzed the data with the assistance of the Co-PI and two research assistants.

Results: Preliminary qualitative results indicated a positive response to participating in the training. Overall quality of life was reported to have improved. Although it was not the intent of the intervention, participants reported their main reason to enroll in the training was to prevent the recurrence of breast cancer. Most participants reported that they experienced extreme stressors before they were diagnosed with breast cancer and hoped to learn how.

Quality of Life, Sexual Function, and Depression between Sex and Sexless Group among Mastectomy Women

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Background/Purpose: This study was to investigate the differences between quality of life, sexual function, and depression according to sexual activity among breast cancer survivors.

Methods: Participants were one hundred and six women who had spouse and participated in self-help group in Gwangju, South Korea. The questionnaires were composed of Quality of Life Index-Cancer Version (Q.L.I.-C) (Ferrans, 1990), self-rating depression scale (Zung, 1965), and Female Sexual Function Index (FSFI) (Rosen et al., 2000). Data were analyzed using the SPSS Win 14.0 K+ for descriptive statistics, t-test, ANCOVA, and MANOVA.

Results: There were no homogeneity at age, job, educational years between sex and sexless group. In sex group, mean age was 46.1, having job 34.5%, bachelor's degree 38.2%, and pre-menopause 79.2%; in sexless group, 49.6, 10.4%, 12.5%, and 52.7% separately. There were significantly differences of quality of life, sexual function, and depression between two groups controlled with four covariates. The quality of life and sexual function in sex group were significantly higher than sexless group ($p < 0.001$). The depression in sex group was significantly lower than sexless group ($p < 0.001$).

Conclusions: This study indicates that nurses are needed to counsel and intervene psychosexual approach especially sexless breast cancer survivors during the recovery period.

<Table 1> Comparisons of QOL, FSFI, and Depression between Two Groups

		Sex group		Sexless group		t	p
		(n=55)		(n=48)			
		M	±SD	M	±SD		
QOL-C	Total	17.27	± 1.62	15.90	± 1.20	4.37	.001
	Family	3.33	± 1.82	1.86	± 1.55	4.327	.001
	Health	2.16	± 1.74	1.23	± 2.41	2.258	.026
	Psychological	2.14	± 2.16	0.30	± 1.84	4.593	.001
	Spiritual	2.20	± 1.88	1.20	± 1.21	3.186	.002
	Economic	1.72	± 1.92	0.10	± 2.50	3.712	.001
FSFI	Total	19.62	±8.74	9.66	±8.30	5.91	.001
	Desire	2.81	+1.33	2.18	+1.33	2.438	.017
	Arousal	2.97	+1.53	1.64	+1.67	4.216	.001
	Lubrication	3.47	+1.78	1.55	+1.63	5.050	.001
	Orgasm	3.31	+1.69	1.33	+1.59	6.104	.001
	Satisfaction	3.39	+1.51	1.63	+1.81	5.295	.001
	Pain	3.67	+2.14	1.33	+1.77	5.978	.001
Depression	Total	37.24	± 6.46	44.66	± 8.50	4.88	.001

QOL : quality of life FSFI : female sexual function index

Fig. 1. Comparisons of QOL, FSFI, and Depression between Two Groups.

<Table2> ANCOVA of Q.L.I.-C, FSFI, and Depression by Sexual Activity

Source	Q.L.I.-C				FSFI				Depression			
	SS	df	F	p	SS	df	F	p	SS	df	F	p
Main effect*	29.80	1	13.75	.001	1411.15	1	22.36	.001	1096.26	1	19.38	.001
Covariates												
1.Age	.05	1	.02	.880	371.19	1	5.88	.017	.99	1	.02	.895
2.Education (yrs)	3.49	1	1.61	.208	349.28	1	5.54	.021	44.93	1	.79	.375
Error	214.61	99			6247.40	99			5487.36	97		
Corrected Total	258.92	102			9903.97	102			6917.49	100		

* Sexual Activity
 Q.L.I.-C : Quality of Life Index-Cancer Version
 FSFI : female sexual function index

Fig. 2. ANCOVA of Q.L.I.-C, FSFI, and Depression by Sexual Activity.

A Preliminary Study of Physician Patient Communication Characteristics in Breast Cancer Care

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Background/Purpose: The purpose of this study is to examine the applicability of the RIAS and to explore the characteristics of physician-patient communication in breast cancer consultation.

Methods: 106 outpatients who visited 10 physicians (5 medical and 5 surgical disciplines) and 26 breast cancer patients who had appointments with one medical oncologist and one surgical oncologist in two university affiliated medical centers were approached and invited to the study. The medical visits were videotaped for whom signed informed consent. The recorded encounters were analyzed using the RIAS, which codes each phrase or complete thought expressed during the visit by either patient or physician into 1 of 42 mutually exclusive categories.

Results: The RIAS categories were applicable to analyze the physician-patient interaction. The characteristics of communication in breast cancer care were different from those of non cancer patient encounters. The physicians of breast cancers showed more psycho-emotional talks than physicians of non cancer patients.

Conclusions: The RIAS seems to be practically applicable to Korea. The further studies are needed to explore characteristics of breast cancer communication and its clinical impact on patient outcomes.

Content Analysis of Needs of Cancer Survivors in Korea

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Background/Purpose: The purpose of this study was to identify needs of cancer survivors from the time of cancer diagnosis through survivorship in Korea.

Methods: Qualitative interviews were conducted with 30 cancer survivors in 2008. The eligibility criteria of participants were: (1) aged 18 or above; (2) diagnosed with one of 6 major cancers (breast, cervix, stomach, lung, colon, and liver); (3) without any marked co-morbidity; (4) able to express one's experience vividly. Participants were recruited from outpatient clinics in one university hospital located in South Korea. All interviews were recorded and transcribed according to content analysis process.

Results: Five main categories were extracted from the content analysis. Those were physical need, emotional need, informational need, relation/support need, and practical help. Informational need had 5 subcategories which were nutrition, activity/exercise, diagnostic test and treatment, comprehensive alternative therapy, and cost. Sixty-five specific needs were identified from the 5 categories such as evidence-based information on nutritional supplements, taking comfort from health professionals, symptom management, etc.

Conclusions: Findings of this study illustrated the needs of Korean cancer survivors from patients' viewpoints. Cancer treatment staff should be especially alert for the needs of cancer survivors and try to match need and service.

Psychometric Evaluation of the Needs Scale for Patients with Cancer

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Background/Purpose: The purpose of this present study was to develop and evaluate psychometric properties of a Needs Scale for patients with cancer (NS-C).

Methods: Forth-seven items of the preliminary NS-C were derived from literature reviews and in-depth interviews with cancer patients. The items had content validated by oncology physicians and nurses. Each item consisted of a five-point Likert scale. The preliminary NS-C and ECOG performance status questionnaires were administered to 818 Korean outpatients recruited from three university hospitals. The data obtained was analyzed using a factor analysis for construct validity, ANOVA for known-groups validity, and Cronbach's alpha for internal consistent validity.

Results: From the factor analysis, a total of 40 items and six subscales were significantly derived. The subscales were named emotional need, diet and exercise, support, physical need, relationship with health professions, and treatment. The patients who had lower performance status tended to have higher level of needs, meaning of that known-groups validity was established. The Cronbach's alpha of the total NS-C was 0.96 and the alpha of the subscales ranged from 0.90 to 0.95.

Conclusions: This study suggests that the NS-C is a reliable and valid instrument to measure the needs of cancer patients. Health professionals may use the NS-C to patients with cancer in practice and research.

Supportive Care Needs of Patients with Advanced Lung Cancer

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Background/Purpose: This study was conducted to examine the supportive care needs perceived by the patients with advanced lung cancer and the related factors influencing on the supportive care needs.

Methods: Data were collected with the Supportive Care Need Survey (SCNS) questionnaire from 105 patients with advanced lung cancer scheduled for palliative chemotherapy or taking chemotherapy. Levels of needs in each domain, differences of needs in each domain by variables and the level of influence of variables on the patients' needs in individual items were analyzed.

Results: The mean standardized scores of supportive care need in each domain were from 24.13+25.89 to 53.44+24.25. Health system & informational needs were highest among all domains. Levels of needs in each domain showed statistically significant differences according to factors; a) age and experience of chemotherapy regimen changes (psychological), b) education level and distant metastasis (physical & daily living), c) marital status (sexuality), d) experience of chemotherapy regimen changes (others). Frequency of high needs in individual items was higher in the group of female, age of sixties, middle school graduates, longer than one year after diagnosis, prior to chemotherapy, more than three times of chemotherapy regimen changes, and distant metastasis.

Conclusions: The patients with advanced lung cancer had high levels of supportive care needs compared with other cancer, especially in health system & informational domain. The patients who changed chemotherapy regimen more than three times experienced higher needs. These results would suggest the direction and priorities in providing patient-centered supportive care for patients with advanced lung cancer.

Concept Analysis of Supportive Care for Cancer Patients

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Background/Purpose: The objective of this study was to clarify the concept of supportive care (antecedents, attributes, and results) applied to cancer patients.

Methods: This study analyzed the concept of supportive care for cancer patients using a hybrid model composed of the stages of theoretical phase, fieldwork phase, and final analytical phase. The subjects of fieldwork phase were 4 medical practitioners who were taking care of cancer patients, 1 guardian, and 1 patient, so a total of 6 people. In order to collect data, we wrote down the contents of in-depth interviews and 8 researchers read and extracted themes jointly from the recorded contents of interviews. In the final analysis phase, we made comparative analysis on the dimensions, precedents, attributes, and results of supportive care extracted from the theoretical phase and fieldwork phase, and redefined supportive care from the viewpoint of cancer patients.

Results: The dimensions of supportive care were divided into emotional, informational, instrumental, physical, spiritual, and social dimensions. The precedents of supportive care were lack of coping abilities, uncertain future, lack of information and knowledge, and role change. The attributes of supportive care were being together, sympathy, religious commitment, social support, provision of information and knowledge, improvement in physical comfort, communication, and trust. The results of supportive care were physical comfort, self-esteem, trust, performance of self-care behaviors, acceptance of realities, and acquisition of information and knowledge.

Conclusions: For cancer patients, supportive care means every available support from nurses. It is necessary to provide adequate supportive care according to the progress of disease.

Changes of Sexual Life and Couple Intimacy in Pre-Post Treatment of Gynecologic Cancer Patients

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Background/Purpose: This is a descriptive study to identify the change of sexual life and couple intimacy in pre-post treatment of gynecologic cancer patients and to provide basic data for developing nursing intervention programs.

Methods: The participants of this study were one hundred fifty married women who were undergoing follow-up for cancer treatment in one university hospital located in Busan. The data were collected by structured questionnaire from January 5 to March 31, 2009, and analyzed with frequency, percentage, mean, paired t-test, ANOVA, Scheffe's test and Pearson's Correlation Coefficients utilizing SPSS/Win 12.0 program.

Results: 1. There was a significant negative change in attitude of sexual behavior (paired $t=-7.892$, $p=0.000$) in post-treatment (6.93 ± 2.83) as compared with pre-treatment (5.21 ± 1.53 , tool range; 4~16) 2. The level of sexual desire in post-treatment was significantly higher than that in pre-treatment ($t=-3.692$, $p=0.000$). coital frequency and frequency of foreplay in post-treatment were significantly lower than that in pre-treatment. 3. There were no significant changes level of couple intimacy in pre-post treatment (paired $t=1.643$, $p=0.103$). 4. There were significant difference in level of attitude of sexual behavior according to age ($F=3.234$, $p=0.024$), religion ($F=3.982$, $p=0.004$), whether sexual education is needed (paired $t=-2.366$, $p=0.019$). 5. There were significant difference in level of couple intimacy according to working status (paired $t=-2.192$, $p=0.030$), insurance payment ($F=3.514$, $p=0.010$), type of treatment ($F=4.095$, $p=0.008$).

Conclusions: These results suggest that the nursing intervention considering changes of sexual behavior is needed to promote the sexual life of gynecologic cancer patients in the affirmative.

Development of a Specific Distress Questionnaire Module for Cancer Treatment Related Hair-Loss in Breast Cancer Patients

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Background/Purpose: ‘Hair loss’ is a common side effect of adjuvant and chemotherapy regimens with breast cancer treatment. It is often described as harder than losing a breast and some patients even refuse chemotherapy because of expected hair loss. However, little research has been conducted. We develop a specific distress questionnaire module to assess psychosocial distress due to treatment related alopecia in breast cancer patients.

Methods: Relevant distress issues were generated from literature searches and interviews and surveys with health professionals and patients. Issues were constructed into items and pretested in 403 patients in 16 different hospitals in Korea.

Results: The resulting module includes 24 items related to physical symptoms, emotion, daily activities, and social relationship issues specific to distress related to hair loss. Women were most likely to have distress related to emotion following by daily activities. Their physical symptoms were least likely to be related to the distress. More than 40% patients reported that they often had distress due to hair loss while 14.5% patients had no stress at. Patients who had severe hair loss experienced more than 10 times distress due to alopecia compared to patient who had no hair loss.

Conclusions: The results of the study ensure that the module will be sensitive to assess the small but important distress in patients who experienced alopecia. The use of the module will provide a comprehensive system of quality of life assessment in breast cancer patients.

The Experiences of Prayer among Terminal Cancer Patients Focusing on Christianity and Buddhism

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Background/Purpose: Terminal cancer patients can experience significant spiritual distress whether they have religion or not. It is necessary that oncology nurses are aware of the unique spiritual needs of living with terminal cancer and provide the spiritual care. The patients use prayer to cope with distressing symptoms and the illness experience, so that prayer appears to be a significant coping strategy. There are several studies only about Christianity nonetheless the prayer is important for them, therefore we want to know the differences and experiences of the prayer depending on the religion. Specific purposes are 1. obtain descriptions of cancer patients' the use of prayer and the meaning from semi-structured interviews, 2. analyze and present these descriptions, 3. identify what they pray about and the outcomes expected, and the differences between Christianity and Buddhism.

Methods: It is an inductive and descriptive study using phenomenology.

Sample

- 1) Participants with terminal cancer who were being treated in the hospital or receiving home hospice care have less 6 months of life duration.

Procedure

- 1) Data was collected during audiotape recorded semi-structured interview.
- 2) Interview took place in researcher's office, head nurse's room and patient's home.

Results: Each taped interview was transcribed verbatim, initially each transcribed interview was read. Two researchers to become intimate with thoughts and feelings of the informants and significant statements were underlined for extraction for the theme. Two researchers compared the data to identify the salient and recurrent themes and compared them across participants to better understanding their meaning.

Could be Bilateral Breast Cancer an Prognostic Factor for Recurrence and Survival?

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Background/Purpose: Recently, because the early detection of breast cancer is increasing and overall survival is improving, increasing number of women at risk of developing a bilateral breast cancer. However, the clinical significance of bilateral breast cancer is unclear and its influence on prognosis is controversial. The goal of this study was to evaluate clinicopathologic characteristics of bilateral breast cancer and to determine whether women with bilateral breast cancer have a worse prognosis than patients with a unilateral tumor.

Methods: Between January 1, 1995 and January 31, 2009, 1,842 women were treated for primary breast cancer. The mean age was 47.9 years; median follow-up time was 56.2 months.

Results: A total 1,842 women with breast cancer, including 54 (3.0%) bilateral breast cancer, were 28 (1.57%) had synchronous bilateral breast cancer, 26 (1.46%) had metachronous bilateral breast cancer. The mean age of the patients with bilateral breast cancer was younger than unilateral breast cancer (44.87 and 48.05 years, $p=0.037$). There was no significant difference in overall survival among the three groups. But patients with bilateral breast cancer had worse 3-years disease-free survival rates compare with unilateral breast cancer patients. On multivariate analysis, bilaterality was independent risk factor for recurrence.

Conclusions: We have found that bilateral breast cancer tends to occur in young age and patients with bilateral breast cancer are at the greater risk for local recurrence than women with unilateral breast cancer. Also patients with bilateral breast cancer, especially metachronous bilateral breast cancer are at greater risk for distant metastasis than women with unilateral breast cancer.

Triple Negative Breast Cancer Has a Worse Prognosis within 3 Years after Treatment Compared to Non-Triple Negative Breast Cancer

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Background/Purpose: Triple negative breast cancers (TNBC) become known as poor prognosis generally. Our purpose was to compare the clinical features and outcomes for TNBC with other subtypes of breast cancers in Korea.

Methods: We included 2,907 patients who diagnosed breast cancer and treated at Asan Medical Center from 2003 to 2005. All features were reviewed throughout medical records retrospectively.

Results: 622 patients (21.4%) had TNBC. TNBC patients was associated with younger age, larger size, higher tumor grade, positive p53 compared non-TNBC. The patients were followed for a median of 54 months (range 1-76 months). Relapse-free survival was 86.3% and 92.6% for TNBC and non-TNBC, respectively, with significant difference ($P < 0.0001$). Overall survival was also 88.9% and 96.1% for TNBC and non-TNBC ($P < 0.0001$). Compared with non-TNBC patients, TNBC had an increased likelihood of recurrence and death within 3 years after diagnosis but not thereafter. In non-TNBC, the recurrence risk and death risk seemed to be relatively constant. In the unadjusted analysis, TNBC patients had an increased likelihood of recurrence and death in entire period and especially within 3 years after treatment. After 3 years, the risk of recurrence and death was not different between two groups. After adjustment for known prognostic variables, the risk of recurrence and death remained higher for TNBC.

Conclusions: TNBC has a worse prognosis than non-TNBC patients, but this effect is limited within 3 years after diagnosis. Therefore we regard that the patients who diagnosed as TNBC must close follow-up carefully, especially during the first 3 years after treatment.

Leptin and Leptin Receptor Expression in Breast Cancer

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Background/Purpose: Leptin is a multifunctional hormone produced by adipose tissue that is involved in the regulation of food intake and energy balance. The aims of this study were to determine leptin and leptin receptor (Ob-R) expression in human breast cancer and the corresponding influence on the prognosis of patients with breast cancer.

Methods: We examined the correlation between leptin and Ob-R expression, and breast cancer-related oncologic markers by immunohistochemistry in 517 patients with breast cancer. We analyzed leptin and Ob-R expression with respect to overall survival and relapse-free survival (RFS).

Results: Positive cytoplasmic immunoreactivity existed in 39% of the patients for leptin and 79% of the patients for Ob-R. The expression of leptin in breast cancer correlated with a high Ki-67 labeling index ($p=0.019$). Based on univariate survival analysis, the clinicopathologic variables with prognostic value included histologic grade, T stage, N stage, HER2 status, Bcl-2, p53, and Ki-67 expression ($p<0.05$). The patients with leptin-positive breast cancers and negative hormone receptor status had a significantly longer overall survival. Multivariate survival analysis showed that positive expression of leptin was an independent prognostic marker for overall survival (hazard ratio, 0.20; 95% CI, 0.04-0.99; $p=0.05$).

Conclusions: Leptin expression in breast cancers is significantly associated with the Ki-67 labeling index, suggesting an association with proliferation activity. On the contrary, leptin expression is an indicator of better survival of breast cancer patients.

Predictive Factors for Breast Cancer in Patients with Diagnosed Atypical Ductal Hyperplasia at Core Needle Biopsy

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Background/Purpose: Percutaneous core needle biopsy (CNB) is considered the standard technique for histologic diagnosis of breast lesions. But, it is less reliable for diagnosing atypical ductal hyperplasia (ADH). The purpose of the present study was to predict, based on clinical and radiological findings, which cases of ADH diagnosed by CNB would be more likely to be associated with a more advanced lesion on subsequent surgical excision.

Methods: Between February 2002 and December 2007, consecutive ultrasound-guided CNBs were performed on suspicious breast lesions at the Kangnam St. Mary's Hospital. A total of 69 CNBs led to a diagnosis of ADH, and 45 patients underwent follow-up surgical excision. We review the medical record and analysis retrospectively.

Results: 69 were diagnosed with ADH at CNB. Of those 69 patients, 45 underwent surgical excision at our institution. Of those 45 patients, 10 (22.2%) were diagnosed with a malignancy after surgical excision (8 with DCIS and 2 with invasive cancer). Univariate analysis revealed that age at the time of core needle biopsy over 50 years ($p=0.006$), size on imaging over 10 mm ($p=0.033$) and combined mass with microcalcification on sonography ($p=0.029$) were associated with underestimation. When those three factors were included in multivariate analysis, only age at the time of core needle biopsy over 50 years ($p=0.035$, HR 6.201, 95% CI [1.135-33.891]) was found to be independent predictors of malignancy.

Conclusions: We consider that for patients diagnosed with ADH at CNB, only complete surgical excision is suitable treatment option.

Expression of ER, P53 and HER-2/Neu in Medullary Carcinoma and Infiltrating Ductal Carcinoma with Medullary Feature

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Background/Purpose: In general, medullary carcinoma expresses positive p53 and negative HER-2/neu. Positive ER is related to good prognosis, and well differentiated cancer is related to its expression. Based on these correlations, the study was designed to make differentiation between medullary carcinoma and infiltrating ductal carcinoma with medullary feature with expression of ER, p53, and HER-2/neu.

Methods: Specimen of 12 medullary carcinoma and 19 infiltrating ductal carcinoma with medullary feature, which were obtained from biopsy or operation at breast clinic in Soonchunhyang university Cheonan hospital underwent immunohistochemical stain.

Results: ER expression in medullary carcinoma was negative in 9 out of 12 cases. In infiltrating ductal carcinoma with medullary feature, it was negative in 14 out of 19 cases, and there was expression of grade 3 in 5 cases. Expression of p53 in medullary carcinoma was 1+ in 5, and 3+ in 5 among 12 cases. In infiltrating ductal carcinoma with medullary feature, it was 1+ in 7, and 3+ in 11 among 19 cases. The expression of HER-2/neu in medullary carcinoma was score 0 in 2, and score 3 in 4 among 12 cases. It was expressed as score 0 in 8, and score 3 in 10 among 19 cases with infiltrating ductal carcinoma with medullary feature.

Conclusions: Expression of p53 and HER-2/neu was not useful in differentiating medullary carcinoma and infiltrating ductal carcinoma with medullary feature. ER was useful only in cases with positive ER expression. Microscopic findings of necrosis and stromal feature, or ultrasonographic findings of tumor margin was considered to be more valuable.

The Timing of Recurrence Dependent on Menopausal Status after Surgery for Breast Cancer

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Background/Purpose: This study was aimed at evaluating the timing of clinical recurrence after surgical removal of the primary tumor.

Methods: The hazard rate for recurrence during the first 5 years after surgery was studied in 1,225 female patients from 1995 to 2003 at Kyungpook National University Hospital. Subset analyses were performed according to menopausal status and axillary lymph node involvement.

Results: The group of premenopausal women has one peak hazard rate in the 18-24-month period after surgery, while that of postmenopausal women has two peaks at 18-24 months and 42-48 months. The hazard rate of node positive group is much higher than node negative group at all periods. In the premenopausal group, patients with less than 3 node metastases have a peak hazard rate at about 18-24 months, while those with more than 4 lymph node metastases have that in 6-12 months. In the postmenopausal group, patients with less than 3 node metastases have the peak hazard rate at 18-24 months, while more than 4 lymph node metastases have two peaks at 18-24 months and 42-48 months.

Conclusions: Both premenopausal and postmenopausal groups similarly show the peaked hazard rate of recurrence at about 2 years after surgery. In premenopausal young women, the status of nodal metastasis affects early recurrence, while in postmenopausal women, more nodal metastasis related with late recurrence at about 45 months. Menopausal status according to axillary node involvement shows the different recurrence pattern.

Negative Prognostic Value of Immunohistochemical P53 Over-Expression is Relevant to Positive Hormone Receptor Status

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Background/Purpose: To confirm an emerging view that estrogen paradoxically obtains an apoptotic action during multiple phases of resistance to anti-hormonal therapy, we investigated the prognostic role of p53, particularly in premenopausal breast cancer patients according to hormone receptor status.

Methods: Data about p53 immunohistochemistry results along with estrogen receptor, progesterone receptor, and HER2 of 60 hospitals' own patients, aged less than 50, were retrospectively retrieved from web-based database of Korean Breast Cancer Society. A total of 9,559 among patients diagnosed between 1997 and 2004 were enrolled in this analysis.

Results: The 5-year overall survival (OS) was 92.1% for negative p53 patients, and 86.4% for positive p53 patients ($p < 0.0001$). The 5-year breast cancer specific survival (BCSS) was 92.4% for negative p53 patients, and 86.7% for positive p53 patients ($p < 0.0001$). In a multivariate analysis, p53 over-expression was significant for OS and BCSS with a hazard ratio for OS of 1.322 (95% CI, 1.109-1.574) and for BCSS of 1.340 (95% CI, 1.122-1.601). In a subgroup analysis by hormone receptor (HR) status, the survival difference was significant for patients with positive HR status ($p < 0.0001$), but not for patients with negative HR status ($p = 0.078$). The prognostic significance of p53 over-expression remained valid only in patients with positive HR status (hazard ratio for OS and BCSS, 1.685 and 1.748; 95% CI, 1.285-2.211 and 1.326-2.305, respectively).

Conclusions: Immunohistochemical p53 over-expression has a prognostic value in premenopausal patients only with HR positive breast cancer. This partly supports the potential clinical implications of the relationship between apoptotic and complex estrogen signaling.

Prognostic Impact of the Combination of P53 and Ki-67 in Lymph-Node Negative Breast Cancer

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Background/Purpose: This study aimed to determine the prognostic significance of p53 and Ki-67 in lymph node negative breast cancer (LNN-BC).

Methods: A total 513 consecutive patients with LNN-BC that underwent surgery at the National Cancer Center, Korea between 2001 and 2006 were enrolled. We, retrospectively, reviewed the clinicopathologic characteristics and disease recurrence. The expression of p53 and Ki-67 in the tumor was assayed using immunohistochemistry (cut-off value: median value).

Results: The median age was 46 years (range: 25-77) and median follow-up period was 52.0 months (range: 6-92). Univariate analysis determined that estrogen receptor (ER) (5-year DFS rate; 96.3 in ER+ vs. 90.0% in ER-; $p=0.01$), progesterone receptor (PgR) (97.5% in PgR+ vs. 91.3% in PgR-; $p=0.01$), p53 (93.0% in positive vs 96.2% in negative; $p=0.03$), and Ki-67 (97.8 in Ki-67 <15% vs. 97.9% in Ki-67 $\geq 15\%$; $p<0.001$) were significant for distant metastasis-free survival (DFS). Of these factors, PgR negativity (HR 3.64; 95% CI, 1.1-11.7; $p=0.03$) and p53 positivity (HR 6.12; 95% CI, 1.9-19.1; $p=0.002$) were identified as independent prognostic factors for DFS based on multivariate analysis. We divided patients into two groups according to p53 and Ki-67 expression (high risk group: p53 [+] and Ki-67 $\geq 15\%$ vs low risk group: p53 [-] or Ki-67 <15%). The survivals of low- and high-risk groups were separated with statistically significant different (96.6% in low-risk group vs. 87.9% in high-risk group; $p<0.001$).

Conclusions: This study demonstrates that p53 and Ki-67 have prognostic impact for DFS in LNN-BC, and the combination of p53 and Ki-67 can provide additional prognostic information.

Prognostic Significance of CK5/6 in Triple-Negative Breast Cancers

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Background/Purpose: CK5/6 is known as a kind of basal cytokeratins. There is several report that CK5/6 positive in triple negative breast carcinoma is associated poor survival rate. The purpose of our report is evaluation of the effect of CK5/ 6 positive in triple negative breast cancer on DFS and OS at our hospital data.

Methods: An immunohistochemical study was performed on tissue microarrays constructed with 946 invasive breast carcinoma samples. We subclassified the TNBCs into CK5/6 phenotype and non-CK5/6 groups by the result of post operative pathologic report retrospectively. We used Cross table as analyzing methods in clinicopathologic factors distributions between two groups. 5 year DFS and OS is analysed by Kaplan Meier method. p-value (<0.05) was meaningful.

Results: There is no age distribution difference between two groups. Tumor size is more bigger in CK5/6 positive group (p=0.0036). Pathologic N-stage according to AJCC is more advanced in CK5/6 group. (p=0.0001). Perivascular invasion is important factor in DFS (p=0.004). The DFS and OS of CK5/6 positive group is lower that of non-CK5/6 groups (p=0.04, p=0.03 respectively).

Conclusions: CK5/6 positive is important in Triple negative breast cancer's survival rate. Adjuvant chemotherapy containing anthracycline iis not important in CK5/6 positive groups.

Effectiveness of Standardized Uptake Values (SUV) from ^{18}F -Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Fusion Imaging (^{18}F -FDG PET/CT) in Breast Cancer

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Background/Purpose: Many researchers have previously reported that high standardized uptake values (SUV) from ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (^{18}F -FDG PET/CT) in primary breast tumors significantly correlated with higher nuclear grade and poorer prognoses of primary breast tumors.

Methods: We investigate the clinicopathological correlation with the level of maximum SUV obtained from preoperative ^{18}F -FDG PET/CT in 53 patients with newly diagnosed primary breast cancer in Konyang University Hospital between June 2007 and May 2009.

Results: The median age of the patients was 48 years (range: 32-85). They were 47 invasive ductal carcinoma, 2 lobular carcinoma, 2 mucinous carcinoma, 1 ductal carcinoma in situ and 1 metaplastic carcinoma. All of them had been performed operation; 35 modified radical mastectomy, 16 lumpectomy and 2 subcutaneous mastectomy with immediate reconstruction. The SUV level was not significantly correlated with tumor size ($p=0.223$), lymph node metastasis ($p=0.141$), histologic grade ($p=0.507$) (mitosis: $p=0.277$, tubular formation: $p=0.133$, nuclear grade: $p=0.911$), immunohistochemical stain (ER: $p=0.260$, PR: $p=0.126$, c-erbB-2: $p=0.249$) and recurrence rate ($p=0.272$). But triple negative breast cancer and high TNM staging breast cancer had high SUV levels significantly ($p=0.025$ and 0.041).

Conclusions: High uptake of ^{18}F -FDG could not be predict of prognosis and aggressive features of cancer cells in patients with primary breast cancer. ^{18}F -FDG PET/CT could not be a useful tool to preoperative predict biological characteristics of breast cancer. But, further studies are necessary to investigate the effectiveness of preoperative ^{18}F -FDG PET/CT due to high SUV levels in triple negative and high staging breast cancer.

P53 Protein Expression Status and Relapse in Breast Cancer Patients Treated with Adjuvant Therapy

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Background/Purpose: The aims of this study were to evaluate the prognosis and treatment response according to p53 expression of breast cancer patients.

Methods: We analyzed data from 4,683 cancer patients enrolled in two institutions between 1997 and 2006. We analyzed the correlation for p53 expression and relapse, response to adjuvant therapy, breast cancer specific survival (BCSS) and relapse free survival (RFS) in primary breast cancer.

Results: p53 expression was positive in 1,091 patients (23.3%). A significant correlation with p53 expression was noted in tumor stage, histologic grade, nuclear grade, negative hormone receptor, and HER2 overexpression. p53 expression yielded more frequent distant failure and visceral metastasis. The patients with p53-positive breast cancer had a shorter BCSS and RFS. Subgroup analysis stratified by age and adjuvant therapy was performed. Multivariate analysis showed that p53-positivity is the prognostic factor in patients treated with hormone therapy following chemotherapy (hazard ratio for BCSS, 2.00; 95% CI, 1.10 to 3.63; p=0.022). The patients aged between 35 to 50 years old, treated with hormone therapy following chemotherapy, had a significantly lower HER2 overexpression rate (23.3%) and the patients older than 50 years treated with chemotherapy only had significantly high HER2 overexpression rate (47.2%). The survival benefit of p53-negative breast cancer had a significant inverse correlation with HER2 overexpression rate.

Conclusions: In the subpopulation aged between 35 to 50 years old, p53-positive patients showed worse prognosis than that of p53-negative patients. and seemed to have less survival benefit from adjuvant hormone therapy.

Relationship between Expressions of VEGF-C and Clinicopathology in Breast Cancer Patients

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Background/Purpose: To investigate the expressions of VEGF-C, C-erbB-2, p53, estrogen receptor (ER) and progesterone receptor (PR) in breast cancer tissue and their clinical significance.

Methods: The expressions of VEGF-C, C-erbB-2, p53, ER, PR in 60 cases of breast cancer tissue were detected by immunohistochemistry, and their clinical significance were statistically analyzed.

Results: Positive expression rate of VEGF-C, C-erbB-2, p53, ER, PR in 60 cases of breast cancer tissue were 56.7%, 76.7%, 40.0%, 41.7%, 51.7%. There were no difference of the expressions of p53, ER, PR in age, tumor volume and in lymph node status of breast cancers ($p>0.05$). There were difference of expression of VEGF-C, C-erbB-2 in lymph node status ($p<0.05$), there were no difference in age, tumor volume of breast cancers ($p>0.05$). The expressions of ER, PR were correlated positively with the expression rate of C-erbB-2 ($p<0.05$), which were not related with VEGF-C and p53.

Conclusions: The high expression VEGF-C and C-erbB-2 were closely related to lymph node metastasis, The VEGF-C and C-erbB-2 may play promoting roles in lymph node metastasis of breast carcinoma. Combined detection of VEGF-C, C-erbB-2, p53, ER and PR may help clinical treatment and prognostic judgement of breast cancer patients.

Predicting Factors of Nonsentinel Lymph Node Metastasis in Breast Cancer Patients with Sentinel Lymph Node Metastasis

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Background/Purpose: The incidence of nonsentinel lymph node (NSLN) metastasis in patients with a tumor-positive sentinel lymph node (SLN) varies greatly from 20% to 70% in the published literature. Current practice is that most patients with a positive SLN undergo a complete axillary lymph node dissection. However, it has been shown by other investigators that a large number of patients with a positive SLN do not necessarily need a complete axillary dissection. The purpose of this study was to investigate the predictors of NSLN metastasis in breast cancer.

Methods: In this analysis, we reviewed the clinicopathologic features of 70 patients who had undergone SLN biopsy and axillary lymph node dissection. The clinical features of patients, histologic parameters and hormonal receptor status of primary tumor and histopathologic features of SLN metastasis were noted retrospectively.

Results: The metastatic tumor size in SLN ($p=0.001$), extracapsular invasion ($p=0.002$), percentage of positive SLNs among the removed SLNs ($p=0.011$), primary tumor size ($p=0.038$) were associated significantly with NSN metastasis statistically in univariate analysis. Based on multivariate logistic regression, the metastatic tumor size was the only prognostic factor of non-SLN metastasis.

Conclusions: We have shown in this study that it would be possible to predict the NSLN status based on the metastatic tumor size in SLN. Although the significance was not achieved in multivariate analysis, the size of primary tumor, extracapsular invasion of metastasis in SLN, percentage of positive SLNs among the removed SLNs had the possibility to be prognostic factor of non-SLN metastasis.

A Case of Pregnancy Following Intensive Adjuvant Chemotherapy for a Breast Cancer under Ovarian Protection by LH-RH Agonist

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Background/Purpose: Breast cancer occasionally occurred in reproductive period. These patients tend to treat with intensive adjuvant or neoadjuvant chemotherapy because of their younger age if cytotoxic chemotherapy is indicated. However, loss of fertility can be occurred after cytotoxic chemotherapy especially using anthracyclins and alkylating agents. There are several reports suggesting possibility of ovarian function preservation by administration of LH-RH agonist concomitant with cytotoxic chemotherapy.

Methods: We report a case of spontaneous pregnancy after chemotherapy using FEC 100 followed by weekly paclitaxel under ovarian protection by goserelin.

Results: A 28-year-old woman received modified radical mastectomy due to a right breast cancer. A histopathological examination revealed following characteristics that invasive ductal carcinoma, negative vascular invasion, nuclear grade 3, negative estrogen and progesterone receptors and without over expression of HER2. Adjuvant chemotherapy was recommended because of high nuclear grade, younger age and negative hormonal receptors. However, the patient and her husband are hoping for the pregnancy in the future. Goserelin was started prior to chemotherapy due to preventing loss of ovarian function by cytotoxic agents. Four cycles of FEC-100 (5FU 500, epirubicin 100, cyclophosphamide 500 mg/m²) every 3 weeks followed by 12 cycles of paclitaxel (80 mg/m²) every week with goserelin 3.6 mg every 4 weeks was administered. Menstruation was recovered 4 months after ending of chemotherapy. She got pregnant spontaneously 15 months after ending of chemotherapy. No abnormal finding of fetus was found at 20 weeks of gestational age.

Conclusions: Fertility may be preserved by ovarian suppression with LH-RH agonist during cytotoxic chemotherapy.

Metastasis to the Breast from Non-Mammary Neoplasm

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Background/Purpose: Breast metastasis from non-mammary neoplasm is rare. We present the cases of metastasis to the breast after review of results in one institute and we want to find the difference of previous report.

Methods: The surgical and pathology databases of Samsung Medical Center from November 1994 to March 2009 were investigated to identify all patients with a diagnosis of metastasis to the breast.

Results: Thirty three patients with breast metastases from extramammary neoplasm were studied; 8 gastric carcinoma, 5 lung cancer, 2 melanoma of skin, 2 lymphoma, 1 squamous cell carcinoma of skin, 2 colon cancer, 2 malignant thymoma, 1 hepatocellular carcinoma, 1 cholangiocarcinoma in the liver and 2 carcinoma of unknown primary and 6 other cancers from various site. Metastasis from hematologic origin was uncommon unlike other reports. However, by comparison of incidence, incidence of melanoma and malignant thymoma was higher than that of stomach (p-value=0.02 and p-value=0.009 respectively). It may caused by high incidence of gastric cancer in Korea. In 24 patients of all 33 patients, there was a known history of primary non-mammary neoplasm. The prognosis of these patients was poor.

Conclusions: Routine pathologic examination and considering known clinical history may be helpful to differentiate the primary breast cancer and metastatic cancer. An accurate diagnosis of breast metastases, differentiating primary from metastatic breast carcinoma, is important for rational and optimum therapy and avoidance of unnecessary radical surgery.

Global Breast Cancer Trends and Challenges a South Korean Perspective

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Background/Purpose: To determine greatest perceived challenges, trends and needs among breast cancer medical, policy and advocacy thought leaders across the world, to identify the opportunities to advance the breast cancer control within and across diverse international countries, and to compare these to perceived challenges and needs among South Korea thought leaders.

Methods: 225 thought leaders associated with breast cancer in 30 countries including Asia, Latin America, and the Middle East participated in a comprehensive survey using horizon scanning methodology. Key informant interviews included medical oncologists, surgeons, other breast cancer specialists, advocacy leaders and cancer policy makers. 20 thought leaders participated from South Korea (18 medical thought leaders, 1 public policy, 1 advocacy leader).

Results: Across all 30 countries, 47% of respondents identified a major challenge to be the ability to provide personalized therapy. 46% identified the need for increased numbers of trained oncology nurses in breast cancer patient care and education. 45% cited the relatively higher observed proportion of younger women in non-Caucasian populations presenting with more aggressive breast tumors. In comparison, thought leaders in Korea, identified the two most important challenges and needs being trained oncology nurses (40%) and keeping up to date with information (30%). Secondly, they noted an increasing number of young women diagnosed with highly aggressive tumors.

Conclusions: In South Korea, further basic, clinical and epidemiological research as well as significant increases in the number of oncology nurses should be a priority, and finally, public education and other advocacy efforts are needed.

The Effects of Laughter Therapy on Mood, Pain and Stress on Mastectomy Patients

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Background/Purpose: The purpose of this study was to identify the effect of the laughter therapy, administered to the mastectomy patient as an adaptive coping mechanism.

Methods: The research design was non-equivalent control group non-synchronized design. The study method had been done by investigating the experimental group and control group through the questionnaire on 40 patients who had been in patients room at S hospital in Busan from July 1 to October 10, 2008. The laughter therapy was provided to the experimental group for 20 minute, 8 times twice a day at in hospital room. Dependent variables were measured by McNair, Lorr & Droppleman's. The profile of Mood State, Sutherland, Walker & Till's Mood inventory and visual analog scale and serum cortisol. The analysis of the collected data had been done for the homogeneity test in which general characteristics of the experimental group and the control group had been tested by χ^2 test and the homogeneity test had been tested by t-test before using the laughter therapy which is for mood, pain, stress and serum cortisol.

Results: 1) Mood score in the experimental group and control group significant difference ($t=-2.314$, $p=0.032$). 2) Pain score in the experimental group and control group non significant difference ($t=-0.699$ $p=0.493$). 3) Stress score in the experimental group and control group significant difference ($t=-2.535$ $p=0.020$). 4) Serum cortisol score in the experimental group and control group non significant difference ($t=-0.690$ $p=0.498$).

Conclusions: In conclusion, the laughter therapy of effect on mastectomy patients in reacting to mood and stress.

Job Analysis of Korean Oncology Advanced Practice Nurses

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Background/Purpose: The purposes of this study were to identify job definition, duties and tasks of Korean oncology APNs and assess frequency, importance and difficulty for each of duty and task through the DACUM job analysis.

Methods: The DACUM committee was organized with nine oncology APNs. The committee derived the job definition, duties and tasks from what they had done at workplace and then validity of the derived duties and tasks was tested by researchers & 6 oncology APNs. Data was collected with questionnaire asked frequency, importance and difficulty for each of task from 53 Oncology APNs.

Results: Job definition, 12 duties and 66 tasks of oncology APNs were identified. Duties were implementation of advanced practice, clinical judgment & decision making, case management, education for patients/families, counseling for patient/families, education for the health care team, consultation & coordination related to treatment & nursing care, activity of research, activity for practice improvement, administration, building the patient support system and self-improvement. As for the all 12 duties, education for patients/families was the most frequently performed and was showed as the most important duty. case management was the most difficult duty, As for all 66 tasks, providing education for patients/families was the most frequently performed. Providing education for patients/families and assessing patient condition comprehensively were showed as the most important duties. Implementing research as the principal investigator was the most difficulty duty.

Conclusions: Through this study, the reality of oncology APNs' performances was recognized, Applying this result to standardization & reshaping job description of oncology APNs is recommended.

Lymphaticovenous Anastomosis for Breast-Cancer-Related Lymphedema

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Background/Purpose: Conservative treatments by manual lymphatic drainage has been performed for breast-cancer-related lymphedema, however, it is difficult to keep up. We have recently performed microsurgical lymphaticovenous anastomosis (LVA) for two patients using indocyanine green (ICG) fluorescence imaging.

Results: Case1: A 70-year-old woman who received mastectomy and axillary node dissection for left breast cancer 15 years earlier. Lymphedema of the left upper extremity with phlegmon was developed 7 days after the surgery. Under local anesthesia, a LVA was made at flexor side of elbow region. Five days after the operation, circumference of the upper extremity decreased by 2 cm and phlegmon was subsided. Case2: A 40-year-old woman who received mastectomy and axillary node dissection for right breast cancer a year earlier. Lymphedema of the right upper extremity was developed soon after the surgery. A LVA was made at radial side of the wrist. Three months after the operation, circumference of the upper extremity decreased by 3.5 cm and edema at dorsum of the hand has been disappeared.

Conclusions: Minimal invasive LVA using ICG fluorescence imaging is valuable technique and has few burdens to the patient in comparison with conservative care. It is considered that we should recommend LVA for comparatively early stage of lymphedema.

Logotherapy Education Program Development and the Effects for Late Adolescents with Terminal Cancer in Korea

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Background/Purpose: This study aimed to determine the efficacy of an logotherapy education program in order to promote meaning in life and quality of life in adolescents with terminal cancer.

Methods: This program was developed according to the theory of logotherapy and consisted of 5 times. This experiment comprised a 5-step educational approach combined with the essence of the distinctive qualities of human's existence, such as the meaning of life, freedom of will, will to meaning, selection and responsibility and the methods of revelation of the meaning in life as creative, experiential, and attitudinal values. A nonequivalent control group, non-synchronized design was conducted with a convenience sample of 44 late adolescents with terminal cancer. The experimental group (n=22) participated in the 'Finding meaning in my life' program which consisted of 5 daily sessions for one week. The control group (n=22) received the usual nursing care. The effects were measured using adolescent meaning in life (AMIL), and quality of life (QOL) scales. The collected data were analyzed by descriptive statistics, Chi-square, and t-test using SPSS/PC 17.0 program.

Results: There were significant differences in AMIL ($t=3.36$, $p<0.05$) and QOL ($t=2.67$, $p<0.05$) between the experimental and control groups.

Conclusions: Logotherapy was effective in improving the meaning in life and quality of life. As an emotional and spiritual intervention in a palliative care setting, the logotherapy demonstrated the potential to effectively improve the QOL and prevent the existential emptiness caused by terminal illness of adolescent patients under serious stress.



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Choi, Jae Hyuck	PO2-053	318	Fukutomi, Takashi	FP1-01	139
Choi, Jae Hyuck	PO2-097	361	Funakoshi, Taku	PO2-051	316
Choi, JP	PO2-012	278	Fushimi, Koya	PO1-024	196
Choi, Jung-Wha	PO2-099	363	Fuzita, Takasi	PO1-048	217
Choi, Seung-Yi	PO1-081	248	Go, Gyeong Ja	PO2-077	343
Choi, Sooyun	PO1-018	190	Go, Yukie	PO1-028	200
Choi, So-Young	PO2-058	323	Gomez, H	FP4-04	161
Choi, Un-Jong	PO1-101	265	Gong, G	PO2-089	353
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Choi, Young Jin	PO1-037	209	Gong, Gyung-Yub	PO1-095	260
Choi, Young Jin	PO2-050	315	Gong, Gyung-Yub	PO2-036	303
Choi, Young Soo	PO1-102	266	Goo, Minyoung	PO2-033	299
Chun, Mison	PO2-074	340	Goo, Minyoung	PO2-055	320
Chun, Mison	PO2-075	341	Gorbounova, Vera	PO2-034	300
Chung, Bok Yae	PO1-078	245	Gwak, Geumhee	PO2-023	285
Chung, Bok Yae	PO2-070	335	Ha, Ji Hee	PO2-022	284
Chung, Hyun-Cheol	PO2-098	362	Ha, Jung Sook	PO1-053	222
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Han, Sang Ah	PO1-052	221	Horikoshi, Hiroyuki	PO2-056	321
Han, Sang Ah	PO2-002	268	Horio, Akiyo	PO1-025	197
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Han, Sunwook	PO2-027	291	Horio, Akiyo	PO1-049	218
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Han, Wonshik	PO1-087	253	Hur, Sung Mo	PO1-009	180
Han, Wonshik	PO1-092	257	Hur, Sung Mo	PO2-007	272
Han, Wonshik	PO2-025	289	Hur, Sung Mo	PO2-046	311
Han, Wonshik	PO2-043	310	Hur, Sung Mo	PO2-047	312
Han, Wonshik	PO2-048	313	Hur, Sung Mo	PO2-053	318
Han, Wonshik	PO2-049	314	Hur, Sung Mo	PO2-097	361
Han, Woonsub	PO2-033	299	Hwang, Eunkyung	PO1-067	235
Han, Woonsub	PO2-055	320	Hwang, Hyewon	PO2-033	299
Hanazaki, Kazuhiro	PO2-051	316	Hwang, Jeong Eun	PO1-088	254
Hashimoto, Shin-Ichiro	PO1-012	184	Hwang, Ki-Tae	PO1-010	181
Hashimoto, Yasuhiro	PO2-064	329	Hwang, Ki-Tae	PO2-022	284
Hato, Yukari	PO1-025	197	Hwang, Moon Sook	PO2-100	364
Hato, Yukari	PO1-048	217	Hwang, Seung Hyun	PO1-036	208
Hato, Yukari	PO1-049	218	Hwang, Seung Hyun	PO2-037	304
Hayashi, Hironori	PO1-025	197	Iglehart, James D.	PO2-010	276
Hayashi, Hironori	PO1-049	218	Iijima, Misa	PO2-056	321
Hayashi, Mitsuhiro	PO2-042	309	Iino, Yuichi	FP2-04	149
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Hayasi, Hironori	PO1-048	217	Iino, Yuichi	PO1-056	225
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Hirakata, Tomoko	PO2-056	321	Im, Seok-Ah	PO2-025	289
Hirakawa, Kosei	PO1-013	185	Im, Seok-Ah	PO2-029	294
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Hojo, Takashi	PO1-031	203	Im, Young-Hyuck	PO2-008	273
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Inoue, Kenichi	PO1-063	232	Jung, So-Youn	PO2-090	354
Ishikawa, Tetsuro	PO1-013	185	Jung, Sung Hoo	PO1-008	179
Ishikawa, Tetsuro	PO1-028	200	Jung, Sung Hoo	PO1-084	250
Ishikawa, Tetsuro	PO2-096	360	Jung, Woo-Hee	PO1-015	187
Ishikawa, Yuko	PO1-063	232	Jung, Woo-Hee	PO2-037	304
Iwasaki, Toshiharu	PO1-020	192	Jung, Yong Sik	FP4-03	159
Iwata, Hiroji	PO1-025	197	Jung, Yong Sik	PO1-005	176
Iwata, Hiroji	PO1-048	217	Jung, Yong Sik	PO1-037	209
Iwata, Hiroji	PO1-049	218	Jung, Yong Sik	PO1-098	262
Jang, Geundoo	PO1-095	260	Jung, Yong Sik	PO2-083	347
Jang, Mi Ae	PO1-058	227	Juon, Hee-Soon	PO1-001	171
Jang, Mijung	PO1-052	221	Kadowaki, Masami	PO1-024	196
Jegal, Young Jong	PO1-021	193	Kang, Bong Joo	PO1-004	175
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Jeon, Mi Seon	PO2-083	347	Kang, Eunyoung	PO2-002	268
Jeon, Young-San	PO2-011	277	Kang, Han-Sung	FP2-05	150
Jeon, Young-San	PO2-035	302	Kang, Han-Sung	FP3-04	155
Jeong, Eun-Mi	PO2-013	279	Kang, Han-Sung	PO1-068	236
Jeong, Jae-Boon	PO2-022	284	Kang, Han-Sung	PO2-090	354
Jeong, Jeong Pil	PO1-047	216	Kang, Heejoon	PO1-060	229
Jeong, Jeong Pil	PO2-040	307	Kang, Hee Sun	PO1-077	244
Jeong, Joon	PO1-015	187	Kang, Hyun Jong	PO1-086	252
Jeong, Joon	PO1-036	208	Kang, Kyung Ah	PO2-103	366
Jeong, Joon	PO2-037	304	Kang, Mi Young	PO1-080	247
Jheon, Sang Hoon	PO1-057	226	Kang, Nam-Uk	FP2-03	148
Ji, Boo Yong	PO2-077	343	Kang, Seok Yun	PO1-098	262
Jo, Baik-Hyeon	PO1-088	254	Kang, Seok Yun	PO2-083	347
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Joukouji, Ryu	PO2-064	329	Kang, Sun Hee	PO1-053	222
Juhng, Seon-Kwan	PO1-101	265	Kang, Sun Hee	PO2-030	296
Jun, Eun Young	FP5-03	166	Kang, Sun Hee	PO2-052	317
Jung, Eun-Jung	PO1-054	223	Kang, Won Ki	PO1-091	256
Jung, Hae Hyun	PO2-008	273	Kang, Won Ki	PO2-008	273
Jung, He Ra	PO2-030	296	Kang, Yoon Joong	PO2-050	315
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Jung, Jin Hyang	PO2-088	352	Kaplan, David	PO2-021	283
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Jung, Kyung Hae	PO1-095	260	Kashiwagi, Shinichiro	PO1-028	200
Jung, Kyung Hae	PO2-036	303	Kashiwagi, Shinichiro	PO2-096	360
Jung, Sang Seol	PO1-004	175	Kato, Makoto	FP3-01	151
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Kawakami, Noriko	PO2-096	360	Kim, Hong Tae	PO1-057	226
Kazuhiro, Takeuchi	PO2-101	365	Kim, Hoon Yup	PO1-055	224
Keiichiro, Hirata	PO2-101	365	Kim, Hun-Soo	PO1-101	265
Kenjiro, Kimura	PO2-101	365	Kim, Hyeong-Reh Choi	PO2-021	283
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Kim, Chi-Ho	PO2-011	277	Kim, Jee-Hyun	PO1-052	221
Kim, Chi-Ho	PO2-035	302	Kim, Jeongseon	FP1-04	142
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Kim, Dal Sook	PO1-075	242	Kim, Jeong Soo	PO2-086	350
Kim, Dal Sook	PO1-078	245	Kim, Je Ryong	PO1-016	188
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Kim, Doy Il	PO1-088	254	Kim, Jin Young	PO2-088	352
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Kim, Eun Jin	PO2-078	344	Kim, Ji Young	PO2-010	276
Kim, Eun Kyoung	PO2-036	303	Kim, Jong Heun	PO1-079	246
Kim, Eun-Kyu	FP1-03	141	Kim, Jong Im	PO1-007	178
Kim, Eun-Kyu	PO1-087	253	Kim, Jong Im	PO2-067	332
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Kim, Guem-won	PO2-092	356	Kim, Jong Ki	PO1-057	226
Kim, Gwang Suk	PO1-062	231	Kim, Jong-Nam	PO1-079	246
Kim, Gyung Duck	PO2-070	335	Kim, Jong-Suk	PO1-008	179
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Kim, Hae Young	PO1-093	258	Kim, Jun Ho	PO2-085	349
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Kim, Hak-Hee	PO1-095	260	Kim, Ki Hyun	PO1-102	266
Kim, Hee Jeong	PO1-032	204	Kim, Ku Sang	FP4-03	159
Kim, Hee Jeong	PO1-035	207	Kim, Ku Sang	PO1-005	176
Kim, Hee Jeong	PO1-042	214	Kim, Ku Sang	PO1-037	209
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Kim, Hee Jeong	PO1-094	259	Kim, Ku Sang	PO2-083	347
Kim, Hee Jeong	PO2-084	348	Kim, Kwan-Il	FP1-02	140
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Kim, Hee Soon	PO1-068	236	Kim, Kwan-Il	PO2-009	274
Kim, Hee Sung	PO2-085	349	Kim, Kweon Cheon	PO2-061	326
Kim, Hee Sung	PO2-093	357	Kim, Kyoung Mi	PO2-072	337

Kim, Kyubo	PO2-025	289	Kim, Sung Hoon	PO2-053	318
Kim, Kyung-Hee	PO2-099	363	Kim, Sung Hoon	PO2-097	361
Kim, Kyung Hye	PO2-070	335	Kim, Sung Hwan	PO2-075	341
Kim, Lee Su	PO1-005	176	Kim, Sung-Won	PO1-005	176
Kim, Lee Su	PO1-060	229	Kim, Sung-Won	PO1-052	221
Kim, Minseok S.	PO2-009	274	Kim, Sung-Won	PO2-002	268
Kim, Min-Suk	FP1-03	141	Kim, Sung Yong	PO2-027	291
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Kim, Sairhee	PO1-052	221	Kim, Sun Mi	PO1-052	221
Kim, Sairhee	PO2-002	268	Kim, Tae Hee	PO2-083	347
Kim, Sang Geon	PO2-022	284	Kim, Tae Hyun	PO2-038	305
Kim, Sang Hyo	PO2-038	305	Kim, Tae-You	PO2-025	289
Kim, Sang Min	PO1-009	180	Kim, Wan Wook	PO1-009	180
Kim, Sang Min	PO2-007	272	Kim, Wan Wook	PO2-007	272
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Kim, Sang Min	PO2-047	312	Kim, Wan Wook	PO2-047	312
Kim, Sang Min	PO2-053	318	Kim, Wan Wook	PO2-053	318
Kim, Sang Min	PO2-097	361	Kim, Wan Wook	PO2-097	361
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Kim, Seok Won	PO1-068	236	Kim, Yeon Sun	PO2-060	325
Kim, Seok Won	PO2-090	354	Kim, Young Ju	PO1-075	242
Kim, Seonhoe	PO2-022	284	Kim, Youngsuk	PO2-003	269
Kim, Seung-Jin	PO1-101	265	Kim, Youn Jeong	PO2-095	359
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Kim, Sue	PO1-062	231	Ko, Beom Seok	PO1-042	214
Kim, Su Jin	FP2-03	148	Ko, Beom Seok	PO1-058	227
Kim, Sung-Bae	PO1-038	210	Ko, Beom Seok	PO2-084	348
Kim, Sung-Bae	PO1-095	260	Ko, BS	PO2-012	278
Kim, Sung-Bae	PO2-029	294	Ko, Byung Kyun	PO2-059	324
Kim, Sung-Bae	PO2-036	303	Ko, Byung Kyun	PO2-060	325
Kim, Sung-Bae	PO2-098	362	Ko, Eun	FP5-04	167
Kim, Sung Hoon	PO1-009	180	Ko, Eun-Sook	FP1-03	141
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Kim, Sung Hoon	PO2-046	311	Ko, Eunyoung	PO1-092	257
Kim, Sung Hoon	PO2-047	312	Ko, Eunyoung	PO2-013	279

Ko, Eunyoung	PO2-022	284	Kwong, Ava	PO1-059	228
Ko, Eunyoung	PO2-048	313	Kwun, Koing Bo	PO2-052	317
Ko, Eunyoung	PO2-049	314	Law, T.T.	PO1-059	228
Ko, EY	PO2-024	287	Lee, Ahwon	PO1-004	175
Ko, Seung Sang	PO1-015	187	Lee, Ahwon	PO2-086	350
Ko, Seung Sang	PO2-057	322	Lee, Anbok	PO2-055	320
Ko, Yun-Hee	FP5-03	166	Lee, Byoung Kil	PO1-008	179
Ko, Yun-Hee	PO1-062	231	Lee, Byoung Kil	PO1-084	250
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Ku, Bokyoung	PO1-058	227	Lee, Eun Sook	FP1-02	140
Ku, Do-Hoon	PO1-052	221	Lee, Eun Sook	FP1-04	142
Ku, Do-Hoon	PO2-002	268	Lee, Eun Sook	PO1-018	190
Kurosumi, Masafumi	PO1-063	232	Lee, Eun Sook	PO1-055	224
Kwak, Mi Kyong	PO2-100	364	Lee, Eun Sook	PO1-068	236
Kwon, Eun Jin	PO1-076	243	Lee, Eun Sook	PO2-009	274
Kwon, In Gak	PO2-076	342	Lee, Hae Kyung	PO2-057	322
Kwon, In Gak	PO2-100	364	Lee, Hanhee	PO1-060	229
Kwon, Kyung Hee	PO1-075	242	Lee, Han Sul	PO1-068	236
Kwon, Mijung	PO1-018	190	Lee, Huckjin	PO1-034	206
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Kwon, Soo Beom	PO1-094	259	Lee, Hy-De	PO1-015	187
Kwon, Soo Bum	PO1-032	204	Lee, Hy-De	PO1-036	208
Kwon, Soo Bum	PO1-035	207	Lee, Hy-De	PO2-037	304
Kwon, Soo Bum	PO1-058	227	Lee, Hyuk jin	FP3-05	156
Kwon, Soo Bum	PO2-084	348	Lee, Hyunjoo	PO1-095	260
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Lee, Jeong Eon	FP4-03	159	Lee, Min-Hyuk	PO1-005	176
Lee, Jeong Eon	PO1-009	180	Lee, Min-Hyuk	PO2-027	291
Lee, Jeong Eon	PO1-091	256	Lee, Min-Hyuk	PO2-087	351
Lee, Jeong Eon	PO2-007	272	Lee, Min Ju	PO1-008	179
Lee, Jeong Eon	PO2-046	311	Lee, Min Ju	PO1-084	250
Lee, Jeong Eon	PO2-047	312	Lee, Mi Ri	FP2-03	148
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Lee, Jeong Eon	PO2-097	361	Lee, Nam Seop	PO1-004	175
Lee, Jeong Won	PO1-058	227	Lee, Nam Seop	PO2-086	350
Lee, Jieun	PO2-033	299	Lee, Ran	PO1-097	261
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Lee, Jin Yong	PO1-034	206	Lee, Seok Jae	FP3-05	156
Lee, Ji Shin	PO1-021	193	Lee, Seok Mo	PO2-038	305
Lee, Ji Shin	PO1-022	194	Lee, Seung Ah	PO1-036	208
Lee, Jong Eun	PO1-015	187	Lee, Seung Ah	PO2-037	304
Lee, Jong Won	PO1-032	204	Lee, Seung Joo	FP3-04	155
Lee, Jong Won	PO1-035	207	Lee, Seung Yeon	PO2-031	297
Lee, Jong Won	PO1-092	257	Lee, Soohyeon	PO1-091	256
Lee, Jong Won	PO1-094	259	Lee, Soo-Jung	PO2-011	277
Lee, Jong Won	PO2-084	348	Lee, Soo-Jung	PO2-035	302
Lee, Ju Hyun	PO2-058	323	Lee, Sook Hyun	PO2-057	322
Lee, Jung-Ah	FP1-02	140	Lee, Suckjae	PO1-034	206
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Lee, Jung Nam	PO1-090	255	Lee, Tae Hoon	PO1-090	255
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Lee, Kang Yeun	PO2-095	359	Lee, Won Hung	PO1-088	254
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Lee, Keun Seok	FP3-04	155	Lee, YM	PO2-012	278
Lee, Keun Seok	PO2-090	354	Lee, Yoonho	PO2-090	354
Lee, Kwang-Man	PO1-101	265	Lee, You Mi	PO1-058	227
Lee, Kwan Joo	PO2-086	350	Lee, Young Don	PO1-090	255

Lee, Young-Eun	PO2-068	333	Miyoshi, Shinichiro	PO1-039	211
Lee, Young-Mee	PO2-073	339	Miyoshi, Shinichiro	PO1-083	249
Lee, Younok	PO1-060	229	Miyoshi, Shinichiro	PO1-100	264
Lee, Yu Mi	PO1-032	204	Miyoshi, Tetsutaro	PO1-024	196
Lee, Yu Mi	PO1-035	207	Moon, Aree	PO2-021	283
Lee, Yu Mi	PO2-084	348	Moon, Aree	PO2-022	284
Li, Xuerui	PO2-063	328	Moon, Byungin	PO2-033	299
Liao, N	FP2-02	146	Moon, Byungin	PO2-055	320
Liao, Ning	PO2-063	328	Moon, Hyeong-Gon	FP3-03	154
Lim, Chul Wan	PO2-027	291	Moon, Hyeong-Gon	PO1-054	223
Lim, Chul Wan	PO2-087	351	Moon, Nan-Mo	FP1-03	141
Lim, Jeong Sun	PO2-067	332	Moon, Seongmi	PO2-074	340
Lim, Ra Joo	PO2-057	322	Moon, Seongmi	PO2-075	341
Lim, Sungjik	PO1-017	189	Moon, WK	PO1-011	183
Lim, W	PO2-012	278	Moon, Woo Kyung	PO2-043	310
Lim, Woosung	PO1-032	204	Morimoto, Takashi	PO2-062	327
Lim, Woosung	PO1-035	207	Morioka, Toru	PO1-033	205
Lim, Woosung	PO1-042	214	Mostafa, Mahmoud	PO1-006	177
Lim, Woosung	PO1-058	227	Mouri, Yukako	FP1-01	139
Lim, Woosung	PO1-094	259	Mu, DB	PO1-029	201
Lim, Woosung	PO2-084	348	Murazawa, Chisa	PO1-012	184
Liu, Chieh-Yu	FP5-02	164	Na, Hye-Kyung	FP1-05	143
Liu, Ching-Hung	FP5-02	164	Na, Hye-Kyung	PO2-014	280
Liu, Jih-Shin	FP5-02	164	Na, Kuk Young	FP4-03	159
Liu, Yanhui	PO2-063	328	Na, Kuk Young	PO1-037	209
Liu, YH	FP2-02	146	Na, Kuk Young	PO1-098	262
Lu, Yan-Shen	FP5-02	164	Na, Kuk Young	PO2-083	347
Luong, Krystal	PO1-066	234	Nagai, Shigenori	PO1-063	232
Makarenko, Ninel	PO2-034	300	Nagaoka, Rin	FP2-04	149
Malki, Ahmed	PO1-023	195	Nagaoka, Rin	PO1-020	192
Maltzman, J	FP4-04	161	Nagaoka, Rin	PO1-030	202
Masuda, Hiroko	PO1-039	211	Nagaoka, Rin	PO1-056	225
Masuda, Hiroko	PO1-083	249	Nagashima, Takeshi	PO1-024	196
Masuda, Hiroko	PO1-100	264	Nakano, Shogo	FP1-01	139
Matsuura, Nariaki	PO2-064	329	Nakano, Taeko	PO1-028	200
Min, Hyo Suk	PO1-007	178	Nakano, Taeko	PO2-096	360
Min, JunWon	PO1-010	181	Nakano, Toru	PO1-065	233
Min, JunWon	PO2-049	314	Nam, Byung-Ho	FP3-04	155
Min, JW	PO2-024	287	Nam, Seok Jin	FP4-02	158
Min, Sun Young	FP3-04	155	Nam, Seok Jin	PO1-009	180
Min, Sun Young	PO2-090	354	Nam, Seok Jin	PO1-091	256
Mine, Mariko	PO2-042	309	Nam, Seok Jin	PO2-007	272
Mitsukawa, Yasuko	PO2-096	360	Nam, Seok Jin	PO2-046	311
Mitsuyama, Shoshu	PO1-065	233	Nam, Seok Jin	PO2-047	312
Miyazaki, Masaru	PO1-024	196	Nam, Seok Jin	PO2-053	318

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Naoki, Aomatsu	PO2-101	365	Oh, Do-Youn	PO2-025	289
Natsuko, Ohashi	PO2-101	365	Oh, Hoon Kyu	PO1-057	226
Ng, Ting Ying	PO2-029	294	Oh, Hyun Sook	PO1-075	242
Nguyen, Ba Duc	PO2-029	294	Oh, Ki-Keun	PO1-098	262
Niikura, Naoki	PO1-033	205	Oh, Ki-Keun	PO2-083	347
Ninomiya, Jun	PO1-063	232	Oh, Kyong Ok	PO1-007	178
Nishii, Takafumi	PO2-101	365	Oh, Pok Ja	PO1-081	248
Nishimura, Reiki	PO2-042	309	Oh, Pok Ja	PO2-026	290
Nishiyama, Keiko	PO1-039	211	Oh, Pok Ja	PO2-065	330
Nishiyama, Keiko	PO1-083	249	Oh, Se-Jeong	PO1-037	209
Nishiyama, Keiko	PO1-100	264	Oh, Se-Jeong	PO2-086	350
Noda, Eiji	PO1-013	185	Oh, Young Taek	PO2-074	340
Noda, Eiji	PO1-028	200	Oh, Young Taek	PO2-075	341
Noda, Satoru	PO2-096	360	Ohshitanai, Risa	PO1-033	205
Nogami, Tomohiro	PO1-039	211	Ohtani, Masahiro	PO1-012	184
Nogami, Tomohiro	PO1-083	249	Ok, Oh-Nam	FP4-02	158
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Noh, Dong-Young	PO1-010	181	Okumura, Yasuhiro	PO2-042	309
Noh, Dong-Young	PO1-054	223	Onai, Yasuhide	PO1-024	196
Noh, Dong-Young	PO1-087	253	Ono, Minoru	PO1-065	233
Noh, Dong-Young	PO1-092	257	Onoda, Naoyoshi	PO1-013	185
Noh, Dong-Young	PO2-013	279	Onoda, Naoyoshi	PO1-028	200
Noh, Dong-Young	PO2-022	284	Onoda, Naoyoshi	PO2-096	360
Noh, Dong-Young	PO2-025	289	Osako, Tomofumi	PO2-042	309
Noh, Dong-Young	PO2-043	310	Otsuka, Hiroko	PO1-014	186
Noh, Dong-Young	PO2-048	313	Ouyang, T	FP2-02	146
Noh, Dong-Young	PO2-049	314	Paik, Nam-Sun	FP1-03	141
Noh, Dong-Young	PO2-098	362	Paik, Nam-Sun	PO1-086	252
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Noh, Woo-Chul	PO1-005	176	Park, Chansung	PO2-090	354
Noh, Young Hee	FP5-04	167	Park, Eunhwa	PO1-060	229
Nomura, Takashi	PO2-062	327	Park, Eun Young	FP4-05	162
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Odawara, Hiroki	PO1-020	192	Park, Geumja	PO2-078	344
Odawara, Hiroki	PO1-030	202	Park, Geunjun	PO1-047	216
Odawara, Hiroki	PO1-056	225	Park, Geunjun	PO2-040	307
Ogasawara, Yutaka	PO1-012	184	Park, Hae Jin	FP2-05	150

Park, Hae Ran	PO2-052	317	Park, Yong Lai	PO2-093	357
Park, Hai-Lin	PO1-061	230	Park, Yong Rae	PO1-037	209
Park, Heung Kyu	PO1-090	255	Park, Young-Mi	PO1-003	174
Park, Ho Yong	PO2-028	292	Pegram, M	FP4-04	161
Park, Ho Yong	PO2-088	352	Pei, Zhou	FP2-01	145
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Park, Hyung Seok	PO2-058	323	Pippen, J	FP4-04	161
Park, In Ae	PO2-025	289	Pivot, X	FP4-04	161
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Park, Je-Kyun	PO2-009	274	Press, M	FP4-04	161
Park, Jeong Seon	PO2-043	310	Putt, David	PO2-021	283
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Park, Man Young	PO1-037	209	Ro, Jungsil	PO2-098	362
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Park, Min Ho	PO1-022	194	Rokutanda, Nana	PO1-020	192
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Park, Rae Woong	FP4-03	159	Rokutanda, Nana	PO1-056	225
Park, Sang Hee	PO2-043	310	Rosner, Bernard	PO2-005	270
Park, Sarah	PO1-004	175	Roter, Debra	PO2-073	339
Park, Sarah	PO2-086	350	Ryu, Dong Won	PO1-040	212
Park, Seho	PO2-058	323	Ryu, Dong Won	PO1-041	213
Park, Seung Yeon	PO1-090	255	Ryu, Dong Won	PO1-043	215
Park, Soon-Ah	PO1-101	265	Ryu, Dong Won	PO2-032	298
Park, So Yeon	PO1-052	221	Ryu, Dong Won	PO2-091	355
Park, Sue K.	PO1-005	176	Ryu, Hee Seon	PO1-021	193
Park, Sung Hwan	PO1-057	226	Ryu, Hee Seon	PO1-022	194
Park, Sungjin	PO2-023	285	Ryu, Woo Sang	PO1-055	224
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Sato, Ayako	PO1-020	192	Son, Byung Ho	PO1-058	227
Sato, Ayako	PO1-030	202	Son, Byung Ho	PO1-094	259
Sato, Ayako	PO1-056	225	Son, Byung Ho	PO2-036	303
Sayeed, Ahmed	PO2-029	294	Son, Byung Ho	PO2-084	348
Schnitt, Stuart	PO2-005	270	Son, Daegu	PO2-030	296
Seika, Tei	PO2-101	365	Son, Doo Min	PO2-027	291
Seo, Hyung-Il	PO1-050	219	Son, Doo Min	PO2-087	351
Seo, Hyung-Il	PO1-085	251	Son, Gill Soo	PO1-055	224
Seo, Jin Young	PO1-032	204	Song, Byung Joo	PO1-004	175
Seo, Jin Young	PO1-035	207	Song, Byung Joo	PO2-086	350
Seo, Jin Young	PO1-058	227	Song, Clara	PO1-002	173
Seo, Jin Young	PO1-094	259	Song, Jae-In	PO2-021	283
Seo, Jin Young	PO2-084	348	Song, Jeong Yoon	PO1-017	189
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Shin, Hee Jung	PO1-038	210	Suh, Eunyoung	PO1-071	238
Shin, Hyeongcheol	PO1-047	216	Suktitipat, Bhoom	PO1-001	171
Shin, Hyeongcheol	PO2-040	307	Sul, Ji Young	PO1-016	188
Shin, Hyuk Jae	PO1-027	199	Sultan, Ahmed	PO1-023	195
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Shin, Hyungsik	PO1-018	190	Sung, Soonhee	PO2-033	299
Shin, Kyung Hwan	FP2-05	150	Sung, Soonhee	PO2-055	320
Shin, Kyung Hwan	FP3-04	155	Surh, Young-Joon	FP1-05	143
Shin, Kyung Hwan	PO2-090	354	Surh, Young-Joon	PO2-014	280
Shin, Min Ho	PO2-061	326	Suzuki, Hiroshi	PO1-024	196
Shin, Mi Soon	PO1-068	236	Suzuki, Yasuhiro	PO1-033	205
Shirouzu, Kazuo	PO1-014	186	Tabei, Toshio	PO1-063	232
Shuji, Noriko	PO2-054	319	Tae, Soonyoung	PO2-027	291
Sien, Tadahiko	PO1-100	264	Tae, Young Sook	PO1-078	245
So, Hyang Sook	FP5-04	167	Tai, Patricia	FP3-02	152
So, Hyang Sook	PO1-078	245	Taira, Naruto	PO1-039	211
So, Hyang Sook	PO2-072	337	Taira, Naruto	PO1-083	249
Sohn, Jang-Shin	PO2-092	356	Taira, Naruto	PO1-100	264
Son, BH	PO2-012	278	Takashima, Tsutomu	PO1-013	185
Son, Byung Ho	PO1-032	204	Takashima, Tsutomu	PO1-028	200
Son, Byung Ho	PO1-035	207	Takashima, Tsutomu	PO2-096	360
Son, Byung Ho	PO1-038	210	Takeda, Masashi	PO2-062	327

Takei, Hiroyuki	PO1-063	232	Wong, H.N.	PO1-019	191
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Takeyoshi, Izumi	PO1-030	202	Woo, Hee Doo	PO2-087	351
Takeyoshi, Izumi	PO1-056	225	Woo, Sang Wook	PO1-055	224
Tamae, Keiyoshi	PO1-065	233	Woo, Sung Koo	PO2-030	296
Tamimi, Rulla	PO2-005	270	Wu, J	FP2-02	146
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Tokuda, Yutaka	PO1-033	205	Yamasaki, Takashi	PO2-064	329
Tokuwame, Artsushi	PO2-096	360	Yamashita, Toshinari	PO1-025	197
Tokuyama, Eijiro	PO1-039	211	Yamashita, Toshinari	PO1-048	217
Totsuka, Katsunori	PO1-030	202	Yamashita, Toshinari	PO1-049	218
Toyoshima, Chieko	PO1-025	197	Yamauchi, Akira	PO1-012	184
Toyoshima, Chieko	PO1-048	217	Yanagita, Yasuhiro	PO2-056	321
Toyoshima, Chieko	PO1-049	218	Yang, Ajin	PO2-031	297
Toyoshima, Satoshi	PO1-065	233	Yang, Ajin	PO2-041	308
Tozuka, Katsunori	PO1-056	225	Yang, Ajin	PO2-080	345
Tsang, Simon	PO1-019	191	Yang, Joo-Sock	PO1-002	173
Tsuda, Banri	PO1-033	205	Yang, Jung Dug	PO2-028	292
Tsuda, Hitoshi	FP1-01	139	Yang, Jung-Hyun	FP4-02	158
Tsuda, Hitoshi	PO1-031	203	Yang, Jung-Hyun	PO1-009	180
Tsujimoto, Masahiko	PO2-064	329	Yang, Jung-Hyun	PO1-091	256
Tsukiyama, Ayumi	PO2-064	329	Yang, Jung-Hyun	PO2-007	272
Tsunekawa, Shoji	PO2-054	319	Yang, Jung-Hyun	PO2-046	311
Uraoka, Takako	PO2-064	329	Yang, Jung-Hyun	PO2-047	312
Villalon, Antonio H.	PO2-029	294	Yang, Jung-Hyun	PO2-053	318
Waller, Annie	PO2-066	331	Yang, Jung-Hyun	PO2-097	361
Wang, CJ	PO1-051	220	Yang, Jung Hyung	PO2-031	297
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Yi, Myungsun	PO1-074	241	Yu, Ben-Long	PO2-010	276
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Yokomise, Hiroyasu	PO1-012	184	Yu, Jong-Han	PO1-092	257
Yokomizo, Jissei	PO1-024	196	Yu, Jong-Han	PO2-013	279
Yom, Cha Kyong	PO2-085	349	Yu, Jong-Han	PO2-048	313
Yom, Cha Kyong	PO2-093	357	Yu, Jong-Han	PO2-049	314
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Yoon, Chan Seok	PO2-057	322	Yun, Min-Young	PO1-088	254
Yoon, Dae-Sung	PO2-092	356	Yun, Young Ho	PO1-068	236
Yoon, Jung Han	PO1-021	193	Zhang, Guochun	PO2-063	328
Yoon, Jung Han	PO1-022	194	Zhang, ZP	PO1-029	201
Yoon, Sei-Ok	PO1-088	254	Zhang, ZP	PO1-051	220
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Yoshida, Miwa	FP1-01	139	Zhong, WX	PO1-029	201
Yoshida, Takashi	PO1-063	232	Zhu, Meihua	PO2-071	336
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