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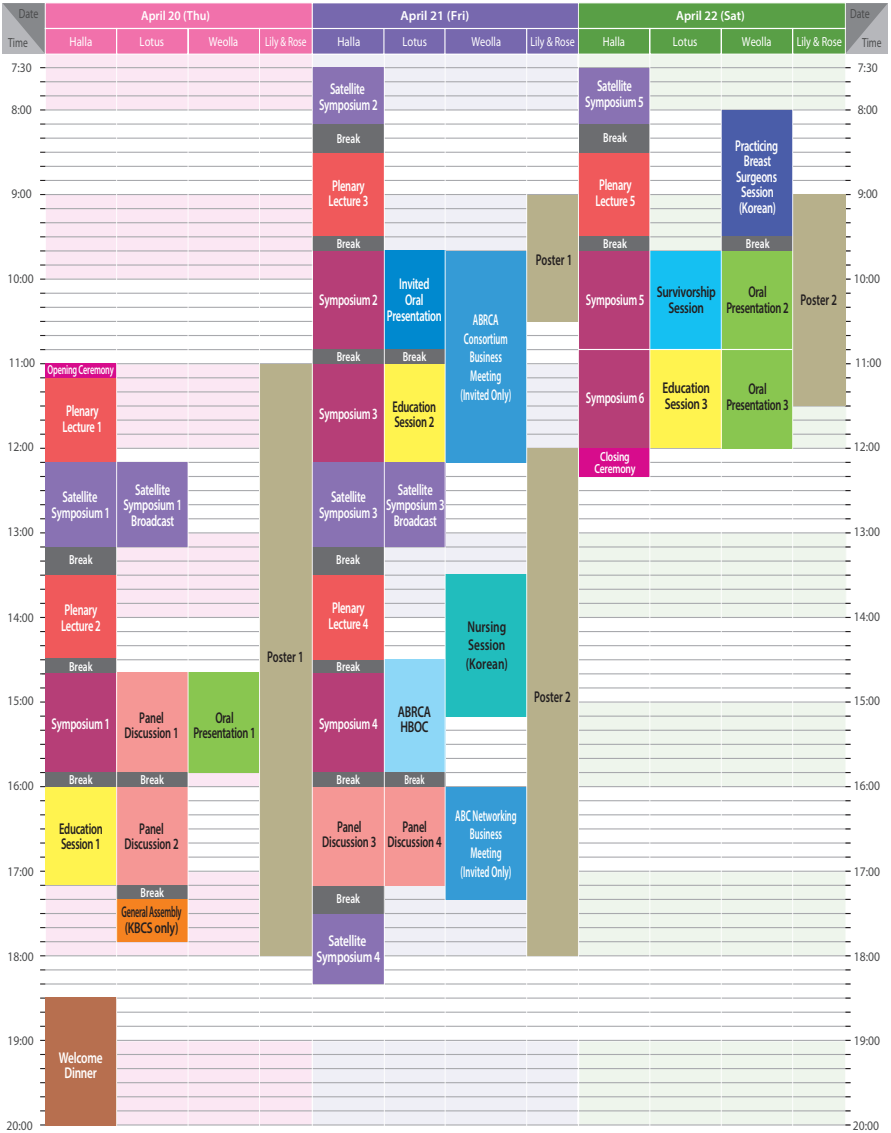
한국유방암학회
Korean Breast Cancer Society

Table of Contents


Date
Time
April 20 (Thu)
April 21 (Fri)
April 22 (Sat)
Halla
Lotus
Weolla
Lily & Rose
7:30
8:00
9:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
18:00
19:00
20:00
Opening Ceremony
Plenary Lecture 1
Satellite Symposium 1
Satellite Symposium 1 Broadcast
Break
Plenary Lecture 2
Symposium 1
Panel Discussion 1
Oral Presentation 1
Education Session 1
Panel Discussion 2
General Assembly (KBCS only)
Welcome Dinner
Poster 1
Satellite Symposium 2
Plenary Lecture 3
Symposium 2
Invited Oral Presentation
Symposium 3
Education Session 2
Satellite Symposium 3
Satellite Symposium 3 Broadcast
Plenary Lecture 4
Symposium 4
ABRCA HBOC
Panel Discussion 3
Panel Discussion 4
Satellite Symposium 4
ABRCA Consortium Business Meeting (Invited Only)
Nursing Session (Korean)
ABC Networking Business Meeting (Invited Only)
Poster 1
Poster 2
Satellite Symposium 5
Plenary Lecture 5
Symposium 5
Survivorship Session
Practicing Breast Surgeons Session (Korean)
Oral Presentation 2
Symposium 6
Education Session 3
Oral Presentation 3
Closing Ceremony
Poster 2

Day 1_April 20(Thu)

Opening Ceremony 11:00-11:10 / Halla

Plenary Lecture 1 11:10-12:10 / Halla

Past and Future Treatment of HER2-positive Breast Cancer

Moderator Sung-Bae Kim
ASAN Medical Center, Korea

Speaker Martine Piccart 2
CAN ANTI-HER2 TREATMENT FOR ADVANCED BREAST CANCER DISEASE BE INDIVIDUALIZED IN 2017?
Institut Jules Bordet, Belgium

Satellite Symposium 1 12:10-13:10 / Halla

The Role of Faslodex in Advanced Breast Cancer Management Pursuing Long Term Treatment Strategy

Moderator Dong-young Noh
Seoul National Univ. Hospital, Korea

Speaker Peter Schmid 78
THE ROLE OF FASLODEX IN ADVANCED BREAST CANCER MANAGEMENT PURSUING LONG TERM TREATMENT STRATEGY
Barts Cancer Institute, Queen Mary Univ. of London, United Kingdom

Coffee Break 13:10-13:30

Plenary Lecture 2 13:30-14:30 / Halla

What is the Current Concept of Molecular Portraits of Human Breast Tumors

Moderator Min-Hyuk Lee
Soonchunhyang Univ. Hospital Seoul, Korea

Speaker Charles M. Perou 4
WHAT IS THE CURRENT CONCEPT OF MOLECULAR PORTRAITS OF HUMAN BREAST TUMORS
Univ. of North Carolina at Chapel Hill, U.S.A.

Coffee Break 14:30-14:40

Symposium 1 14:40-15:50 / Halla

Breast Cancer Prevention and Screening

Moderator Eun Sook Lee
National Cancer Center, Korea

Moderator Steven A Narod
Women's College Research Institute, Women's College Hospital, Dalla Lana School of Public Health, Univ. of Toronto, Canada

Speaker Steven A Narod 29
BREAST CANCER SCREENING: HARM OR GOOD?
Women's College Research Institute, Women's College Hospital, Dalla Lana School of Public Health, Univ. of Toronto, Canada

Day 1_April 20(Thu)

Speaker	Antonis Antoniou	*30*
	ASSESSMENT OF BREAST CANCER RISK WITH GENETIC POLYMORPHISMS *Univ. of Cambridge, United Kingdom*	
Speaker	Po-Han Lin	*31*
	GERMLINE TESTING FOR HEREDITARY CANCER WITH MULTIGENE PANEL *National Taiwan Univ. Hospital, Taiwan*	

Panel Discussion 1 — 14:40-15:50 / Lotus

Elderly Breast Cancer

Moderator	Janice Tsang *Hong Kong Breast Oncology Group (HKBOG), Hong Kong*	
Speaker	Jee Hyun Kim	*11*
	COMPREHENSIVE GERIATRIC ASSESSMENT FOR ELDERLY PATIENTS *Seoul National Univ. Bundang Hospital, Korea*	
Speaker	Seho Park	*12*
	LOCAL THERAPY *Yonsei Univ. College of Medicine, Korea*	
Speaker	Janice Tsang	*13*
	SYSTEMIC THERAPY *Hong Kong Breast Oncology Group (HKBOG), Hong Kong*	

Oral Presentation 1 — 14:40-15:50 / Weolla

Moderator	Jeong Soo Kim *The Catholic Univ. of Korea Uijeongbu St. Mary's Hospital, Korea*	
Moderator	Woo-Chan Park *The Catholic Univ. of Korea Yeouido St. Mary's Hospital, Korea*	
Speaker	Gautam Sethi	*103*
	POTENTIAL APPLICATION OF GUGGULSTERONE AS A NOVEL ANTAGONIST OF CXCR4 EXPRESSION IN TRIPLE-NEGATIVE BREAST CANCER *National Univ. of Singapore, Singapore*	
Speaker	Bum-Sup Jang	*104*
	A RADIOSENSITIVITY GENE SIGNATURE AND PD-L1 STATUS PREDICT CLINICAL OUTCOME OF PATIENTS WITH INVASIVE BREAST CARCINOMA IN THE CANCER GENOME ATLAS (TCGA) DATASET *Seoul National Univ. Hospital, Korea*	
Speaker	Chao Wang	*105*
	INTERPLAY BETWEEN MEVALONATE AND HIPPO PATHWAYS REGULATES DDX20 VIA YAP IN INVASIVE BREAST CANCERS *National Univ. of Singapore, Singapore*	
Speaker	Michael Co	*106*
	CO-EXISTENCE OF DUCTAL CARCINOMA WITHIN PHYLLODES TUMOR - A REVIEW OF 557 PHYLLODES TUMORS FROM A TWENTY-YEAR REGION-WIDE DATABASE IN HONG KONG AND SHENZHEN, CHINA *The Univ. of Hong Kong, Hong Kong*	

Day 1_April 20(Thu)

Speaker	In Hae Park	*107*
	RANDOMIZED PHASE III TRIAL OF IRINOTECAN COMBINED WITH CAPECITABINE VERSUS CAPECITABINE IN PATIENTS WITH METASTATIC BREAST CANCER (MBC) PREVIOUSLY TREATED WITH ANTHRACYCLINE AND TAXANES PROCEED TRIAL	
	National Cancer Center, Korea	
Speaker	Han-Byoel Lee	*109*
	DETECTION OF SPLICEOMIC SIGNATURES FOR PREDICTING ENDOCRINE RESISTANCE IN ESTROGEN RECEPTOR-POSITIVE BREAST CANCER	
	Seoul National Univ. Hospital, Korea	
Speaker	Min Min Tan	*110*
	INHERITED MUTATIONS IN BRCA1 AND BRCA2 IN AN UNSELECTED MULTI-ETHNIC COHORT OF ASIAN BREAST CANCER PATIENTS AND HEALTHY CONTROLS FROM MALAYSIA	
	Cancer Research Malaysia, Malaysia	
Speaker	Eun-Shin Lee	*111*
	CLINICAL APPLICATION OF MULTIGENE PANEL TESTING AND GENETIC COUSELING FOR HEREDITARY/FAMILIAL BREAST CANCER RISK ASSESSMENT: PROSPECTIVE SINGLE CENTER STUDY	
	Seoul National Univ. College of Medicine, Korea	

Coffee Break 15:50-16:00

Education Session 1 — 16:00-17:10 / Halla

New Issues in Cancer Research and Treatment

Moderator	Woong-Yang Park	
	Samsung Medical Center, Korea	
Moderator	Naoto Ueno	
	The Univ. of Texas, MD Anderson Cancer Center, U.S.A.	
Speaker	Byung Joo Chae	*54*
	CLINICAL UTILITY OF LIQUID BIOPSY IN CANCER	
	The Catholic Univ. of Korea, Seoul St. Mary's Hospital, Korea	
Speaker	Woong-Yang Park	*56*
	ACTIONABLE GENOME ANALYSIS FOR HUMAN CANCER	
	Samsung Medical Center, Korea	
Speaker	Tae-Min Kim	*57*
	NEW ISSUES IN CANCER GENOMICS FOR THE RESEARCH AND TREATMENT	
	College of Medicine, The Catholic Univ. of Korea, Korea	

Panel Discussion 2 — 16:00-17:10 / Lotus

Special Issues in Stage IV Breast Cancer

Moderator	Jin Zhang	
	Tianjin Medical Univ. Cancer Center, China	
Speaker	Jin Zhang	*14*
	SURGERY FOR STAGE IV BREAST CANCER: NO BENEFIT AT ALL?	
	Tianjin Medical Univ. Cancer Center, China	

Day 1_April 20(Thu)

Speaker	Hee Kyung Ahn NEW THERAPEUTIC STRATEGY FOR CNS METASTASES IN BREAST CANCER *Gachon Univ. Gil Medical Center, Korea*	*16*
Speaker	Louis Chow HOW LONG SHOULD WE TREAT PATIENTS WITH METASTATIC BREAST CANCER? IS CURE POSSIBLE? *Macau Univ. of Science and Technology, Hong Kong*	*17*

Coffee Break 17:10-17:20

General Assembly (KBCS Only) 17:20-17:50 / Lotus

Welcome Dinner 18:30-20:00 / Halla

Day 2_April 21(Fri)

Satellite Symposium 2 — 07:30-08:10 / Halla

Dose Intensity and the Importance of Febrile Neutropenia Prevention

Moderator King-Jen Chang
National Taiwan Univ. Taiwan

Speaker Yeon Hee Park *80*
DOSE INTENSITY AND THE IMPORTANCE OF FEBRILE NEUTROPENIA PREVENTION
Samsung Medical Center, Korea

Coffee Break 08:10-08:30

Plenary Lecture 3 — 08:30-09:30 / Halla

Has Axillary Clearance Become Obsolete?

Moderator Soo-Jung Lee
Yeungnam Medical Center, Korea

Speaker Emiel Rutgers *5*
HAS AXILLARY CLEARANCE BECOME OBSOLETE?
Netherlands Cancer Institute, Netherlands

Coffee Break 09:30-09:40

Symposium 2 — 09:40-10:50 / Halla

Immuno-Oncology – Where We Are?

Moderator Kyong Hwa Park
Korea Univ. Anam Hospital, Korea

Moderator Mary L. Disis
Univ. of Washington, U.S.A.

Speaker Peter Schmid *32*
IMMUNE CHECK-POINT BLOCKADE FOR BREAST CANCER
Barts Cancer Institute, Queen Mary Univ. of London, United Kingdom

Speaker Yasir Nagarwala *33*
IMMUNE APPROACHES TO THE TREATMENT OF BREAST CANCER, AROUND THE CORNER?
Merck & Co., Inc., U.S.A.

Speaker Mary L. Disis *34*
IMMUNE MONITORING FOR IMMUNO-ONCOLOGY CLINICAL TRIALS
Univ. of Washington, U.S.A.

Invited Oral Presentation — 09:40-10:50 / Lotus

Moderator Sang Seol Jung
Bundang CHA Hospital, Korea

Moderator Yoon Sim Yap
National Cancer Centre Singapore, Singapore

Day 2_April 21(Fri)

Speaker	In Hae Park	*97*
	SUBGROUP ANALYSIS OF ASIAN POPULATION AMONG PALOMA-2 TRIALS *National Cancer Center, Korea*	
Speaker	Yoon Sim Yap	*98*
	FIRST-LINE RIBOCICLIB + LETROZOLE IN POSTMENOPAUSAL ASIAN WOMEN WITH HORMONE RECEPTOR-POSITIVE (HR+), HER2-NEGATIVE (HER2-) ADVANCED BREAST CANCER (ABC): A SUBGROUP ANALYSIS OF MONALEESA-2 *National Cancer Centre Singapore, Singapore*	
Speaker	Woo Kyung Moon	*99*
	BREAST MRI MONITORING FOR YOUNG BREAST CANCER PATIENTS AFTER BREAST CONSERVATION THERAPY: A MULTICENTER PROSPECTIVE STUDY *Seoul National Univ. Hospital, Korea*	
Speaker	Hee-Jeong Kim	*100*
	A PROSPECTIVE, RANDOMIZED, MULTICENTER, OPEN-LABEL PHASE III NEOADJUVANT STUDY TO COMPARE CHEMOTHERAPY WITH ENDOCRINE THERAPY IN PREMENOPAUSAL PATIENTS WITH HORMONE RECEPTOR POSITIVE, HER2 NEGATIVE BREAST CANCER *ASAN Medical Center, Korea*	

ABRCA Consortium Business Meeting (Invited Only) 09:40-12:10 / Weolla

Coffee Break 10:50-11:00

Symposium 3 11:00-12:10 / Halla

Young Age Session

Moderator	Jung Sil Ro *National Cancer Center, Korea*	
Moderator	Shinji Ohno *Cancer Institute Hospital, Japan*	
Speaker	Elizabeth Ginsburg	*36*
	FERTILITY PRESERVATION *The Brigham and Women's Hospital, U.S.A.*	
Speaker	Yeon Hee Park	*37*
	CHEMOTHERAPY-ENDOCRINE THERAPY SEQUENCE IN PREMENOPAUSAL PATIENTS *Samsung Medical Center, Korea*	
Speaker	Shinji Ohno	*38*
	LONG-TERM TOXICITY OF ENDOCRINE THERAPY *Cancer Institute Hospital, Japan*	

Education Session 2 11:00-12:10 / Lotus

Mutational Landscape and Its Implications for Treatment of Breast Cancer

Moderator	Kyung Hae Jung *ASAN Medical Center, Korea*
Moderator	Charles M. Perou *Univ. of North Carolina at Chapel Hill, U.S.A.*

Day 2_April 21(Fri)

Speaker	Wonshik Han	*58*
	OVERCOMING HETEROGENEITY: SINGLE CELL SEQUENCING OF BREAST CANCER *Seoul National Univ. Hospital, Korea*	
Speaker	Naoto Ueno	*59*
	PRACTICAL IMPLICATIONS OF NEXT GENERATION SEQUENCING IN BREAST CANCER : PROMISES AND CHALLENGES *The Univ. of Texas, MD Anderson Cancer Center, U.S.A.*	
Speaker	Charles M. Perou	*60*
	MOLECULAR HETEROGENEITY OF TRIPLE-NEGATIVE BREAST CANCER *Univ. of North Carolina at Chapel Hill, U.S.A.*	

Satellite Symposium 3 — 12:10-13:10 /Halla

Recent Insight into Clinic for HER2+ mBC Patients

Moderator	Chanheun Park *Kangbuk Samsung Hospital, Korea*	
Speaker	Tae-Yong Kim	*82*
	RECENT INSIGHT INTO CLINIC FOR HER2+ mBC PATIENTS *Seoul National Univ. Hospital, Korea*	

Coffee Break 13:10-13:30

Plenary Lecture 4 — 13:30-14:30 / Halla

Immuno-Oncology of Breast Cancer

Moderator	Young-Hyuck Im *Samsung Medical Center, Korea*	
Speaker	Mary L. Disis	*7*
	IMMUNO-ONCOLOGY OF BREAST CANCER *Univ. of Washington, U.S.A.*	

Nursing Session (Korean) — 13:30-15:10 / Weolla

Management of Metastatic, Recurrent and Intractable Breast Cancer

Moderator	Mi Young Kang *Cheil General Hospital, Korea*	
Speaker	Yaelim Lee	*90*
	SURVIVORSHIP ISSUES OF THE METASTATIC, RECURRENT AND INTRACTABLE BREAST CANCER *Chung-Ang Univ., Korea*	
Speaker	Hyejin Cho	*91*
	NURSING CARE IN BONE METASTASIS *Ewha Womans Univ. Mokdong Hospital, Korea*	
Speaker	Seung Hee Seon	*92*
	NURSING CARE IN VISCERAL METASTASIS *Korea Univ. Guro Hospital, Korea*	
Speaker	Su Jin Lee	*93*
	SPECIALIST NURSING ROLES FOR THE PATIENT WITH METASTATIC, RECURRENT AND INTRACTABLE BREAST CANCER *Dankook Univ. Hospital, Korea*	

Day 2_April 21(Fri)

Speaker	Eun-Young Jun COMPLEMENTARY AND ALTERNATIVE THERAPIES *DaeJeon Univ., Korea*	*94*

Coffee Break 14:30-14:40

ABRCA & HBOC Session 14:30-15:50 / Lotus

Moderator	Seigo Nakamura *Showa Univ. School of Medicine, Japan*	
Moderator	Sung-Won Kim *Daerim St. Mary's Hospital, Korea*	
Speaker	Ava Kwong BREAST CANCER GENETICS- HOW IS IT CHANGING OUR PRACTICE *The Univ. of Hong Kong, Hong Kong*	*72*
Speaker	Soo-Hwang Teo PANEL TESTING AND SNP TESTING (POLYGENIC RISK SCORE) IN ASIAN WOMEN *Cancer Research Malaysia, Malaysia*	*73*
Speaker	Steven A Narod BREAST CANCER GENETICS AND CANCER POLICY *Women's College Research Institute, Women's College Hospital, Dalla Lana School of Public Health, Univ. of Toronto, Canada*	*74*
Speaker	David Goldgar GENETIC SUSCEPTIBILITY TO BREAST CANCER: ROLES OF HIGH- MODERATE- AND MODEST-PENETRANCE ALLELES *Univ. of Utah School of Medicine, U.S.A.*	*75*

Symposium 4 14:40-15:50 / Halla

Challenges in the Implementation of Biosimilar: New Frontiers in Oncology

Moderator	Joon Jeong *Gangnam Severance Hospital, Korea*	
Moderator	Xavier Pivot *Univ. Hospital of Besancon, France*	
Speaker	Chul Kim CLINICAL CONSIDERATIONS FOR THE DEVELOPMENT OF BIOSIMILARS IN ONCOLOGY *Samsung Bioepis Co., Ltd., Korea*	*40*
Speaker	Fumikata Hara G-CSF (PEG-GCSF) BIOSIMILAR : CLINICAL APPLICATION AND EXPERIENCE *National Hospital Organization Shikoku Cancer Center, Japan*	*41*
Speaker	Xavier Pivot TRASTUZUMAB BIOSIMILAR *Univ. Hospital of Besancon, France*	*42*

Coffee Break 15:50-16:00

Day 2_April 21(Fri)

Panel Discussion 3 — 16:00-17:10 / Halla

Minimizing Local Therapy

Moderator Yong Sheng Wang
Shandong Cancer Hospital Affiliated to Shandong Univ., China

Speaker Han-Byoel Lee — *18*
DO WE NEED EXCISION IN cCR PATIENTS AFTER NEOADJUVANT CHEMOTHERAPY
Seoul National Univ. Hospital, Korea

Speaker Jeong Eon Lee — *19*
CAN WE OMIT SENTINEL LYMPH NODE BIOPSY IN SOME PATIENTS
Samsung Medical Center, Korea

Speaker Yong Bae Kim — *21*
EXTENT AND ROLE OF RADIATION THERAPY IN pCR PATIENTS
Yonsei Cancer Center, Korea

Panel Discussion 4 — 16:00-17:10 / Lotus

Role of Imaging in the Era of ALND Omitting of N1 Breast Cancer

Moderator Emiel Rutgers
Netherlands Cancer Institute, Netherlands

Speaker Chiun-Sheng Huang — *23*
USG OR FNA FOR PREDICTING NODE POSITIVE IN BREAST CANCER
Taiwan Breast Cancer Consortium, Taiwan

Speaker Emiel Rutgers — *25*
ACCURACY OF PET FOR LYMPH NODE EVALUATION
Netherlands Cancer Institute, Netherlands

Speaker Wonshik Han — *27*
NOMOGRAM TO PREDICT 3 OR MORE LYMPH NODE METASTASIS
Seoul National Univ. Hospital, Korea

Asian Breast Cancer Networking Business Meeting (Invited Only) — 16:00-17:20 / Weolla

Coffee Break 17:10-17:30

Satellite Symposium 4 — 17:30-18:20 / Halla

Prognostic Diagnosis for HR+/HER2- Early Breast Cancer Patient Based on the Algorithm through the Gene Expression Signature

Moderator Byung-Joo Song
The Catholic Univ. of Korea, Korea

Speaker Young Kee Shin — *85*
PROGNOSTIC DIAGNOSIS FOR HR+/HER2- EARLY BREAST CANCER PATIENT BASED ON THE ALGORITHM THROUGH THE GENE EXPRESSION SIGNATURE
Seoul National Univ., Korea

Day 3_April 22(Sat)

Satellite Symposium 5 — 07:30-08:10 / Halla

Enhancing Endocrine Therapy for Hormone Receptor - Positive Advanced Breast Cancer

Moderator Nam-Sun Paik
Ewha Womans Univ. Cancer Center for Women, Korea

Speaker Sung-Bae Kim *88*
ENHANCING ENDOCRINE THERAPY FOR HORMONE RECEPTOR - POSITIVE ADVANCED BREAST CANCER
ASAN Medical Center, Korea

Coffee Break 08:10-08:30

Practicing Breast Surgeons Session (Korean) — 08:00-09:30 / Weolla

Current Issues in Breast Clinic

Moderator Dong Seok Lee
Bunhongbit Hospital, Korea

Speaker Tae Ik Eom
ROLE OF KABTS IN THE MANAGEMENT OF BREAST CANCER IN KOREA
Hiu Breast & Thyroid Clinic, Korea

Speaker Dongwon Kim
ROLE OF ULTRASOUND IN BREAST CANCER SCREENING
Daerim St. Mary's Hospital, Korea

Speaker Hyewon Ro
BIRADS CATEGORIZATION IN PRACTICE: UNDER OR OVER-CATEGORIZATION OF BREAST LESIONS
Honest U Surgery Clinic, Korea

Speaker Kyung Ho Cha
VABB IN BREAST CLINIC
Mamma Breast Clinic, Korea

Speaker Junho Kim
CURRENT ISSUES IN BREAST CLINIC
Dr. Kim Breast Thyroid Clinic, Korea

Plenary Lecture 5 — 08:30-09:30 / Halla

Haute Couture Tailoring of Radiation Therapy in Breast Cancer

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

Speaker Philip Poortmans *9*
HAUTE COUTURE TAILORING OF RADIATION THERAPY IN BREAST CANCER
Institut Curie Paris, France

Coffee Break 09:30-09:40

Day 3_April 22(Sat)

Symposium 5 — 09:40-10:50 / Halla

To Treat or Not

Moderator	Philip Poortmans *Institut Curie Paris, France*	
Moderator	Doo Ho Choi *Samsung Medical Center, Korea*	
Speaker	Su Ssan Kim POST-BCS WBRT: INVASIVE CARCINOMA & DCIS *Univ. of Ulsan College of Medicine, ASAN Medical Center, Korea*	*43*
Speaker	Hae Jin Park PMRT IN pN1 *Hanyang Univ. Hospital, Korea*	*45*
Speaker	Philip Poortmans IMN: BALANCING RISKS AND BENEFITS *Institut Curie Paris, France*	*47*

Survivorship Session — 09:40-10:50 / Lotus

Advances in Breast Cancer Survivors' Care

Moderator	Jung Han Yoon *Chonnam National Univ. Hwasun Hospital, Korea*	
Moderator	Ava Kwong *The Univ. of Hong Kong, Hong Kong*	
Speaker	Miyako Takahashi BREAST CANCER SURVIVORSHIP RESEARCH AND CARE PRACTICES FROM A JAPANESE PERSPECTIVE *National Cancer Center, Japan*	*66*
Speaker	Hyukjai Shin LIFE AFTER BREAST CANCER IN AUSTRALIA *Myongji Hospital, Medical School of Seonam Univ., Korea*	*67*
Speaker	Jihyoun Lee HEALTH STATUS AND HEALTHCARE UTILIZATION OF BREAST CANCER SURVIVORS *Soonchunhyang Univ. Hospital, Seoul, Korea*	*69*

Oral Presentation 2 — 09:40-10:50 / Weolla

Moderator	Young Up Cho *Yonsei Univ. College of Medicine, Korea*	
Moderator	Ho Yong Park *Kyungpook National Univ. Hospital, Korea*	
Speaker	Nirmala Sirisena GENETIC DETERMINANTS OF SPORADIC BREAST CANCER IN A COHORT OF SRI LANKAN POSTMENOPAUSAL WOMEN *Univ. of Colombo, Sri Lanka*	*112*

Day 3_April 22(Sat)

Speaker	Jisun Kim	*113*
	LUMINAL ANDROGEN RECEPTOR AND ANDROGEN RECEPTOR-HIGH TRIPLE-NEGATIVE BREAST CANCERS ARE GENETICALLY SIMILAR TO LUMINAL BREAST CANCERS *ASAN Medical Center, Korea*	
Speaker	Ji-Yeon Kim	*114*
	CIRCULATING TUMOR DNA PRESENTS VARIABLE CLONAL RESPONSE OF BREAST CANCER DURING NEOADJUVANT CHEMOTX *Samsung Medical Center (Samsung Seoul Hospital), Korea*	
Speaker	Heejung Chae	*115*
	PREDICTIVE ROLE OF FCRR3A-158 POLYMORPHISM AND STROMAL TUMOR INFILTRATING LYMPHOCYTES IN PATIENTS WITH HER2 POSITIVE METASTATIC BREAST CANCER *ASAN Medical Center, Korea*	
Speaker	Anjie Zhu	*116*
	PHASE II STUDY OF APATINIB PLUS VINORELBINE, A NOVEL COMBINATION OF ALL-ORAL REGIMEN IN HEAVILY PRETREATED PATIENTS WITH METASTATIC HER2-NEGATIVE BREAST CANCER *Chinese Academy of Medical Science Pumc, China*	
Speaker	Yirong Sim	*117*
	BREAST CANCER TRENDS IN YOUNG WOMEN - A SINGAPOREAN PERSPECTIVE *Singhealth Duke-nus Breast Centre, Singapore*	
Speaker	Chi-Cheng Huang	*118*
	RISK STRATIFICATION WITH ENDOPREDICT SIGNATURE FOR LUMINAL SUBTYPE BREAST CANCERS: RE-ANALYZING MICROARRAY EXPERIMENTS WITH HAN CHINESE ORIGIN *Cathay General Hospital, Taiwan*	
Speaker	Naoki Hayashi	*120*
	INTRODUCING THE JAPANESE BREAST CANCER REGISTRY AND THE ACTIVITY *St. Luke's International Hospital, Japan*	

Symposium 6 — 10:50-12:00 / Halla

Personalized Therapy

Moderator	Joohyuk Sohn *Yonsei Cancer Center, Korea*	
Moderator	Martine Piccart *Institut Jules Bordet, Belgium*	
Speaker	Yu Shyr	*49*
	HOW TO INTERPRET THE OMICS BIG DATA AND APPLY TO THE CLINICAL PRACTICE *Vanderbilt Univ. Medical Center, U.S.A.*	
Speaker	Martine Piccart	*50*
	PERSONALIZED ADJUVANT THERAPY BASED ON CLINICAL TRIALS IN BREAST CANCER: DREAM OR REALITY? *Institut Jules Bordet, Belgium*	
Speaker	Masakazu Toi	*52*
	WHERE ARE WE NOW, TO THE PRECISION MEDICINE *Kyoto Univ. Hospital, Japan*	

Day 3_April 22(Sat)

Education Session 3 — 10:50-12:00 / Lotus

Cell Cycle, CDKs and Breast Cancer: A Changing Paradigm

Moderator Seock-Ah Im
Seoul National Univ., Korea

Moderator Melanie Cruz
Chinese General Hospital and Medical Center, Philippines

Speaker Seock-Ah Im *61*
CELL CYCLE REGULATION AND TARGETING CDK 4/6 FOR TREATMENT OF BREAST CANCER
Seoul National Univ., Korea

Speaker Jin-Hee Ahn *62*
CDK 4/6 INHIBITORS FOR THE TREATMENT OF BREAST CANCER: A REVIEW OF CLINICAL DATA
ASAN Medical Center, Korea

Speaker Soohyeon Lee *64*
ONGOING CLINICAL TRIALS COMBINING CDK 4/6 INHIBITORS AND RELATED BIOMARKERS
Pfizer Oncology, Korea

Oral Presentation 3 — 10:50-12:00 / Weolla

Moderator Tae Hyun Kim
Inje Univ. Busan Paik Hospital, Korea

Moderator Lee Su Kim
Hallym Univ. Sacred Heart Hospital, Korea

Speaker Soo Jung Lee *121*
EXOSOMAL DEL-1 AS A POTENT DIAGNOSTIC MARKER FOR BREAST CANCER: A PROSPECTIVE COHORT STUDY
Kyungpook National Univ. School of Medicine, Korea

Speaker Hyokjo Kang *123*
A SINGLE CENTER STUDY OF RISK REDUCING MANAGEMENT IN BRCA MUTATION CARRIERS AFTER DIAGNOSIS OF BREAST CANCER
National Cancer Center, Korea

Speaker Choonghyun Ahn *124*
DNA METHYLATION PATTERNS OF CANCER TISSUES ASSOCIATED WITH BREAST CANCER SURVIVAL
Seoul National Univ. College of Medicine, Korea

Speaker Jisun Kim *125*
MYBL1 REARRANGEMENTS AND MYB AMPLIFICATION IN BREAST ADENOID CYSTIC CARCINOMA LACKING THE MYB-NFIB FUSION GENE
ASAN Medical Center, Korea

Speaker Chin-Yau Chen *126*
PREDICOTRS FOR COSMETIC OUTCOME IN ONCOPLASTIC MASTOPEXY TECHNIQUES
National Yang-ming Univ. Hospital, Taiwan

Speaker Gajanan Bhat *127*
RANDOMIZED PHASE 2, OPEN-LABEL, DOSE-RANGING STUDY OF A NOVEL, LONG-ACTING G-CSF, EFLAPEGRASTIM (SPI-2012, ROLONTISTM) OR PEGFILGRASTIM FOR THE MANAGEMENT OF NEUTROPENIA IN PATIENTS WITH BREAST CANCER
Spectrum Pharmaceuticals, U.S.A.

Speaker	Alan Prem Kumar	*128*
	WNT-DP103-GSK3β CASCADE PROMOTES WNT/β-CATENIN SIGNALING IN PARENTAL AND STEM CELLS FROM TRIPLE NEGATIVE BREAST CANCER *National Univ. of Singapore, Singapore*	

Closing Ceremony 12:00-12:20 /Halla

레트로졸 치료가 필요한 모든 환자에게...

브레트라

(레트로졸/letrozole)

폐경후 여성*의 국소적으로 진전된 또는 전이성 유방암에서 **1차 치료**

*에스트로겐 또는 프로게스테론 수용체 양성이거나 또는 수용체 상태가 알려지지 않은 폐경후 여성

항에스트로겐 요법후 재발된 자연적 또는 인공적으로 폐경이 된 여성의 **진전된 유방암**

5년동안 타목시펜 보조요법 이후 **연장 보조요법***

*에스트로겐 또는 프로게스테론 수용체 양성이거나 또는 수용체 상태가 알려지지 않은 폐경후 여성의 침습성 조기 유방암에서

호르몬수용체 양성인 폐경후 여성의 **침습성 조기 유방암**에서의 보조요법

브레트라 정 [성분/함량] 레트로졸 2.5mg **[보험코드(KD코드)/약가]** 648501310 [A00307321] / 2,915원/1정(2015.09.01) **[효능,효과]** 1.에스트로겐 또는 프로게스테론 수용체 양성이거나 또는 수용체 상태가 알려지지 않은 폐경후 여성의 국소적으로 진전된 또는 전이성 유방암에서 1차 치료 2.항에스트로겐 요법 후 재발의 자연적 또는 인공적으로 폐경이 된 여성의 진전된 유방암 3.에스트로겐 또는 프로게스테론 수용체 양성이거나 또는 수용체 상태가 알려지지 않은 폐경후 여성의 침습성 조기 유방암에서 5년동안 타목시펜 보조요법 이후 연장 보조요법 4.호르몬수용체 양성인 폐경후 여성의 침습성 조기 유방암에서의 보조요법 **[용법,용량]** 성인 및 고령자 : 권장용량은 식사와 상관없이 레트로졸로서 1일 1회 2.5 mg을 경구투여한다. 복용을 잊은 경우, 생각난 즉시 복용한다. 하지만 다음 복용시간에 가까운 경우는 복용을 생략하고 정해진 스케줄대로 복용한다. 권장용량인 2.5 mg을 넘지 않도록 두배용량을 복용해서는 안된다. 전이성 질환 환자인 경우에는 암의 진행이 확인될 때까지 투여를 계속한다. 보조요법 및 타목시펜 보조요법 이후의 연장보조요법의 경우 5년 동안 투여할 수 있으며, 투여 중 암이 재발하면 투약을 중지한다(타목시펜 보조요법 이후의 연장보조요법의 경우, 장기간 투여와 관련한 최적의 치료기간은 확립되어있지 않다.) 간장애 환자 : 간경변으로 인한 중등도의 간기능저하를 갖고 있는 환자에서 이 약의 혈액농도가 약간 증가하나 경증 - 중등도 간기능 저하 환자의 경우 용량조절은 필요하지 않다. 그러나 중증의 간기능장애 환자(Child-Pugh score C)에게 이 약을 사용할 경우 지속적이고 세심한 감독이 이루어져야 한다. 신장애 환자 : 크레아티닌청소율 10 mL/min 이상인 신장애 환자에 대한 용량조절은 필요하지 않다. **[금기]** 1.이 제제의 구성성분에 대한 과민반응이 있는 환자 2.폐경 전 내분비 상태인 여성 3.임부, 수유부 **[주의]** 1.크레아티닌 클리어런스가 10mL/min미만인 여성환자에 대한 연구는 시행되지 않았다. 그러므로 이러한 환자에 대한 이 약 치료의 잠재적 유익성 및 위험성을 투여 전에 신중히 고려해야 한다. 2.심한 간부전환자(Child-Pugh score C)에서 전신 노출 및 소실 반감기는 건강한 사람의 약 두 배이다. 그러므로 이러한 환자에서는 세심한 관찰하에 투여되어야한다. 반복투여에 대한 임상경험은 없다. **[이상반응]** 식욕부진,식욕증가, 고콜레스테롤혈증, 우울증, 두통, 어지러움, 구역, 구토, 소화불량, 변비, 설사, 탈모증, 발한 증가, 발진, 관절통, 안면홍조, 피로, 말초 부종, 체중 증가 등

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PLENARY LECTURE

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CAN ANTI-HER2 TREATMENT FOR ADVANCED BREAST CANCER DISEASE BE INDIVIDUALIZED IN 2017?

Martine Piccart

Institut Jules Bordet, Belgium

The recognition of the importance of HER2/neu oncogene amplification as a poor prognostic factor 20 years ago and the implementation of anti-HER2 therapies in the clinical setting has revolutionized the treatment paradigm for breast cancer. Since then, drugs targeting HER2 have emerged and clinicians now have at their disposal four approved anti-HER2 therapies to use in the advance setting: trastuzumab, lapatinib, T-DM1 and pertuzumab. Due to constant international collaborative efforts, a better understanding of the sequencing of those agents has risen and resulted in international guidelines. Anti-HER2 blockade with trastuzumab and pertuzumab in association with a taxane in first line has led to nearly a doubling of the survival rate when compared with single HER2 blockade.

Today, there is international consensus on adequate assessment of HER2 status in order to define patients who will likely benefit from anti-HER2 treatments. Nonetheless, significant continuous research efforts attempt to produce predictive biomarkers in order to allow tailored anti-HER2 treatment. So far, translational researches have addressed many potential targets in hope to individualize anti-HER2 treatments for advanced disease in 2017. Unfortunately, the search for additional biomarkers has proven to be unsuccessful so far.

Possible biomarker candidates such as mutations in the PI3K pathway, present in a third of breast cancers, have failed to be of additional help thus far. Indeed, even if associated with a worse prognostic, PIK3CA mutations carriers still showed consistent PFS benefit from pertuzumab and T-DM1 in the CLEOPATRA and EMILIA trials respectively. Expression levels of HER2 mRNA in these trials were also not found to be predictive for response to treatment, even though it proved to be a favourable prognostic factor. Disappointingly, the analysis of biomarkers known to be associated with resistance to anti-HER2 targeted therapies such as HER ligands, membrane receptors and components of the downstream signalling pathway could not establish any predictive biomarkers in the CLEOPATRA trial.

Recently, translational research curiosity has been focusing on tumors microenvironment. Indirect evidence that the communication between cancer cells and their surrounding stroma portends a critical importance has emerged from certain trials. The LUX-Breast 1 study, which compared afatinib plus vinorelbine to trastuzumab plus vinorelbine in women who had failed

one prior trastuzumab based regimen, and the EGF104900 study, which compared lapatinib plus trastuzumab to lapatinib alone in women who had failed multiple trastuzumab based regimens, reported a similar progression free survival of the different treatment arms. Surprisingly, comparable PFS translated into worse overall survival for the non trastuzumab arms in LUX-Breast 1 trial (20.5 vs. 28.6 months; HR, 1.48; 95% CI, 1.12-1.95; $p = 0.0048$) and EGF104900 trial (9.5 vs. 14.0 months; HR, 0.74; 95% CI, 0.57-0.97; $p = 0.026$). If post progression therapies could not explain this difference, it is possible to hypothesize that the immune mechanisms related to trastuzumab treatment may be as important as the inhibition of signal transduction by trastuzumab. Moreover, a recent retrospective analysis of the CLEOPATRA study has shown that stromal tumor-infiltrating lymphocytes (TILs) are of prognostic value. Each increase of 10% in TILs was associated with an 11% decrease in the risk of death. The ongoing PANACEA trial evaluates if immunotherapy with anti-PD-1 therapy is able to induce long lasting remissions. This phase Ib/II trial evaluates pembrolizumab in association with trastuzumab in women with advanced HER2/PD-L1 positive disease who have progressed on trastuzumab.

Finally, the ZEPHIR trial brings an exciting new insight on the possible contribution of metabolic imaging for selecting patients who will/will not benefit from T-DM1. This academic-led trial, demonstrated the important heterogeneity of HER2 expression in metastatic HER2 positive breast cancer patients. Using HER2-PET/CT imaging before receiving T-DM1, intrapatient heterogeneity was found in 46% of the patients while 29% had negative HER2-PET/CT. Maybe more importantly, a negative HER2-PET/CT could be predictive of patients that would be non-responders to T-DM1 treatment.

To conclude, almost two decades after the approval of trastuzumab, research efforts have failed to identify additional predictive biomarkers other than HER2 status by IHC/FISH that would help clinicians to go beyond HER2 status for tailoring patients treatment. The path towards optimal personalized medicine will take further collaboration of muldisiciplinary and international teams - and critically of governments - in order to develop molecular and imaging-based biomarkers.

WHAT IS THE CURRENT CONCEPT OF MOLECULAR PORTRAITS OF HUMAN BREAST TUMORS

Charles M. Perou

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Gene-expression profiling has had a considerable impact on our understanding of breast cancer biology. During the last 15 years, 5 intrinsic molecular subtypes of breast cancer (Luminal A, Luminal B, HER2-enriched, Basal-like and Claudin-low) and a normal breast-like group have been identified and intensively studied. In this presentation, I will focus on recent data regarding the potential clinical implications of the intrinsic molecular subtypes beyond the current pathological-based classification endorsed by the 2015 St. Gallens Consensus Recommendations. Within hormone receptor (HR)-positive and HER2-negative breast cancer, the Luminal A and B subtypes represent the vast majority of cases. Compared to Luminal A tumors, Luminal B tumors are characterized by higher expression of proliferation/cell cycle-related genes and lower expression of several luminal-related genes such as the progesterone receptor (PR). Clinically, Luminal B tumors show higher pCR rates following neoadjuvant multi-agent chemotherapy but worse distant recurrence-free survival at 5-years and 10-years regardless of adjuvant systemic therapy compared to Luminal A. This Luminal A vs. B classification, together with tumor size and encompassed with the ROR Score, also predicts distant recurrence within the 5 to 10-years of follow-up and thus may inform decisions concerning the length of endocrine therapy treatments (i.e. 5 years vs. 10 years).

Interestingly, although we and others have proposed pathology-based surrogate definitions of the Luminal A and B subtypes using semi-quantitative IHC scoring of Ki-67 and PR, the discordance rate versus multi-gene expression assays is still high (30-40%). Within clinically HER2+ disease, all the 4 main intrinsic subtypes can be identified beyond HR status, albeit with different proportions. Among them, the HER2-enriched subtype represents the majority of HER2+ tumors and shows higher expression of HER2 and lower expression of luminal genes compared to both luminal subtypes. In addition, recent data suggests that patients with HER2-enriched disease benefit the most from neoadjuvant trastuzumab, or dual HER2 blockade with trastuzumab/lapatinib, in combination with chemotherapy.

HAS AXILLARY CLEARANCE BECOME OBSOLETE?

Emiel Rutgers

Department of Surgerical Oncology, Netherlands Cancer Institute, Netherlands

The knowledge whether regional axillary- lymph nodes contain metastatic disease is important for two reasons:

– It provides prognostic information: should the patient receive adjuvant systemic treatments? It should be kept in mind that nowadays important prognostic information can also be gathered from the primary tumour: Grade, lymphatic invasion, size, UPA/PAI-1 level, gene expression arrays as MammaPrint and Oncotype Dx. Nodal status is far less important as prognosticator for chemotherapy indication.

– To guide elective regional treatment in case of metastasis in the lymph nodes: wait and see policy, axillary lymph node dissection, radiotherapy to the axilla or to the other regional lymph node basins.

SN biopsy has become standard of care to identify lymph node metastases in clinically N0 breast cancer. It is perfectly safe to forego further axillary treatment in patients who have no cancer (isolated tumor cells to be considered as negative) in their sentinel lymph nodes .

In many guidelines, complete axillary lymph node clearance is advised in patients with more the isolated tumorcells in their SN. However, the past years this treatment paradigm has been challenged.

Recently, three important trials with respect to axillary management in patients with metastatic breast cancer in the sentinel node are presented and published, and has caused a paradigm shift in management of the axilla.

First the American College of Surgeons Oncology Group Z0011 trial. The conclusion of Giuliano et al. was that despite the potential for residual axillary disease after SLND, SLND without ALND can offer excellent regional control and provides a reasonable management for selected patients with early-stage breast cancer treated with breast-conserving therapy and adjuvant systemic therapy.

In the multicentre, randomised, non-inferiority, phase 3 IBCSG trial 23-01, patients were eligible if they had clinically non-palpable axillary lymph node(s) and a primary tumour of 5 cm or less and who, after sentinel-node biopsy, had one or more micrometastatic (≤ 2 mm) sentinel lymph nodes with no extracapsular extension. Also this trial showed extremely low axillary re-

currence rates in the no ALND group, without any difference is disease free and overall survival.

The EORTC 10981-22023 AMAROS trial accrued from 2001 to 2010 4,806 patients with cT1-2N0 primary breast cancer. Patients with a positive SN were randomized between ALND and ART. The primary endpoint was 5-year axillary recurrence rate (ARR). Of the 1425 patients with a positive SN, 744 patients were randomized to the ALND-group and 681 to the ART-group. With a median follow up of 6.1 years, the 5-year ARR was 0·43% after ALND and 1.19% after ART. Lymphoedema was found significantly more often after ALND compared to ART. There was no significant difference in shoulder mobility, and no significant difference in QoL. ART provided excellent axillary control which was comparable to ALND, and caused less morbidity. Therefore, ART can be considered a validated alternative for ALND in those patients.

The next challenge is for those patients who have proven macrometases in their axilla (either by FNA cytology or core biopsy). How to manage these patients? Usually the patients are candidates for upfront systemic treatments: chemotherapy or anti-estrogen treatments. Particularly up front chemotherapy may render positive nodes to tumor negative. In this situation, the patient can as well be spared axillary clearance. A number of studies have shown that by marking the proven tumor positive lymph node (for instance by a I125 seed, or clip) and removing selectively the node, the histological status of this node is predictive for the other axillary nodes with high predictive values. In patients with tumor negative marked nodes after chemotherapy, a wait and see policy, or radiotherapy to the axilla, appears a reasonable option.

Take home message

- Patients who have a negative SN should not have any further axillary treatments.
- In patients with macro- or micro-metastases >0.2 mm in their sentinel lymph nodes from the axilla, further treatment of the axilla is advised. Complete axillary clearance is standard of care, but radiotherapy to the axilla is a validated alternative with less long term side effects. Patients who undergo breast conserving therapy including radiotherapy to the breast AND adjuvant systemic treatments, axillary clearance is of no benefit and should be omitted.
- In patients with proven axillary nodal metastases upfront chemotherapy should be considered, and minimally invasive axillary management should be explored.

IMMUNO-ONCOLOGY OF BREAST CANCER

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Breast cancer has become one of the most commonly studied immunogenic cancers. Some breast cancer patients express tumor specific genetic signatures of an adaptive immune response that are associated with improved survival. High levels of tumor infiltrating lymphocytes (TIL) are not only prognostic in some patients, but can predict clinical response to conventional therapy. Over the last several years immunologic studies of breast cancer have shown that (1) immunogenicity varies according to breast cancer subtype, (2) only a minority of patients express the robust levels of TIL associated with improved outcomes, and (3) breast cancer is dominated by a Type II immune microenvironment which can suppress the generation and proliferation of cytotoxic T-cells (CTL) needed for cancer eradication.

Triple negative breast cancer is the subtype of breast cancer readily modulated by immune checkpoint inhibitors. Clinical trials of either anti-PD-1 or PD-L1 monoclonal antibodies have shown clinical response rates of 15-20% in patients with treatment refractory metastatic disease. In most studies, the most common clinical response was the development of stable disease, in about a quarter of patients, with durations of months. Prolonged intervals of stable disease indicate the development of immune equilibrium, a time period in which the evolving immune response is controlling tumor progression. Clinical strategies designed to further augment Type I immunity during immune equilibrium may result in tumor regression or even eradication; active immunization to further expand Type I T-cells or treatment with agents that suppress immune cells that limit the expansion of CTL of such as M2 macrophage or T-regulatory cells (Treg). Combinations of immunotherapy with chemotherapy administered earlier in the course of disease may allow better control of tumor progression giving time for the evolving immune response to mediate a full anti-tumor effect.

HER2+ breast cancer is immunomodulated with trastuzumab. Patients treated with trastuzumab can develop high levels of Type I T-cells specific for HER2. Exploratory studies in both the neoadjuvant and adjuvant setting have associated the level of peripheral blood Type I HER2 specific T-cells developing with therapy with favorable clinical outcomes. Tumor pathologic assessments have also demonstrated that trastuzumab therapy can significantly increase the number of Tbet+ T-cells (Type I T-cells) infiltrating the tumors of breast cancer patients. HER2+ breast cancer may need therapeutic approaches that first generate Type I immunity prior to further expansion with immune checkpoint inhibitor therapy. Strategies that augment

the antibody dependent cell mediated cytotoxicity (ADCC) induced by trastuzumab or pertuzumab therapy may be particularly effective.

Hormone receptor (HR) positive breast cancer is the subtype least likely to be associated with a robust tumor lymphocytic infiltrate. Estrogen is involved in the regulation of immunity. Estrogen receptor (ER) alpha is found on Treg and when bound by estrogen enhances the immunosuppressive function of these cells. The ER complex can augment TGF-beta production, a further immune suppressant. Clinical approaches are needed to generate and maintain Type I immunity to a threshold level needed to allow further expansion while simultaneously controlling immunosuppressive elements in this subtype. Combination and multi-modality approaches will be key to allow immunotherapies to be effective in HR+ breast cancer.

HAUTE COUTURE TAILORING OF RADIATION THERAPY IN BREAST CANCER

Philip Poortmans

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Breast cancer is the commonest cancer in women in the industrialised western countries with a sharp increase in age-standardized incidence over the last decades. Simultaneously, mortality rates decreased clearly, leading to a current ratio of 1 death for every 6 diagnosis per year compared to 1 death per 2.5 diagnoses 40 years ago.

Decreasing the burden of radiation therapy for breast cancer should entail tailoring the extent of, rather than completely omitting radiation therapy. Possible options include the lowering of the total dose, like selective omission of the boost, hypofractionated radiation therapy to shorten the duration of treatment and the selective introduction of partial breast irradiation. Moreover, modern radiation therapy techniques including contemporary target volume contouring lead to a decrease in the size of the irradiated volumes.

Elective regional nodal irradiation showed in several randomised trials and meta-analyses to significantly impact on local-regional control, disease-free survival, breast cancer mortality and overall survival. The generalizability of these results remains complex in the light of the decreasing use of axillary lymph node dissection, the use of more effective adjuvant systemic therapy, the increasing use of primary systemic therapy and continuously improving radiation therapy techniques.

In general, radiation therapy tends to compensate for the lessening extent of surgery to the breast and the axillary lymph nodes, eliminating residual tumour cells while maintaining better aesthetic and functional results. As a drawback in some occasions, however, the indications for the extent of radiation therapy have to be based on less extensive pathological staging information as we were used to in the past. Research is ongoing to individualise radiation therapy also more on the basis of biological factors including gene expression profiles. When considering age, treatment decisions should rather be based on biological instead of formal age.

The aim of this lecture is to put current evidence into the right perspective, and to search for an appropriate appreciation of the balance between efficacy and side effects of local-regional radiation therapy.

PANEL DISCUSSION

Global Breast Cancer Conference

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COMPREHENSIVE GERIATRIC ASSESSMENT FOR ELDERLY PATIENTS

Jee Hyun Kim

Department of Internal Medicine, Seoul National University Bundang Hospital, Korea

Older patients have decreased organ function and progressive decline in stress tolerance due to restriction in the functional reserve of multiple organ systems. They are at an increased risk of developing complications after cancer treatment such as surgery and or chemotherapy. Especially in the frail elderly, minimal stress may precipitate severe and even lethal complications. Therefore, it is of crucial importance to identify those patients fit enough to tolerate cancer treatment and those who cannot tolerate cancer treatment and are likely to develop serious complications. Moreover, providing adequate geriatric intervention for those problems found at geriatric assessment before applying cancer treatment may enable vulnerable patients to receive cancer treatment successfully.

Geriatric assessment is a multidimensional tool developed to evaluate elderly patients' global health status. It focuses on defining the functional age of the patients and can help to detect, manage and follow up on multiple problems of older patients. Geriatric assessment has some essential domains; functional status, comorbidities, psychological status, nutritional status, cognitive function, social support, presence of geriatric syndromes, assessment of mobility and polypharmacy. Geriatric assessment has been reported to provide more comprehensive information on the status of older patients, better than ECOG performance status. Multiple studies showed that geriatric assessment can predict chemotherapy toxicity, postoperative complications and survival in older patients with cancer. By performing geriatric assessment, cancer treatment plan can be changed in up to half of older patients.

In the areas where there are limited medical resources, it would be advisable to use screening tools to save time and medical resources for geriatric assessment, It would also be very important to develop their own model of care for older patients with cancer. In the meeting, practical application of geriatric assessment in cancer care will be reviewed and Korean model of onco-geriatric care will be shared.

LOCAL THERAPY

Seho Park

Department of Surgery, Yonsei University College of Medicine, Korea

As older population has been increasing, elderly patients with breast cancer have also been increasing. But we have limited data of prospective clinical trial enrolled this subgroup and optimal therapeutic recommendations are not clearly established.

Although curative surgical resection is the mainstay of treatment for breast cancer in not only young but also elderly patients, a number of prospective trials have demonstrated excellent outcomes for elderly patients with small, hormone receptor-positive tumors who receive tamoxifen alone instead of surgery or surgery with tamoxifen. Even some studies demonstrated higher local failure rates in patients who were not treated with surgery but overall survival was not significantly different between patients underwent surgery and those did not. Particularly in frail elderly women who have significant comorbidities with high perioperative risk, therefore, endocrine therapy alone can be an alternative option considering life expectancy.

Recently, quality of life can be an important issue in older patient during remaining their life as much as in young women. When elderly patients are endurable to surgery, clinicians may concern limited local therapies to their breast or axilla. Rather, breast reconstruction can be an additional issue in a certain clinical situation.

In older patients with low risk and hormone receptor-positive disease, omission of radiation therapy after breast-conserving surgery or no axillary staging in clinically node-negative disease has also become an option with administration of endocrine therapy. In general, these studies examining omission of local therapy in older patients have consistently shown that although local failure rates increase, survival is rarely impacted in cases with a low-risk breast cancer. Hypofractionated radiotherapy, accelerated partial breast irradiation, or omission of completion axillary node dissection for sentinel node-positive disease could be a good alternative to standard local therapy.

However, standard local therapies remain the standard of care, regardless of patients age and should be considered in every patient with breast cancer. Therefore, informed decisions should be made case by case and should be personalized to her situation and competing risks.

Clinical challenge is to make an optimal decision for treating elderly breast cancer patients while minimizing complications. Herein, the current evidence and recommendations for optimal local therapies in elderly women with breast cancer will be discussed.

SYSTEMIC THERAPY

Janice Tsang

Hong Kong Breast Oncology Group (HKBOG), Hong Kong

While cancer is an aging disease, breast cancer has been the most common female breast cancer in the world and in the Asia-Pacific region. With aging population and people living much longer in recent decades, the incidence of breast cancer has been increasing, being a common health challenge for both the young and the elderly population. Over the last decades, there have been evolution of breast cancer treatment with particular reference to systemic therapy as breast cancer is not considered as a local disease anymore but a systemic disease since the advent of adjuvant chemotherapy with the leadership of Bernard Fisher, and the work of subsequent countless medical and clinical oncologists, breast surgeons, clinicians and scientists. There is further evolution from "personalised medicine" from the advent of the added value of anti-HER2 therapy for HER2 positive breast cancer to the reality of "precision medicine" over the last 2 decades, and the recent identification of emerging multiple "drugable" targets.

Yet, throughout the breast cancer research development, the elderly population, especially those aged above 70, have always been excluded in landmark studies or multi-centred clinical trials, and the age of a patient, has been a negative impact on the equal access and intensity of treatment as compared to the young breast cancer patients. There are indeed unmet needs of the elderly population while the biology of the breast cancer for both the young and the elderly population being always different. This presentation will give an overview of the evidence-based medicine on the systemic therapy for elderly breast cancer patients, and walk us through the challenges and opportunities ahead for this growing population living with breast cancer with particular reference in the Asian population.

SURGERY FOR STAGE IV BREAST CANCER: NO BENEFIT AT ALL?

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Of all patients with breast cancer, approximately 38 percent of women with breast cancer in Europe and the USA have metastatic disease at initial presentation. However, in most Asian countries, about 1,025 per cent of patients present with distant metastases. Traditionally, metastatic breast cancer would be considered an incurable disease with the main goals of treatment being prolongation of survival and palliation of symptoms. The recommended approaches for metastatic breast cancer were systemic therapy, which included chemotherapy, endocrine therapy, and targeted drugs. Recent advances in chemotherapy, endocrine therapy and targeted therapy have achieved a rapid response and increased survival in most metastatic breast cancer patientswhereas, the role of surgery in stage IV breast cancer patients is still controversial.

Over the past decade, several retrospective studies have compared surgery versus no local therapy in women presenting with stage IV breast cancer with an intact primary tumor. All showed a survival advantage for the surgical cohort. However, these studies also noted that patients undergoing surgery were younger and healthier, likely introducing bias and confounding practical interpretation of these data. A recent meta-analysis including 15 retrospective case series, found that surgery of the primary tumor was independently associated with longer survival (HR 0.69; $p < 0.0001$). The survival benefits were independent of age, tumor burden, type of surgery, margin status, site of metastasis, hormonal receptor status, and HER2 status. Another meta-analysis found survival benefit in women with small primary tumors, fewer comorbidities, and lower metastatic burden. Furthermore, there were also some retrospective studies that found surgery to be associated with improved survival in patients with ER/PR-positive disease, while little or no survival benefit was observed in those with triple-negative disease.

To avoid the selection biases in these retrospective studies, two open-label, randomised controlled trials are performed to determine whether local therapy would prolong survival in stage IV breast cancer patients. In one study from Indian, the median overall survival was 19.2 months in the locoregional treatment group and 20.5 months in the no locoregional treatment group (Hazad ratio = 1.04; $p = 0.79$), and no subgroup defined by menopausal status, metastatic disease burden, oestrogen or progesterone receptor status, or HER2 receptor status showed a significant survival benefit from surgical excision. Therefore, it concluded that there was no evidence to suggest that locoregional treatment of the primary tumour conferred an overall sur-

vival advantage in patients with metastatic breast cancer and this procedure should not be routinely done. Another randomized clinical trial from Turkey, there were 140 women in the surgery group and 138 in the no-surgery group. With more than 20 months of follow-up, the study suggested that patients with solitary bone metastases had significantly improved survival following complete excision of the primary breast tumor and regional nodes.

Last year, two new retrospective cohort studies using data from the Surveillance, Epidemiology, and End Results (SEER) program to explore the impact of surgery on the survival of patients with stage IV breast cancer were published. The Thomaset al analysis from 21372 stage IV breast cancers reported that survival in stage IV breast cancer had improved and was increasingly of prolonged duration, particularly for some women undergoing initial breast surgery. Meanwhile, initial surgery to the primary tumor may be important because systemic therapy advances provided better control of distant disease in stage IV breast cancer, and women presented with lower distant disease burdens. Yinuo Tan al also found that patients who underwent surgery for stage IV breast cancer showed better overall survival than the no resection group especially in HR+ subgroups by analysis 10,441 eligible stage IV breast cancer patients.

In conclusion, benefits of surgical resection of the primary tumor in stage IV breast cancer might exist to improve patients prognosis. More well-designed and powerful randomized, controlled trials would be valuable to understanding the underlying causal relationship between the association of receipt of surgery and improved survival. Local therapy with surgery to the primary tumor may offer critical disease control for select patients and could be an essential component of prolonged survival.

NEW THERAPEUTIC STRATEGY FOR CNS METASTASES IN BREAST CANCER

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Breast cancer is the second leading cause of metastases in central nervous system (CNS). For decades, cornerstones for treatment of brain metastases are radiation therapies and surgery. Role of conventional systemic chemotherapy is limited due to blood brain barrier, and patients with intracranial metastases have been underrepresented in clinical trials.

Recent growing understanding of the breast cancer biology is changing landscape of brain metastases. Each subtype of breast cancer has different clinical features regarding CNS metastases, which is attributed to development of systemic treatment as well as to the intrinsic tumor biology. Despite recent progresses, treatment outcome of patients with breast cancer brain metastases is still worse than those without intracranial disease.

Based on better understanding of biology, several novel agents penetrating blood brain barriers are being investigated focusing brain metastases. In this session, I will discuss current landscape of breast cancer brain metastases, including evidences and recent advances of potential targeted therapies to date.

HOW LONG SHOULD WE TREAT FOR PATIENTS WITH METASTATIC BREAST CANCER? IS CURE POSSIBLE?

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Advances in the management of breast cancer have considerably improved the survival rates. Based on 2006-2012 data, the Surveillance, Epidemiology, and End Results (SEER) has estimated that 89.7% of women with breast cancer will survive 5 years post-diagnosis. Yet, such a high chance of survival may blur the fact that metastatic breast cancer (MBC) remains a deadly disease and notoriously difficult-to-treat. The 5-year survival rate for MBC was estimated to be between 22 and 26 percent.

The goals of treating MBC are to control tumor growth and prolong life while also maintaining quality of life. To achieve these, the patient and treating physician should attempt to set a mutual goal to achieve a balance between the treatment regimen and quality of life. Targeted therapies are available for HER2(+) or ER/PR(+) patients, however, cytotoxic chemotherapy may eventually be needed. Despite this, promising results have been shown by novel targeted agents in clinical trials such as CLEOPATRA, BOLERO-2, and PALOMA improved progression free-survival has been demonstrated in patients with advanced or MBC. Recent investigations on the so called real-time liquid biopsy are also believed to play a significant role to the better understanding of MBC. The highly informative, albeit non-invasive, assessment of circulating tumor cells (CTCs) or cell-free circulating tumor DNA (ctDNA) is expected to provide vast improvements over traditional tumor biopsy.

Cure itself is a controversial term, more so in the field of oncology. A previous survey on 180 oncology clinicians revealed that the majority would never tell a patient that he/she is cured, perhaps due to the risk of late recurrence. A long-term disease free survival for 10-20 years or more was argued to represent cure in cancer patients. Whilst such long-term survivals for MBC patients are rare, there was evidence of the superior prognosis in patients with oligometastatic breast cancer a distinct subgroup of MBC with limited number and sites of metastasis. This might suggest that patients with limited MBC might be approached with the intention to cure, instead of just palliative care. Nonetheless, warranting a clinical cure for MBC patients is practically impossible as of now. A recent study on almost 20,000 women with primary, invasive, non-MBC revealed that there was an overwhelming lack of evidence for cure; continued excess mortality was found up to 12 years post-diagnosis. Cure was reasonably defined as a group of cancer patients who do not have excess mortality due to their cancer, in comparison with the population. This suggests that even in non-MBC patients, the concept of cure is still highly arguable.

DO WE NEED EXCISION IN cCR PATIENTS AFTER NEOADJUVANT CHEMOTHERAPY

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Since neoadjuvant chemotherapy (NCT) was introduced for locally advanced breast cancer, many studies evaluated the effectiveness of surgery and/or radiotherapy for locoregional treatment in patients with clinical complete response (cCR). Most studies performed in the 1970-90s had shown higher locoregional failure rates in patients who did not receive surgery after NCT. More recently, however, dramatic improvements in chemotherapy regimens and targeted agents resulted in higher pathologic complete response (pCR) rates, especially in the triple-negative and human epidermal growth factor 2-positive subtypes. It is also being accepted that individual patients who attain a pCR have a more favorable long-term outcome. The role of surgical excision for selected patients who achieve pCR may be limited to pathological staging, with minimal part in local control.

To consider omitting surgery in patients with cCR, effective imaging criteria for predicting complete response, as well as reliable methods to obtain breast tissue from these patients for pathologic evaluation is necessary. MRI is considered to have the best correlation with surgical specimen pathology compared to physical examination, mammography, and ultrasonography. However, its accuracy is not sufficient to replace a pathologic diagnosis. Several studies have evaluated the ability of minimally invasive biopsy techniques, such as core needle biopsy or vacuum-assisted biopsies, to predict pCR in comparison to surgical excision. MRI can be used to effectively select the patients whose tumor is expected to have pCR and thus are candidates to undergo biopsy for pathologic evaluation.

Results from prospective randomized controlled trials with detailed inclusion criteria is warranted to accurately assess the safety of omitting surgical excision in patients where minimally invasive biopsy suggested pCR. Previous studies that evaluated minimally invasive biopsies to predict pCR and current ongoing trials for omitting surgery will be discussed.

CAN WE OMIT SENTINEL LYMPH NODE BIOPSY IN SOME PATIENTS

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Since the release of the American College of Surgeons Oncology Group (ACOSOG) Z0011 and the European Organization for Research and Treatment of Cancer (EORTC) AMAROS trial data, the local treatment for the axilla in clinically node-negative early breast cancer has been debated and changed. From those reports, it seems like that one or two axillary node-positive patients may be saved from the further axillary lymph node dissection, at least for the ACOSOG Z0011-eligible patients. It is based on the finding that the clinical outcome is not significantly different no matter what the further axillary lymph node dissection was provided or not. It is also suggested that this little difference may be resulted from the adjuvant treatment such as radiation therapy as well as systemic treatment following surgery. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 study in which no radiation and no systemic treatment was given, 1 in every 2.2 patents with disease left in the axilla experienced axillary recurrence. In contrast, the NSABP B-32 study where more than 70% of the patients were treated with radiation and chemotherapy, this ratio decreased to 1 in 13 or 14 patients with disease left in the axilla.

The actual positive rate of sentinel lymph node is not so high in clinically T1-2N0 patients. In a paper which the surgeons of Memorial Sloan-Kettering Cancer Center (MSKCC) published in 2014 following the ACOSOG Z0011 study, the positive rate of sentinel lymph node was 17.6% in their breast conserving surgery cohort. In a report from Mayo Clinic Rochester, the positive rate of sentinel lymph node was only 13% for those patients with clinically node-negative by preoperative axillary ultrasound (AUS) with or without fine needle aspiration biopsy (FNA). In a report from Germany, the positive rate of sentinel lymph node was 21.1%. This means that we may omit sentinel lymph node biopsy safely in some selected clinically T1-2N0 patients minimizing the comorbidities such as lymphedema, numbness or paresthesia, limitation of arm mobility.

How can we identify those patients for whom we may skip the axillary evaluation itself? The most feasible examination in clinical setting is AUS, which shows somewhat low sensitivity (26-76%) and high specificity (88-98%). With additional use of FNA, the specificity may increase to almost 100%. Although some doctors in America do not support the use of AUS to find out clinically node-negative patients, AUS is a widely adopted way to evaluate axillary status if pro-

vided by well-trained radiologists. PET-CT and MRI also provide the similar diagnostic assist to AUS, they are not always recommended considering their high cost and feasibilities. However, there still exists the weak point of imaging modalities that a small burden of tumor cells less than 5 mm in axillary nodes cannot be visualized.

Indeed there were prospective randomized studies which compared standard axillary surgery to no axillary surgery. In NSABP B-04 study, there was no significant difference in DFS and OS in radical mastectomy versus mastectomy alone versus mastectomy plus radiation groups. The smaller clinical trials comparing ALND versus no axillary surgery also showed there was no significant difference in terms of DFS and OS. None of these studies included patients with clinically suspicious axillary lymph node. Can we replace sentinel lymph node biopsy with axillary radiation (ART) for the clinically T1-2N0 patients? Although the incidence of morbidity ART after SLNB does not seem to be high, it has not been recommended because it may be an overtreatment if we give ART in patients without SLN metastasis. The following question is naturally if it is mandatory or not to evaluate axillary status with SLNB.

To answer these issues, SOUND and INSEMA trials were planned and activated. Both trials include the BCS candidates with clinically node-negative early stage breast cancer. They are using AUS +/- FNA according to the suspicion level of metastatic axillary nodes. Given that the biology of primary tumor is playing more important role than the anatomical tumor burden to make a systemic spread of tumor cells, it is important to provide the best multidisciplinary combination of local and systemic treatments to the patients. We should answer how carefully and effectively identify the clinically node-negative patients who can be safely saved from unnecessary axillary procedures.

EXTENT AND ROLE OF RADIATION THERAPY IN pCR PATIENTS

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The use of neoadjuvant chemotherapy (NCT) in breast cancer has the advantage of targeting both systemic and local-regional sites of disease. The main practical benefit to NCT may be an enhanced ability to tailor and limit subsequent local-regional treatment. As there are no randomized trials addressing the role of RT following NCT and mastectomy, there is limited data guiding recommendations for postmastectomy RT (PMRT). Retrospective data from MD Anderson Cancer Center (MDACC) and the prospective NSABP B-18 and B-27 currently form the primary basis for RT recommendations. MDACC demonstrated that confined to patients who attain pathologic complete response (pCR) after NCT, stage I-II patients who received PMRT had a 0% 10-year LRR rate, vs. 33% for stage III patients who did not receive PMRT. This rate decreased to 7.3% in patients who received PMRT ($p = 0.040$) (1). Notwithstanding the retrospective studies, MDACC data suggested that PMRT reduce LRR in stage III patients, and could be omitted in early stage disease with low risk of LRR.

Analyses from the randomized trials NSABP B-18 and B-27 provide additional important data in prospective trials with uniformly mandated omission of PMRT after mastectomy and regional nodal RT after BCT. The data showed independent predictors of LRR were clinical nodal status and pathologic nodal status/breast tumor response regardless of surgical extent in addition to age (lumpectomy) and clinical tumor size (mastectomy). After publication of combined analysis of NSABP B-18 and B-27, Bellon et al. suggested the treatment recommendations for PMRT per various clinical situations in patients receiving NCT (2). PMRT should be administered in stage III/locally advanced cancer patients irrespective of pathologic response, and in stage I-II patients with residual LN after NCT. In stage I-II patient with residual disease in breast but not lymph nodes, Tailored decision on radiation therapy based on age, extent of residual disease, tumor subset, and apparent response to treatment; in general, consider radiation therapy for patients age ≤ 40 years with residual LVI, endocrine-unresponsive breast cancers, close/positive margins, and extensive residual invasive cancer. No radiation therapy is required for stage I-II patients with complete pathologic response in breast and lymph nodes after NCT.

The updated ASCO-SSO-ASRO guideline recommended that regional nodal irradiation (RNI) covers supraclavicular, axillary and internal mammary nodes in patients treated with NCT and

PMRT. However, the role of RNI was not defined in pCR patients treated with NCT in this guideline (3). The increasing use of NCT for operable breast cancer has raised questions about optimal local therapy for the axilla. The optimal assessment of lymph nodes in the setting of NCT remains unclear as sentinel LN biopsy is more popular recently. Three prospective randomized trials were performed to evaluate the efficacy of sentinel LN biopsy after NCT. These studies showed false negative rates came down below 10% in patients who have more than three removed sentinel nodes, respectively (4). Further studies are needed whether sentinel LN biopsy replace axillary LN dissection in these patients.

Future trials will address unresolved issues in the role of RT following NCT and surgery. For patients who have no residual disease in the axillary nodes, NSABP B51/RTOG 1304 is enrolling patients with clinical T1-3N1 disease and needle biopsy demonstrating axillary nodal disease, who undergo NCT and surgery with axillary lymph node dissection, and are found to have a nodal pCR. Patients who received BCT will undergo either breast irradiation or irradiation to the breast plus regional lymph nodes; patients who received mastectomy will undergo PMRT vs. no PMRT.

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USG OR FNA FOR PREDICTING NODE POSITIVE IN BREAST CANCER

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The 2014 ASCO guideline confirmed sentinel lymph node dissection (SLND) is the standard method of axillary lymph node staging for clinically node negative early breast cancer. When sentinel lymph node (SLN) is negative, patients should not undergo axillary lymph node dissection (ALND). In addition, the ASCO guideline supported the conclusion of Z0011 study and suggested that clinicians should not recommend axillary lymph node dissection (ALND) for women with early breast cancer who have one or two sentinel lymph node metastases and will receive breast conserving surgery with conventionally whole-breast radiotherapy and systemic therapy.

Several studies have reported that ultrasound evaluation of axilla can help to identify suspicious lymph nodes preoperatively so that ALND can be proceeded directly and SLND spared in patients with positive lymph nodes proved by ultrasound-guided fine needle aspiration cytology or core biopsy. Among surgeons who follow the results of Z0011, some practice changes, such as omitting the use of intraoperative evaluation of SLN by cytology or frozen section, have been observed. Some surgeons also consider preoperative ultrasound not necessary. However, in our experience, when pre-operative ultrasound is negative, the chance of having more than two positive SLNs or positive non-SLNs is low (about 2%), and it should be safer to omit ALND when only two SLNs are positive. In addition, intraoperative cytology or frozen section can definitely be spared if patient is undergoing breast-conserving treatment. On the other hand, if patient is receiving total mastectomy with a negative axillary ultrasound, intraoperative examination will be done (the chance of positive SLN is about 25% in out experience), and followed by ALND immediately if SLN cytology is positive. In addition, surgeons can feel more comfortable to schedule immediate reconstruction without the fear that there will be more than 3 positive nodes after ALND and post-mastectomy radiation will complicate the reconstruction options.

AUS is also helpful in guiding whether ALND could be saved in patients receiving SLNB before or after neoadjuvant chemotherapy. If SLND is desired before neoadjuvant chemotherapy and pre-chemotherapy AUS is negative, the chance of having more than 2 positive SLNs is low. When there are 1 or 2 positive SLNs and breast-conserving treatment is planed after neoadjuvant chemotherapy, ALND may still be waived according to Z0011 study. If AUS or ultra-

sound-guided biopsy is positive before neoadjuvant chemotherapy, one may consider SLNB after neoadjuvant chemotherapy. Since positive nodal status before chemotherapy might be converted to negative nodal status after chemotherapy, SLND done after neoadjuvant chemotherapy may save these patients from ALND. Recent studies demonstrated that in these node-positive patients undergoing neoadjuvant chemotherapy first, dual tracer with isotope and blue dye should be used for SLNB mapping, and only patients with two or more SLNs harvested after neoadjuvant chemotherapy and negative AUS before surgery can be considered to undergo SLNB alone after neoadjuvant chemotherapy. ALND should be considered not only for patients with micrometastatic or macrometastaic SLNs but also in patients with isolated tumor cells in SLN.

ACCURACY OF PET FOR LYMPH NODE EVALUATION

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The identification of spread of breast cancer to regional lymph nodes is relevant for treatment management. In clinically node negative breast cancer patients, sentinel node procedure is standard of care to exclude clinically relevant nodal involvement, or to identify lymph node involvement to further indicate management of the lymph node basins.

In clinically node negative breast cancer patients, 18F-FDG PET/CT is insufficiently reliable to identify nodal micro- metastases. In a meta analysis of Cooper et al. (1) comprising 7 studies of PET/CT (n = 862), the mean sensitivity was 56% (95% CI: 44-67%) and mean specificity 96% (90-99%). In a prospective study, Kathy Pritchard (2) evaluated 325 women with operable breast cancer the value of PET/CT. They found that the sensitivity for PET was 23.7% (95% CI, 15.9% to 33.6%), specificity was 99.6% (95% CI, 97.2% to 99.9%), positive predictive value was 95.8% (95% CI, 76.9% to 99.8%), negative predictive value was 75.4% (95% CI, 70.1% to 80.1%).

However, the high positive predictive values may render PET/CT scans valuable for women with proven axillary cN +ve breast cancer to further identify clinically relevant- nodal metastases in other lymph node basins (periclavicular and IMC = ve nodes), to indicate all-field radiotherapy.

For that purpose we evaluated the 18F FDG PET/CT scan in patients treated with neoadjuvant chemotherapy (NAC) who had proven N+ve disease. (3) Conventional regional staging consisted of US with fine needle aspiration and/or sentinel lymph node biopsy. Patients were classified as low-risk (cT2N0), intermediate-risk (cT0N1, cT1N1, cT2N1, cT3N0), or high-risk (cT3N1, cT4, cN2-3) for LRR. The presence and number of FDG-avid nodes were evaluated and the proportion of patients that would be upstaged by PET/CT, based on detection of ≥ 4 FDG-avid axillary nodes defined as cN2(4+) or occult N3-disease, was calculated. In total, 87 of 278 patients were considered high-risk based on conventional staging. PET/CT detected occult N3-disease in 5 (11%) of 47 low-risk patients. In 144 intermediate-risk patients, PET/CT detected ≥ 4 FDG-avid nodes in 24 (17%) patients and occult N3-disease in 22 (15%) patients, thereby finally upstaging 38 (26%) of intermediate-risk patients. Of 43 (23%) upstaged patients, 18 were ypN0, 12 were ypN1, and 13 were ypN2-3. In our population, 23% of patients treated with NAC were upstaged to the high-risk group based on PET/CT information, potentially benefiting from regional radiotherapy. After a median follow-up (FU) of 50 months the RFS, LRFS and OS were 87%, 88%, and 92% respectively for the whole group. Patients upstaged with

PET/CT had more events for all three analyses compared to the original risk groups, which resulted in a significantly worse RFS (69.8%; $p = 0.03$) a nearly significantly worse LRFS ($p = 0.052$) and so far no effect in OS ($p = 0.433$). (4)

Take home messages.

- 18F FDG PET?CT is insufficiently sensitive to identify microscopic lymph node involvement. Whether this is clinical relevant remains to be elucidated.
- In proven cN+ breast cancer PET/CT is able to identify extra-axillary nodal involvement in a substantial proportion of patients
- In patients with PET/CT proven N2/3 disease, radiotherapy to these nodal basins is warranted
- If PET/CT is negative N2/3 basins, one could consider to refrain from elective radiotherapy to those fields.

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NOMOGRAM TO PREDICT 3 OR MORE LYMPH NODE METASTASIS

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The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial reported that complete dissection of axillary lymph nodes (ALNs) may not be warranted in women with clinical T1-T2 tumors and one or two involved ALNs who were undergoing lumpectomy plus radiation followed by systemic therapy. The present study was conducted to identify preoperative imaging predictors of ≥ 3 ALNs.

The training set consisted of 1,917 patients with clinical T1-T2 and node negative invasive breast cancer. Factors associated with ≥ 3 involved ALNs were evaluated by logistic regression analysis. The validation set consisted of 378 independent patients. The nomogram was applied prospectively to 512 patients who met the Z0011 criteria.

Of the 1917 patients, 204 (10.6%) had ≥ 3 positive nodes. Multivariate analysis showed that involvement of ≥ 3 nodes was significantly associated with ultrasonographic and chest CT findings of suspicious ALNs ($p < 0.001$ each). These two imaging criteria, plus patient age, were used to develop a nomogram calculating the probability of involvement of ≥ 3 ALNs. The areas under the receiver operating characteristic (ROC) curve of the nomogram were 0.852 (95% confidence interval [CI] 0.820-0.883) for the training set and 0.896 (95% CI: 0.836-0.957) for the validation set. Prospective application of the nomogram showed that 60 (11.7%) of 512 patients had scores above the cut-off. Application of the nomogram reduced operation time and cost, with a very low re-operation rate (1.6%).

Patients likely to have ≥ 3 positive ALNs could be identified by preoperative imaging. The nomogram was helpful in selective intraoperative examination of sentinel lymph nodes.

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BREAST CANCER SCREENING: HARM OR GOOD?

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The debate continues regarding whether or not population based mammographic screening programs do more harm or good. Potential benefits include a reduction in breast cancer mortality and a down staging in cancer size, leading to less aggressive therapies. Potential harms include cost, anxiety, false positive mammograms and over diagnosis.

In the Canadian National Breast Screening Study, we saw no evidence of a decline in mortality from breast cancer associated with annual mammography screening. The study has been criticized on methodology grounds. An alternate explanation of the lack of effectiveness of mammography is on biological grounds, that is that while size is associated with survival in breast cancer, a reduction in tumour size is not associated with a reduction in mortality. Tumour size is a marker of aggression as is lymph node status and is not directly associated with cancer mortality. Evidence in support of this hypothesis is presented.

ASSESSMENT OF BREAST CANCER RISK WITH GENETIC POLYMORPHISMS

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Advances in genomic technologies have enabled far more rapid, less expensive genetic sequencing than was possible only a few years ago. These technologies allow for the comprehensive genetic profiling for assessing breast cancer risk and include multiplex sequencing panels of several genes (in which rare mutations are often associated with moderate to high risks of developing breast cancer) and panels of common single-nucleotide polymorphisms (SNPs) identified through genome-wide association studies. More than 150 SNPs have now been identified which are associated with breast cancer risk. Individually, the SNPs are associated with modest increases in breast cancer risk, but their combined effects, through polygenic risk scores, are much larger. However, the clinical utility of such multiplex gene- and SNP-panels is limited by the lack of breast cancer risk prediction models that consider the multifactorial etiology of breast cancer susceptibility. Therefore, there is a need for breast cancer risk prediction models that consider the joint effects of all known genetic susceptibility variants, together with other established risk factors. To construct such multifactorial models it is important to understand the underlying models of genetic susceptibility for breast cancer. Using data from the large collaborative studies of the Breast Cancer Association Consortium (BCAC) and the Consortium of Investigators of Modifiers of BRCA1/2 (BCAC) the presentation will review the latest evidence on: (1) the joint effects of common genetic polymorphisms on breast cancer risk; (2) the joint effects of common and other rare mutations (such as BRCA1, BRCA2, PALB2, CHEK2) and (3) how the common genetic variants interact with lifestyle and hormonal risk factors for breast cancer. The presentation will review the implications for breast cancer risk stratification, and finally describe the efforts to develop BOADICEA, a comprehensive risk prediction model for breast cancer, that includes the explicit effects of mutations in BRCA1, BRCA2, PALB2, CHEK2, and ATM, the common breast cancer susceptibility variants and of other lifestyle/hormonal risk factors.

GERMLINE TESTING FOR HEREDITARY CANCER WITH MULTIGENE PANEL

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Gene testing for risk-assessment has become a part of clinical practice for hereditary cancer syndromes such as hereditary breast and ovarian cancer syndrome, Lynch syndrome, Li Fraumeni syndrome and other conditions based on their autosomal dominant and high penetrance. In the post-genomic era, many putative cancer susceptibility genes are identified. In hereditary breast and ovarian cancer syndrome, BRCA1 and BRCA2 are only contributes to 10-20% breast cancer in patients with familial and/or early-onset breast cancer. Nowadays, several homologous recombination (HR) genes are known to associate with moderate-to-high penetrance of hereditary cancer risk, including ATM, CHEK2, BARD1, BRIP1, MRE11, RAD50, RAD51C, and PALB2. Therefore, a gene panel is usually offered for genetic testing.

When more than one gene can explain a hereditary cancer syndrome, the design of a gene panel should include multiple genes. Most predisposing genes in hereditary cancer syndromes are tumor suppressor genes and DNA repair genes. For example, genes involved in the mismatch repair are known as Lynch syndrome, associated with increased risk of colon cancer; the defect of HR genes are considered to predispose the breast and/or ovarian cancer. In addition, the genes of DNA mismatch repair are related to increased risk of ovarian cancer. In our study, we then design a customized sequencing panel including 68 genes that had cancer risk association for patients with early-onset or familial breast cancer. We use captured-based method to enrich the target genes; the captured regions are performed from upstream untranslated area to 3'UTR of the target genes so that we can comprehensively analyze the small indel and large genomic rearrangement. A total of 133 patients were enrolled and 30 (22.6%) were found to carry germline deleterious mutations, 9 in BRCA1, 11 in BRCA2, 2 in RAD50, 2 in TP53 and one each in ATM, BRIP1, FANCI, MSH2, MUTYH, and RAD51C. Triple-negative breast cancer was associated with the highest mutation rate (45.5%, $p = 0.025$). Mutation carriers were considered as moderate-to-high risk to develop malignancy and advised to receive cancer screening, mainly based on the NCCN guideline suggestions. In conclusion, we consider that multiple gene sequencing in cancer risk assessment is clinically valuable.

IMMUNE CHECK-POINT BLOCKADE FOR BREAST CANCER

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IMMUNE APPROACHES TO THE TREATMENT OF BREAST CANCER, AROUND THE CORNER?

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Triple-negative breast cancer (TNBC) is histologically defined by a lack of estrogen receptor and progesterone receptor expression and the absence of human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification. TNBC represents up to 20% of all breast cancers. Although not synonymous with the basal-like subtype defined by gene expression profiling, approximately 70% of TNBCs have basal-like characteristics. TNBC is more common in younger women those of African descent and those with BRCA1 germline mutations.

TNBC tumors are frequently of high histologic grade present at an advanced stage are typically more aggressive and difficult to treat than hormone receptorpositive tumors and are associated with a higher risk of early relapse. The lack of estrogen receptor, progesterone receptor, and HER2 expression precludes the use of targeted therapies, and the only approved systemic treatment option is chemotherapy. Responses to chemotherapy occur, but are often short lived and are frequently accompanied by considerable toxicity. Given the suboptimal outcomes with chemotherapy, new targeted therapies for TNBC are urgently needed.

Immune checkpoint inhibition has been demonstrated to be an effective anticancer strategy. Several lines of evidence support the study of immunotherapy in triple-negative breast cancer (TNBC). We assess the safety and antitumor activity of the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab in patients with advanced TNBC.

Pembrolizumab is a high-affinity, highly selective, humanized monoclonal IgG4-k antibody against PD-1. Pembrolizumab blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells. Pembrolizumab is approved in several countries for the treatment of Hodgkins lymphoma, advanced melanoma, metastatic lung cancers, and head & neck cancers. Additionally, clinical studies with pembrolizumab have demonstrated promising efficacy with durable responses and a manageable safety profile in many advanced malignancies, including gastric cancer, myeloma and urothelial cancer.

The KEYTRUDA (pembrolizumab) clinical development program includes more than 30 tumor types in more than 360 clinical trials, including nearly 200 trials that combine KEYTRUDA with other cancer treatments. Currently, Merck has the largest immuno-oncology clinical development program in breast cancer, with 27 trials underway involving KEYTRUDA as monotherapy and in combination, including registration-enabling studies.

IMMUNE MONITORING FOR IMMUNO-ONCOLOGY CLINICAL TRIALS

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The evaluation and development of immuno-oncology biomarkers and immune monitoring is a rapidly evolving field driven by the clinical success of recently approved immune checkpoint inhibitor therapies. Identifying biomarkers predictive of response to immune therapies will enable the identification of patients likely to benefit from treatment, while evaluation of immune pharmacodynamic and pharmacokinetic biomarkers will provide monitoring capabilities to clinical trials. Immune biomarkers can be divided into several categories: prognostic, predictive, pharmacodynamic, pharmacokinetic, and correlative or surrogate endpoints. Prognostic biomarkers are biomarkers that provide information on the likely course of the disease in an untreated individual. An example is the evaluation of tumor infiltrating T-cells (TIL). Predictive biomarkers are defined as biomarkers which can be used to identify subpopulations of patients most likely to respond to a given therapy. An example of a predictive biomarker is tumor expression of programmed death-ligand (PD-L1) that is predictive of which patients are likely to respond to anti-PD-L1 or anti-PD-1 therapy. Pharmacodynamic (PD) biomarkers are molecular indicators of therapy effect on the disease related targets. An example is an increased T-cell receptor (TCR) clonality after immune checkpoint inhibitor therapy. Pharmacokinetic (PK) biomarkers are biomarkers of distribution, metabolism, and excretion. An example is chimeric antigen receptor T-cell therapy, in which the persistence of the CAR T-cell can be measured by flow cytometry. A correlative or surrogate endpoint is a marker that may be associated with a positive clinical endpoint. Defining a surrogate endpoint is an area of active investigation and no biomarkers have been validated to date.

The role of immune monitoring in immuno-oncology has evolved over time. Early in the development of the field, the focus of immune monitoring was detecting tumor antigen-specific immune responses and interferon-gamma (IFN-γ) ELISPOT and flow-based assays demonstrated induction of antigen specific T-cells. This approach did not account for the tumor microenvironment and the role that additional immune cells and molecules play inhibiting and augmenting tumor specific immune responses. As the complexity of both innate and adaptive immune cells in generating anti-tumor immunity has evolved so have methods that assess a broader view of the tumor immune environment.

Immune therapy is becoming a standard component of cancer management for multiple tu-

mor types. Immune biomarkers will be critical in predicting which patients will respond to therapy. Immune monitoring while on treatment will allow an assessment of the evolving immune response and aid in the detection of immune mediated therapeutic resistance. Advances in assay technology (such as genomic analyses and antibody microarrays) have driven the detection and tracking of multiple immune biomarkers to new levels. These technologies provide the ability to use immune biomarkers in an increasingly comprehensive manner to interrogate both the tumor and systemic immune environments for clinical trial monitoring. It will be critical to the success of the immuno-oncology field to fully characterize and statistically validate each immune biomarker to maximize their use in the ongoing development of current and future immunotherapies.

FERTILITY PRESERVATION

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The impact of chemotherapy and the delay of conception attempts on fertility should be discussed with young breast cancer patients prior to treatment. Ovarian reserve is reduced after chemotherapy for breast cancer, and decreased ovarian reserve is a risk factor for infertility. Although young breast cancer patients may be fertile even following chemotherapy, those who are infertile have low pregnancy rates even with in-vitro fertilization treatment. Increasing age at the time that conception attempts begin is likely to reduce the likelihood of pregnancy; the impact of 10 years of Tamoxifen treatment in women with estrogen receptor positive disease is expected to increase the risk of subsequent age-related infertility. Studies show that women who are counseled about fertility preservation options prior to breast cancer treatment have a better sense of well-being during treatment.

Options for fertility preservation should include oocyte (egg) and embryo cryopreservation, but such treatments require approximately 2 weeks and should ideally occur prior to chemotherapy. Alternative options for fertility preservation are less optimal, and includes un-stimulated egg retrieval, which results in obtaining few, immature eggs.

An advantage to oocyte and embryo cryopreservation is that a future pregnancy can be carried by a gestational carrier in situations where the breast cancer patient has recurrent disease, is nervous about carrying a pregnancy, or wishes to complete 10 years of Tamoxifen treatment.

The other fertility preservation option generally considered to be experimental is ovarian tissue cryopreservation. This involves laparoscopic surgery to remove ovarian tissue, with subsequent replacement of tissue in the pelvis in the future, requiring additional surgery. Pregnancies reported have been both through natural conception as well as through in vitro fertilization with stimulation of the re-implanted tissue. Re-implanted tissue has an expected survival and function of several years, and does not return the ovaries to a normal premenopausal status.

A multidisciplinary team including administrators, nurses, medical and surgical and radiation oncologists as well as reproductive endocrinologists is critical in order for fertility preservation consults to be scheduled soon after breast cancer diagnosis. A commitment to expediting the fertility preservation consultation and a coordinated approach results in minimal or no delay in planned breast cancer treatments.

Pregnancy rates with eggs or embryos obtained from fertility preservation treatment depend on the age of the woman at the time of egg retrieval, as well as the number of eggs and embryos obtained. Pregnancy rates from ovarian tissue cryopreservation are still unclear.

CHEMOTHERAPY-ENDOCRINE THERAPY SEQUENCE IN PREMENOPAUSAL PATIENTS

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Hormone receptor positive (HR-positive) breast cancer (BC) represents the most common subgroup, and advances in treatment options have been brisk in the past two decades. Endocrine therapy has been standard and cornerstone in the treatment of ER+ metastatic breast cancer (MBC) patients. Furthermore, recent advance of endocrine overcoming strategies with CDK 4/6 inhibitors has brought new era of endocrine therapy for patients with HR+ MBCs.

Unlike many Western countries, Asian breast cancer patients show different demographic feature as younger peak age and premenopausal patients take up majority of HR-positive breast cancer patients. According to ABC3 guideline, endocrine treatment (ET) after chemotherapy (CT) (maintenance ET) to maintain benefit is a reasonable option for patients with ER+/HER-2 negative MBC although this approach has not been assessed in randomized trials. Limiting to premenopausal women with ER+/HER2-MBC, chemotherapy has been used preferentially than in postmenopausal women in real world practice; 1) only a few endocrine options, 2) more aggressive tumor behavior, 3) higher tumor burden, 4) shorter disease free survival, 5) young age, and etc. In addition, there are some issues for young BC patients including fertility preservation. HR-positive and premenopausal MBC in Korea seems to appear to have more visceral disease at baseline, and chemotherapy may be preferred as first line palliative treatment.

In this presentation, Id like to explore that which treatment sequence would be optimal for patients with ER+ MBC in premenopausal women and introduce an example of the real world practice.

LONG-TERM TOXICITY OF ENDOCRINE THERAPY

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Adjuvant endocrine therapy has been proven effective at reducing recurrences and deaths in patients with early breast cancer. Optimal duration of adjuvant endocrine therapy is considered to be five to ten years. In spite of clinical efficacy, adjuvant endocrine therapy can cause toxicity, which makes it impossible for patients to continue the therapy for scheduled time. Management of side effects is essential to maintain a good quality of life, to ensure that patients continue therapy, and to gain the maximum benefits possible. The short-term side effects of endocrine therapy are well known, whereas little is reported as for long-term toxicity of endocrine therapy.

The side effects of endocrine therapy depend on the type of drug or treatment. For premenopausal women with breast cancer, endocrine therapy options include tamoxifen alone, ovarian ablation (OA)/ovarian suppression (OS) alone, or OA/OS in combination with either tamoxifen or aromatase inhibitor . According to the age, the study at the Edinburgh Breast Unit between 1996 and 1998 demonstrated that younger women experienced strikingly more flashes and sweats (74% premenopausal versus 53% postmenopausal) and weight gain (61% vs. 39%).

Tamoxifen, a selective estrogen receptor modulator, binds to estrogen receptors, and can potentially not only block estrogen activity but also mimic estrogen effects. The most frequent side effects are menopausal symptoms including hot flashes, fatigue and nausea and gynecologic complications such as uterine bleeding, vaginal dryness, dyspareunia, impaired sexual desire. Endocrine therapy also disrupts the menstrual cycle. Rare but serious toxicities are increased risks of endometrial cancer and deep venous thrombosis, venous thromboembolism, pulmonary embolism, cardiovascular and ischemic cerebrovascular events.

Ovarian function can be suppressed temporarily by treatment with luteinizing hormone-releasing hormone (LH-RH) agonists. Treatment with LHRH agonists is associated with menopausal side effects such as hot flashes, mood changes and sexual problems. Chemotherapy for premenopausal patients has potential to induce amenorrhea and cause menopausal side effects. In the Suppression of Ovarian Function (SOFT) trial, more frequent adverse events in patients treated with exemestane compared with tamoxifen were sexual complaints, including vaginal dryness, decreased libido, and dyspareunia, musculoskeletal complaints and osteoporosis.

Longer duration of endocrine therapy might be standard therapy, and we should make efforts to improve adherence of patients and continuation of treatment. Factors associated with non-

compliance with chronic oral medications include toxicity, cost, patient age, poor patient-provider communication, multiple comorbidities, and beliefs about both medications and disease recurrence. We previously reported that discontinuation was observed in 32 of 266 premenopausal women (12.0%), which was not significantly different from 47 of 420 postmenopausal patients (11.2%) (Breast Cancer 2016).

Long-term risks include diminished bone density/fracture, thromboembolic events, uterine cancer, and potentially increased cardiac disease In fact, the discontinuation rate varied from 8-28% in clinical trials, and 12.9-73% in clinical practice settings. Although the incidence of uterine cancer was reported to be higher in tamoxifen-treated patients, no significant difference was observed in women younger than 45 years (15-year incidence, 0.4% vs. 0.3%; $p = 0.97$). Similarly, thromboembolism was observed in greater frequency in tamoxifen-treated patients vs. control, all of which occurred in women aged 55 to 69 years. Osteoporosis is a long-term side effect that may occur with chemotherapy and LHRH agonists.

Improved survival is the goal of adjuvant endocrine therapy, both of the short-term and long-term complications of the treatment should be taken care of, especially in younger women, who are likely to have extended years of survival. Take into account reasons for discontinuations were changed by time, not only side effects but understanding for the risk and benefit during informed consent must be important in order to continue the adjuvant endocrine therapy.

CLINICAL CONSIDERATIONS FOR THE DEVELOPMENT OF BIOSIMILARS IN ONCOLOGY

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As an essential component of cancer therapy, biologics are widely used to treat various types of cancer. Despite their prevalence and importance, the cost of these biologics, especially monoclonal antibodies, has greatly limited their use in treatment of patients globally. Patent expiration of several biologics in recent and upcoming years has triggered the development of biosimilars. A biosimilar is "a biological medicinal product that contains a version of the active substance of an already authorized original medicinal product," as defined by EMA, and is a cost-effective alternative to existing biologic treatment options that provides equivalent clinical benefits. The upcoming wave of monoclonal antibody biosimilar launch in oncology, including trastuzumab and rituximab, has put a spotlight on biosimilars in cancer treatment.

The assessment of biosimilars differs from that of its original counterpart, in that the development process of biosimilars is aimed at showing similarity in terms of molecular characteristics and biological mechanisms of action rather than at demonstrating clinical benefits. Because analytical data plays a major role in biosimilar development, highly advanced technology, using state-of-the-art equipment, is required for sensitive detection of subtle differences between biosimilars and the reference product. The similarity ranges used to compare between biosimilars and reference products are determined through a variety of analyses of multiple batches of the reference product.

Clinical studies of biosimilars can be largely divided into two parts: a Phase I bioequivalence study that evaluates pharmacokinetic equivalence, and a larger Phase III study, which includes the evaluation of efficacy, safety, and immunogenicity in comparison to the reference product. Clinical studies are not designed to prove efficacy per se, but are designed to show biological equivalence in the most sensitive indication, which the reference product is intended to treat, and using the most sensitive endpoint. Valid clinical endpoints used in oncology biosimilar clinical studies may differ from those in clinical studies of new drugs in oncology.

The implementation of biosimilars is still in relatively early stages, but their potential economic and clinical value is promising and remains an area of high opportunities for all stakeholders including regulatory agencies, industries, and the clinical society.

G-CSF (PEG-GCSF) BIOSIMILAR : CLINICAL APPLICATION AND EXPERIENCE

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Chemotherapy-induced febrile neutropenia (FN) is a potentially fatal complication of cancer treatment. Prophylactic administration of granulocyte-colony stimulating factor (G-CSF) provides protection for patients at risk of FN. In the current value-based health care, it is important to focus on maximizing clinical benefit and decreasing cost. Biosimilar is a biotechnological drug product developed to be comparable regarding quality, safety and efficacy to an already approved biotechnology-derived product of a different company. Use of biosimilar G-CSFs could yield potential cost savings and improve patient access to G-CSFs. Several G-CSF biosimilars are now in clinical use. Most recent G-CSF guidelines of EORTC, ASCO and NCCN recommend use of biosimilar G-CSFs as well as the reference product to prevent FN. However, biosimilars cannot be identical copies of original product, unlike generics because of their complexity. Therefore, rigorous clinical studies such as PK/PD tests and trials on efficacy and safety are required to demonstrate similarity or comparability. Moreover, traceability and pharmacovigilance are critical because long term efficacy and safety, and immunogenicity are not sufficient at the time of approval. This presentation will review the evidence and clarify issues of biosimilar G-CSFs.

TRASTUZUMAB BIOSIMILAR

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Trastuzumab has transformed the treatment of HER2-positive breast cancer. Because of patent expiry, numerous trastuzumab biosimilars are currently undergoing comparability exercises for marketing authorization. Obstacles are expected for trastuzumab resulting from its nature as a monoclonal antibody, its extensive biochemical complexities and its historical dramatic impact on overall survival. Key questions will be addressed for the evaluation of biosimilars efficacy regarding studies design, appropriate clinical endpoint, statistical criteria to valid equivalence, safety comparability taking into account the concurrent administration with chemotherapy, immunogenicity monitoring among immune-compromised patients. There is a pressing need to evaluate all biosimilars carefully, with scientific, economic and medical expertise. The main goal of this presentation will be to provide tools able to sort a hierarchy database of the respective trastuzumab biosimilars approved for routine use. This would help the choice of the oncological community for our patients.

POST-BCS WBRT: INVASIVE CARCINOMA & DCIS

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Several randomized trials and meta-analyses have reported than breast conserving therapy showed equivalent oncologic results with mastectomy. It was also shown that adjuvant radiation therapy (RT) after breast conserving surgery (BCS) increased local recurrence free and overall survival. So, whole breast irradiation (WBI) following BCS has served as standard of care for early-stage breast cancer patients.

But standard fractionation WBI usually consists of 6-8 weeks of daily treatments including tumor bed boost. It costs a lot of socio-economic payments. And breast RT may cause toxicities of adjacent tissues including lung, heart, contralateral breast, and skin. Several randomized trials were reported to answer the question whether adjuvant treatment could be reasonably omitted in low-risk group patients. It was reported that, even in selected low-risk patients group, the addition of RT decreased local relapse significantly. But overall survival did not increase with adjuvant RT. With the recognition of breast cancer heterogeneity according to the molecular subtypes, ongoing trials are testing the feasibility of omission of adjuvant RT for patients with low-risk biologic subtype.

As for ductal carcinoma in situ (DCIS) of breast, adjuvant WBI has been recommended to reduce local recurrences since five prospective randomized clinical trials of BCS with or without RT reported the efficacy of adjuvant RT. But considering absence of survival benefit of RT and indolent clinical courses of DCIS, controversy is present regarding whether RT is necessary in selected low-risk DCIS patients. A few prospective trials tested and reported that the omission of RT after BCS resulted in higher rates of local recurrence even in highly selected patients group. Ongoing trials are trying to identify truly low risk group with genetic assays and biomarkers in which adjuvant RT can be safely omitted.

With the advance of radiation therapy techniques and the recognition of the fact that most breast cancer recurrences occur in and around the lumpectomy cavity, accelerated partial breast irradiation (APBI) is proposed to reduce RT burden and overcome shortcomings of WBI for invasive cancer and DCIS. It was shown that APBI could achieve equivalent oncologic and cosmetic results in selected patients group. So, adjuvant RT options such as omission, APBI, and WBI can be precisely tailored to breast cancer patients who underwent BCS.

In elderly breast cancer patients, quality of life is extremely important as well as oncologic results. Because long-term administration of endocrine therapy can also cause toxicities, comorbidities and life expectancies should be considered when providing adjuvant treatment options. Efforts should be made to present patient-specific tailored treatment option with the consideration of not only biological tumor characteristics but also socioeconomic and physiological status of patients.

PMRT IN pN1

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The use of postmastectomy radiotherapy (PMRT) has been widely accepted for breast cancer patients with locally advanced tumor (pT3T4) or four or more positive lymph nodes (LNs) (pN2 or higher) [1-3], but there is still controversy regarding the application of PMRT for those with small tumor (pT1T2) and limited nodal metastasis (pN1).

Studies have reported the effects of PMRT on tumor recurrence and mortality in patients with 13 axillary LNs, including the Danish Breast Cancer Cooperative Group trial and a recent meta-analysis by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) [4,5]. The Danish trial showed the substantial benefit of PMRT on loco-regional recurrence (LRR) and overall survival in patients with pN1 and pN2 disease. The most recent EBCTCG meta-analysis also showed a similar result such that PMRT to the chest wall and regional lymphatics reduced both recurrence and breast cancer mortality in patients with pN1 and pN2 disease. In the pN1 subset analyses in which when axillary dissection was performed and systemic therapy was routinely administered, the 10-year rate of isolated LRR was 21.0% without PMRT and 4.3% with PMRT ($p < 0.001$). The 10-year rate for any recurrence was 45.5% without PMRT and 33.8% with PMRT ($p < 0.001$), and the respective 20-year rates of breast cancer mortality were 49.4% and 41.5% ($p = 0.01$).

However, the trials included by the EBCTCG were performed in the 1960s and 1990s, and the rates of LRR or any recurrence reported in this meta-analysis were considerably higher than those reported in many contemporary studies. The most recent series conducted since 1990 have reported much lower 5- to 10-year actuarial LRR rates lower than 10% [6-11], which resulted from a use of increasingly effective systemic therapy, more thorough axillary examination, and a decrease in average tumor size and smaller average number of positive lymph nodes. Therefore, it is reasonable that not all the patients treated with current axillary dissection and modern systemic therapy would likely benet from PMRT. And researchers have tried to find a group of high-risk of recurrence, in which the absolute benet of PMRT seems likely to be greater. Several prognostic models has been proposed based on the risk of mainly LRR by combining several factors such as patients age, tumor size, number of positive axillary LNs or nodal ratio, tumor grade, lympho-vascular invasion, hormone receptor status, biological subtype, and systemic therapy [8,11,12]. None of these models have yet to be validated.

An American Society of Clinical Oncology, American Society for Radiation Oncology, and

Society of Surgical Oncology recently published a guideline update concerning use of PMRT [13]. They discussed focused on ongoing controversy, including the use of PMRT for pN1 patients, the use of PMRT after neoadjuvant systemic therapy, and the extent of regional nodal irradiation. The question of whether PMRT is indicated in patients with pT1-T2 tumors and a positive sentinel node biopsy who do not undergo completion axillary lymph node dissection is also discussed. The panel unanimously agreed that available evidence shows that PMRT reduces the risks of locoregional failure (LRF), any recurrence, and breast cancer mortality for patients with pT1-2 breast. However, some subsets of these patients are likely to have such a low risk of LRF that the absolute benet of PMRT is outweighed by its potential toxicities. When clinicians and patients elect to omit axillary dissection after a positive sentinel node biopsy, the panel recommends that these patients receive PMRT only if there is already sufcient information to justify its use without needing to know additional axillary nodes are involved. Patients with axillary nodal involvement after neoadjuvant systemic therapy should receive PMRT. The panel recommends treatment generally be administered to both the internal mammary nodes and the supraclavicular-axillary apical nodes in addition to the chest wall or reconstructed breast.

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IMN: BALANCING RISKS AND BENEFITS

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Locoregional radiation therapy improves locoregional control, disease-free survival and overall survival for patients treated with breast conserving therapy and for patients after mastectomy with risk factors including involved axillary lymph nodes. As it was, however, linked to an increased risk for late cardiovascular morbidity and mortality as a result of cardiac exposure to radiation, especially the treatment of the internal mammary lymph node target volume was abandoned by many radiation oncology centres worldwide. This was most often attributed to the use of out-dated radiation therapy techniques.

Currently, the outcome of the EBCTCG meta-analyses is supported by an important bulk of available evidence from the results of recently completed prospective trials that were initiated to evaluate the contribution of lymph node irradiation to overall outcome for early stage breast cancer patients. The interoperation of these results is important to fully understand the complex interaction between the long-term effects of locoregional and systemic treatments on survival for breast cancer patients.

The results of the recent regional radiation therapy studies show similar overall results with an increased disease-free survival rate as a consequence of a decreased rate of distant metastases. Moreover, a trend towards an improved overall and (statistically significant for some of the studies) breast cancer specific survival was demonstrated. No increase was seen in the other causes of death and, at a median follow-up of around 10 years, no significant or clinical relevant increased toxicity was found, apart from a slight increase in the risk for pulmonary toxicity.

By eliminating microscopically non-detectable cancer cells in the lymph nodes with radiation therapy, the risk of secondary metastasising of those cells and thereby ultimately the overall risk of recurrence of breast cancer will be reduced. This is in line with the findings of the EORTC trial in which a trend was seen towards more benefit for patients who where treated with both hormonal treatment and chemotherapy and less benefit for the small group of patients with 10 or more involved axillary lymph nodes: patients with a better prognosis (lower risk factors and/or better systemic therapy) experience more benefit from locoregional radiation therapy.

These trials where initiated in a time where treatment techniques just started to improve, enabling to limit the dose to the organs at risk. With modern radiation therapy techniques, the benefits of optimising locoregional control will likely much less are even not at all be counter-

balanced by side effects including late cardiovascular mortality. Moreover, the new ESTRO guidelines for target volume delineation enables us to clearly reduce the size of the target volumes while simultaneously considering the regional lymph nodes even more than before as a whole. We also calculated that the real benefit of loco-regional radiation therapy used to be diluted in the past (including the recently presented trials) by suboptimal dose coverage of the target volumes.

Therefore, we expect that with contemporary radiation therapy techniques and appropriate target volume delineation, not only a significant reduction of the dose to the organs at risk but also a much better coverage of especially the internal mammary lymph nodes is achievable, which is likely to result in a further improvement of the benefit of locoregional radiation therapy for patients with early stage breast cancer that have a risk for bearing microscopical tumor deposits in the regional lymph nodes.

HOW TO INTERPRET THE OMICS BIG DATA AND APPLY TO THE CLINICAL PRACTICE

Yu Shyr

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The Holy Grail of precision medicine is the comprehensive integration of patient genotypic with phenotypic data to develop personalized disease prevention and treatment strategies. Next-generation sequencing technologies (NGS) and other types of high-throughput assays such as proteomics, single cell sequencing, liquid biopsy, and 4D Nucleome have exploded in popularity in recent years, thanks to their ability to produce an enormous volume of data quickly and at relatively low cost compared to more traditional laboratory methods. The ability to generate big data brings us one step closer to the realization of precision medicine; nevertheless, across the life cycle of such data, from experimental design to data capture, management, analysis, and utilization, many challenges remain. In this talk, I will introduce a recent report from the Institute of Medicine (IOM) of the National Academies of Sciences, Engineering, and Medicine, which reviewed the state-of-the-art in biomarker testing for selection of targeted therapies. I will also discuss potential pathways for the seamless integration of cellular and molecular data with clinical, physiological, behavioral, and environmental parameters a critical next step in advancing the goals of precision medicine for breast cancer.

PERSONALIZED ADJUVANT THERAPY BASED ON CLINICAL TRIALS IN BREAST CANCER: DREAM OR REALITY?

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The development of adjuvant therapy has increased the cure rates for early breast cancer. However, most clinical gains obtained thus far have been in large part based on one size fits all therapeutic escalation, in other words, the increase of the number of drugs or of the durations and intensity of treatments within a framework of limited understanding about which patients would actually benefit. Despite the gains achieved, it is important for us to realize that this has had negative consequences. Health systems have dealt with more and more expensive drugs for longer periods of time and are at the breaking point. Patients endure longer and more toxic regimens and, with more cures, come more frequent long term sequelae. To add insult to injury, currently available data very clearly shows that only a fraction of patients benefit from any single instance of escalation.

The HERA trial, one of the adjuvant trials published 12 years ago, made trastuzumab a treatment standard for HER2-positive early breast cancer, shows that even a drug of remarkable effectiveness like trastuzumab only helped about 10% of patients. Twelve years later, and after multiple translational efforts, we have yet to produce a marketable predictive biomarker capable of detecting these elusive patients. In the meantime, the results of the NEOSPHERE trial have further captivated us with the possibility of targeted therapy alone. Six years after presentation of initial results, we are no closer to using this strategy in clinical practice. Even more seriously, the results of the APHINITY trial of pertuzumab and trastuzumab vs. trastuzumab alone after chemotherapy in early breast cancer is likely to change the standard. It is important to note that from a biological point of view; patients are still selected based on the very same biomarker used in HERA HER2 status alone. Treatment duration remains the same empirically chosen 1 year. Even though a large number of samples for translational research were collected in APHINITY, will we be able to produce a biomarker before the standard is escalated yet again?

While HER2-positive disease has for a long time been the sole example of success in breast cancer targeted therapy, this is no longer the case, first with the results of everolimus in estrogen receptor positive metastatic breast cancer, and more recently and far more likely to be of consequence, of palbociclib. The results of the PALOMA studies have made palbociclib the standard of care for ER+ metastatic breast cancer in first line. The PALLAS adjuvant trail, though results are still far away, may bring palbociclib to the early setting, for an empirical 2 years. It is impor-

tant to note that the design of PALLAS does not take into consideration any predictive biomarker for patient inclusion. Therefore, while this trial, we hope, will further improve outcomes, it will also risk maintaining current trends in terms of drawbacks for patients and society. One can only conclude that personalized medicine in early breast cancer, should we continue to rely on traditional trial designs and traditional drug development, will remain a mirage

Successful biomarker research for personalizing breast cancer treatment, though possible, is not easy to achieve. The MINDACT Trial, designed to prove the clinical utility of a 71 gene essay capable of sparing chemotherapy for some early breast cancer patients took 12 years and thousands of women to achieve its results. Scientific, organizational and regulatory boundaries added to a lack of appetite by large pharmaceutical partners, renders biomarker research incredibly challenging. Therefore, in order to advance in a sustainable manner toward personalized breast cancer medicine, it is vital that drug development is conducted in tandem with biomarker development, and that trial design be explicitly geared towards allowing for sensitive patient detection. An alternative approach is to freeze the treatment of populations of good prognosis be it based on traditional clinical and pathological criteria, be it on complex next generation sequencing and the recent success of the

Tolaney regimen shows this is achievable. Additionally, if duration of necessary treatment is to be determined, current, isolated initiatives such as the PHARE study comparing 1 year to 6 months of trastuzumab will not suffice.

To conclude, the current scenario for drug development in breast cancer does not favour personalization in adjuvant therapy. However, it is possible, that by constructing high level cooperation between researchers, pharmaceutical companies and governments, tentative successes achieved so far may lead to a different future.

WHERE ARE WE NOW, TO THE PRECISION MEDICINE

Masakazu Toi

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Breast cancer biology analyses have elucidated the essence of the disease in the last decade. The disease composition of primary breast cancers was described and therapeutic strategies have been made based on that. In addition, quite recently days, the metastasis has been understood gradually from the point of molecular analyses and of clinical trails. The prediction of prognosis and therapeutic outcomes became more precise than ever according to standardized methodologies to assess tumor stage, disease extent, pathological phenotype and biological characteristics, and to a concept of therapeutic personalization, where single or multiple selected and achievable therapies are recommended to each subpopulation of the disease group of patients with simulation of probabilities on the prognostic and therapeutic clinical results. These concepts and trend penetrated into practice globally, and new therapy development seems to be also engaged in. For the near future, we will be able to use more biological information and novel targeted therapeutics for selected or enriched subpopulation defined by OMICs or real therapeutic responses.

New clinical trial concepts and systems would be also created.

EDUCATION SESSION

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CLINICAL UTILITY OF LIQUID BIOPSY IN CANCER

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Liquid biopsies are non-invasive blood tests that detect circulating tumor cells (CTCs), cell-free DNAs (cfDNAs) and exosomes that are released into the blood from tumor sites. It has recently received enormous attention because of its role in personalized medicine. Current studies are mainly focused on CTCs and cfDNAs, but the attention to exosome is increasing. In this session, I will introduce liquid biopsy and review its current clinical utility in cancer with a focus on breast cancer.

Compared to conventional tissue biopsy, liquid biopsy has the advantage of minimal invasive sampling, homogeneous representation of the tumor and limitless utility regardless of metastatic site. A major advantage of liquid biopsies is that it can also provide the genetic landscape of primary and metastatic lesions, reflecting intra- and inter-tumor heterogeneity. The key areas of clinical application of liquid biopsies includes early detection of cancer, prediction of prognosis, monitoring of tumor burden and systemic therapies response and stratification of patients for selected targeted therapy.

In breast cancer, studies have mainly focused on the prognostic value of liquid biopsies. Currently, CellSearch CTC test is the only FDA-approved CTC test for prognostic value in metastatic breast cancer. In the contrary, it has failed to show a predictive value in metastatic breast cancer, therefore not being included in clinical guidelines. In early breast cancer, CellSearch CTC test has also been proven to be prognostic but it is still missing FDA approval. There are currently no validated tests for cfDNA analysis but recently the FDA approved a cfDNA test for EGFR mutation in lung cancer, opening opportunities to other cancers also. Although cfDNA has a lack of validated test in breast cancer, the role of prognosis prediction and longitudinal monitoring has been presented in several studies. Also, the detection of PIK3CA, ESR1 and TP53 mutations in cfDNAs have opened the possibility of treatment stratification and therapy monitoring. In the area of cancer screening and detection, the low detection rate of CTCs and ctDNAs is a high obstacle to overcome. On the other hand, microRNAs have recently emerged as tool for breast cancer screening. Cancer exosomes are also anticipated in the potential heterogeneity it carries, but currently comprehension of the precise physiological function of exosomes is critical to determine its role in cancer.

The advantages and disadvantages of CTCs and ctDNAs are quite straight-forward and counter to each other. The current issue is not to choose one type of liquid biopsy, but to use all types

complementary. Currently more reliable liquid biopsy assays are needed to be validated and in the future, an integrated system will be needed to isolate CTCs, ctDNAs and exosomes at once from one sample. To apply liquid biopsy in the clinic, a predictive value must be proven, and this will be possible through randomized clinical intervention studies in which therapy decisions are based on liquid biopsy analysis.

ACTIONABLE GENOME ANALYSIS FOR HUMAN CANCER

Woong-Yang Park

Samsung Genome Center, Samsung Medical Center, Korea

Single-cell RNA-seq provides tools to understand the characteristics of individual cells from heterogeneous tumor tissue. We analyzed whole transcriptome of more than 500 unsorted single cells from 11 breast cancer tissues. Using inferred copy number variation data from the single-cell RNA-seq data, carcinoma cells were separated from non-cancer cells. At a single cell level, carcinoma cells showed common features within tumors, and also intra-tumoral genetic heterogeneity with mixed signature of different breast cancer subtypes. Non-cancer cells were mostly immune cells, with three distinct populations of T lymphocytes, B lymphocytes, and macrophages. T lymphocytes and macrophages displayed immunosuppressive characteristics; regulatory or an exhausted phenotype. Single cell trascriptome profile could figure out the range of intra-tumoral heterogeneity made of tumor cells as well as immune cells within breast cancer tissue, which might determine the response to therapy.

NEW ISSUES IN CANCER GENOMICS FOR THE RESEARCH AND TREATMENT

Tae-Min Kim

Department of Medical Infomatics, College of Medicine, The Catholic University of Korea, Korea

Immune checkpoint blockade treatment has shown its clinical efficacy across various cancer types but it is still poorly understood as to which patients will benefit from the treatment. Mutation burden of the tumor genome, i.e., the number of somatic mutations, is expected to be proportional to the abundance of neoantigens, which will elicit the antitumor response. As shown in melanomas, lung and colorectal cancers, the increased mutation burden has been proposed as genomic factors that may predict the efficacy to the immunotherapy. Unlike the melanomas and lung cancers with excessive mutation rates and the colorectal cancers often with microsatellite instability-high (MSI-H), the hypermutation of breast cancers is not well understood. Using the mutation profiles of more than 1,000 breast cancers in the Cancer Genome Atlas (TCGA) consortium, we show that a substantial number of breast cancers can be designated as 'hypermutated' as potential candidates of responder to the immunotherapy. The hypermutated breast cancer genomes are further distinguished in those with mismatch repair (MMR) deficiency and those not using the predictive model of MSI-H cases. These genomes are further investigated in terms of the gene expression, mutation signatures and potential mutation drivers beyond MMR genes. Our study would provide the rationale of immunotherapy for breast cancer with excessive mutations and also the mechanistic insights on the hypermutation in the cancer genomes.

OVERCOMING HETEROGENEITY: SINGLE CELL SEQUENCING OF BREAST CANCER

Wonshik Han

Department of Surgery, Seoul National University Hospital, Korea

Cancers display intra-tumoral heterogeneity which interferes with the precise analyses of the tumor entity and which may affect therapeutic outcomes of targeted treatments. Breast cancer in particular display a vast diversity of genomic profiles within a tumor and show specific characteristics according to subtypes.

Single-cell transcriptome profiling of tumor tissue isolates allows the characterization of heterogeneous tumor cells along with neighboring stromal and immune cells. Here we adopt this powerful approach to breast cancer and analyze 515 cells from 11 patients. Inferred copy number variations from the single-cell RNA-seq data separates carcinoma cells from non-cancer cells. At a single cell resolution, carcinoma cells display common signatures within the tumor as well as intratumoral heterogeneity regarding breast cancer subtype and crucial cancer-related pathways. Most of the non-cancer cells are immune cells, with three distinct clusters of T lymphocytes, B lymphocytes, and macrophages. T lymphocytes and macrophages both display immunosuppressive characteristics: T cells with a regulatory or an exhausted phenotype and macrophages with an M2 phenotype. These results illustrate that the breast cancer transcriptome has a wide range of intratumoral heterogeneity, which is shaped by the tumor cells and immune cells in the surrounding microenvironment.

Another technology we developed is Phenotype-based High-throughput Laser Isolation and Sequencing (PHLI-seq), which enables a high-throughput isolation of a single-cell or a small number of cells and their genome-wide sequence analysis to map genomic information to its tissue of origin.

Spatially resolved analysis of genome-wide molecular information so that the data is connected to histopathology of cancer is crucial to understand cancer biology and clinical impacts that cancer heterogeneity has on patients. However, in contrast to recent progresses in spatially resolved transcriptomics, spatial mapping of genomic data in a high-throughput and high-resolution manner has been challenging due to technical limitations. Through PHLI-seq, we discover heterogeneity of a HER2-positive breast cancer tissue and map cells' genomic landscape to their corresponding spatial locations and identify their genetic history.

PRACTICAL IMPLICATIONS OF NEXT GENERATION SEQUENCING IN BREAST CANCER : PROMISES AND CHALLENGES

Naoto Ueno

Department of Breast Medical Oncology, The University of Texas, MD Anderson Cancer Center, U.S.A.

Next-generation sequencing of breast cancer samples has yielded extensive information related to genomic changes. We now have a comprehensive catalog of somatic mutations in breast cancer. However, the question remains whether this information can affect treatment decisions.

Both The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC) provide platforms to analyze the data and in addition some of the data is associated with microRNA, DNA methylation, and proteomics. In breast cancer, patients with recurrent disease have poor outcomes owing to metastasis. Metastasis may occur in part from the resistance of breast cancer to standard systemic therapy. We can classify this resistance into three types: 1) intrinsic resistance due to molecular characteristics present before the initiation of systemic therapy, 2) adaptive resistance due to molecular changes that occur soon after therapy is initiated, and 3) acquired resistance as indicated by residual or recurrent disease after prolonged treatment.

Understanding the three types of resistance will lead to the development of novel targeted therapy for breast cancer. Many new targeted therapies are in development (e.g., inhibitors of PI3K, MEK, mTOR, Akt, AR, MELK, HER2, JNK, and immune checkpoints). However, it remains unclear how these targets are related to specific types of therapy resistance and how best to incorporate these exciting new targeted therapies into the current mutational landscape to overcome resistance.

Furthermore, because of the complexity of the resistance mechanisms, the timing of breast cancer biopsies can have a substantial impact on how we map genomic changes. Unfortunately, in our current practice, we can collect breast samples either at the time of diagnosis or at the time of metastasis. This limited number of biopsies suppresses our capability to understand the biology of the disease.

The learning objective of this talk is to address the challenges in developing novel treatments based on the genomic changes identified using the current technology. We will review the ongoing research supporting our current knowledge of breast cancer molecular changes to determine how this information can contribute to treatment selection for patients with breast cancer.

MOLECULAR HETEROGENEITY OF TRIPLE-NEGATIVE BREAST CANCER

Charles M. Perou

Department of Genetics, University of North Carolina at Chapel Hill, U.S.A.

Triple Negative Breast Cancers (TNBC = ER-, PR-, and HER2-negative) are amongst the most clinically challenging because of their poor prognosis and paucity of treatment options. TNBC are more common in younger women, and African American women, which contributes to racial disparities in mortality due to breast cancer. TNBC is composed of multiple disease subtypes including Basal-like, Claudin-low/Mesenchymal, and Luminal-type tumors, each of which may require distinct therapeutic strategies.

Within TNBC, the Basal-like disease predominates (70-80%), but again, all the intrinsic subtypes can also be identified. Interestingly, luminal/TNBC or HER2-enriched/TNBC show similar gene expression patterns as Luminal/HR+ or HER2-enriched/HER2+, except for ERBB2 (and the genes in the 17q amplicon), which is not found overexpressed in HER2-enriched/TNBC. Importantly, the distinction between Basal-like versus non-Basal-like within TNBC seems to be important for predicting survival following (neo)adjuvant multi-agent chemotherapy, bevacizumab benefit in the neoadjuvant setting (CALGB40603), and docetaxel vs. carboplatin benefit in first-line metastatic disease (TNT study). Overall, this data suggests that intrinsic molecular profiling provides clinically relevant information beyond current pathology-based classifications.

CELL CYCLE REGULATION AND TARGETING CDK 4/6 FOR TREATMENT OF BREAST CANCER

Seock-Ah Im

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Endocrine therapy has been the standard of care for the management of hormone receptor (HR)-positive, Her2-negative advanced breast cancer (ABC) without visceral crisis for decades. However, the rapidly accumulating data regarding the biological role and safety of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors and the first-in-class approval of palbociclib have made these novel agents an essential component of treatment for HR-positive ABC. In the frontline setting, palbociclib in combination with letrozole showed an improvement in progression-free survival (PFS) by 10 months to nearly 25 months when compared with letrozole alone and a clinical benefit rate (CBR = stable disease > 24 weeks + partial response + complete response) of 85%., Recently another pivotal clinical trial showed that the PFS was significantly prolonged with adding ribociclib to first line letrozole. Furthermore, clinically meaningful improvements in PFS were seen in combination with fulvestrant for patients with prior endocrine therapy, including premenopausal women. While neutropenia is experienced by most patients, it is typically uncomplicated and palbociclib is otherwise well tolerated. Recent analysis also demonstrated improved quality of life and reassuring evidence of no compromise in benefit from subsequent therapies after progression on palbociclib. Along with palbociclib, the CDK4/6 inhibitors ribociclib and abemaciclib are being evaluated in a variety of settings (metastatic, neoadjuvant, and adjuvant), alone and in combination with endocrine therapy, chemotherapy, and targeted therapies in HR-positive and HER2-negative or HER2-positive breast cancer. RB1 expression and HR-positive disease have been the clear predictors of therapeutic benefit. CDK4/6 inhibitors impact on PFS, high CBR, and tolerability have made its use a preferred option for treating many HR-positive, Her2-negative ABC patients.

CDK 4/6 INHIBITORS FOR THE TREATMENT OF BREAST CANCER: A REVIEW OF CLINICAL DATA

Jin-Hee Ahn

ASAN Medical Center, Korea

A number of highly effective CDK4/6 inhibitors are currently in development as treatments for patients with MBC. In the randomized phase II PALOMA 1 trial evaluating palbociclib in combination with letrozole in treatment-nave patients, an improvement in PFS could be seen (20.2 vs. 10.2 months, $p = 0.0004$). The results of the phase III PALOMA 2 trial evaluating letrozole with or without palbociclib in HR-positive, HER2-negative ABC patients confirmed these positive findings (median PFS 24.8 vs. 14.5 months, $p < 0.001$). This study was stopped early given the efficacy of the combination. Recent results from the phase III PALOMA 3 trial also showed that adding palbociclib to fulvestrant more than doubled the duration of disease control (median PFS 9.5 vs. 4.6 months, $p < 0.0001$). At this point, palbociclib (Ibrance) has gained FDA approval as a frontline therapy with letrozole and as a second-line therapy with fulvestrant for patients with HRpositive breast cancer.

Abemaciclib is another agent that has received a breakthrough therapy designation from the FDA for its potential use as a monotherapy for patients with HR-positive, HER2-negative ABC. Phase II MONARCH 1 trial showed that abemaciclib induced a response rate of nearly 20% in heavily pretreated patients with refractory HR-positive, HER2-negative MBC. Median PFS was 6 months and median OS was 17.7 months. At present, abemaciclib is being evaluated in two phase III clinical trials: MONARCH2 to evaluate the combination of abemaciclib and fulvestrant for the treatment of HR+, HER2- MBC in postmenopausal women, and MONARCH 3 to evaluate the combination of abemaciclib and a nonsteroidal AI in HR+, HER2- ABC in postmenopausal women.

Additionally, there are two Phase 2 MONARCH trials: neoMONARCH, which is evaluating abemaciclib in combination with a nonsteroidal AI in the neoadjuvant setting, and monarcHER, which is evaluating abemaciclib plus trastuzumab (with or without fulvestrant) in women with HR+, HER2+ locally advanced or MBC.

The FDA also granted a breakthrough designation to another drug in this class, ribociclib, in combination with letrozole for its potential as a frontline therapy for patients with HR-positive, HER2-negative MBC. The designation was based on findings from the phase III MONALEESA-2 trial, in which ribociclib and letrozole significantly improved PFS compared with letro-

zole alone (HR 0.56; 95% CI, 0.43 to 0.72; $p = 3.29$ X 10-6).

The most notable difference between the CDK 4/6 inhibitors is their toxicity profiles. Myelosuppression, particularly neutropenia, is the primary dose-limiting toxicity (DLT) for palbociclib and ribociclib. Rates of neutropenia are approximately 40% for both agents. In studies of abemaciclib, patients had milder hematologic toxicity, and it was not a DLT. Because myelosuppression is less of a side effect with abemaciclib, it can be given continually without an off-treatment week per cycle. Gastrointestinal toxicity, however, is more common with abemaciclib than with the other CDK 4&6 inhibitors. Lowering the dosage of abemaciclib may help eliminate or reduce the severity of this side effect, and supportive medications may help.

In conclusion, targeting of CDK4 and CDK6 represents a novel, efficacious, and safe therapeutic approach for the treatment of patients with ER-positive breast cancer.

ONGOING CLINICAL TRIALS COMBINING CDK 4/6 INHIBITORS AND RELATED BIOMARKERS

Soohyeon Lee

Department of Oncology, Pfizer Oncology, Korea

Clinical and preclinical data support a significant role for inhibitors of the cyclin-dependent kinases (CDKs) 4 and 6 in the treatment of patients with breast cancer. Recently, based on data showing improvement in progression-free survival, the use of palbociclib (Ibrance; Pfizer, Inc.) and ribociclib (LEE011; Novartis) in combination with endocrine agents was approved to treat patients with hormone receptor-positive advanced disease. Another CDK4/6 inhibitor, abemaciclib (LY2835219; Lilly) are also in the late stage of clinical development.

I will focus on clinical data on these 3 drugs, highlighting their differences in terms of single-agent activity, central nervous system penetration, and common adverse events. In addition, I will present the ongoing clinical trials with HR+/HER2- as well as HER2+ subtype and discuss related biomarkers with future directions in the field.

SURVIVORSHIP SESSION

Global Breast Cancer Conference

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BREAST CANCER SURVIVORSHIP RESEARCH AND CARE PRACTICES FROM A JAPANESE PERSPECTIVE

Miyako Takahashi

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Cancer survivorship encompasses diverse themes, both in research and practice. Breast cancer diagnosis presents major survivorship issues in East Asian countries; the age-adjusted incidence rate of the disease being the highest among cancers affecting Japanese women.

Although each person's cancer journey is unique, cultural beliefs, customs, and health policies can all strongly influence attitudes and behaviors in the post-treatment phase. In particular, interpersonal relationships, such as couple and parentchild relationships, are affected by sociocultural backgrounds. Another important survivorship issue, employment- and finance-related challenges, is associated with laws related to occupational health and business customs. Support activities therefore need to be tailored for breast cancer survivors and caregivers in accordance with cultural and societal contexts so the target populations successfully accept such programs. Furthermore, survivors perspectives and unmet needs should be explored so activities can yield optimal results.

This is a brief review of the current situation of breast cancer survivorship research and care practice in Japan, focusing on marital and sexual issues as well as employment-related challenges. Also included is an introduction to recent changes in cancer control policies in Japan - the Basic Cancer Control Act, revised in 2016, and the Third Basic Plan to Promote Cancer Control Programs of 2017 - which emphasize promotion of survivorship research and care practices.

LIFE AFTER BREAST CANCER IN AUSTRALIA

Hyukjai Shin

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Breast cancer is the most common cancer in Australian women, such as in European and American women. Because most breast cancer patients have higher survival rates, the breast cancer survivorship is rapidly increasing now. Breast cancer survivorship care has become more important thing. Until now, most of the survivorship care has been managed by breast cancer specialists (Breast surgeon and Medical Oncologist). Survivors increase rapidly with increasing breast cancer patients, but the number of breast care professionals is very limited. Therefore, a new management system is needed for the management of many breast cancer survivors. And BREAST CANCER SURVIVORSHIP PROGRAM AND SHARED CARE was started at early 2000 and has been developing until now.

Let me introduce Australian BREAST CANCER SURVIVORSHIP PROGRAM AND SHARED CARE First of all, the human composition system of the medical system is different. The breast cancer survivor care in Australia is responsible for Breast Surgeon, Medical Oncologist, Radiation Oncologist, Breast care Nurse, Breast Physician, General Practitioner. The position of Breast Physician and Breast care nurses are not in South Korea. So Let me specially introduce about Breast Physician and Breast care nurses. A Breast Physician is a doctor working in the specialised area of diagnosis and management of benign and malignant breast disease.

Breast Physicians have a wide range of skills that may include: clinical breast examination/interpretation of mammography and breast ultrasound/performance of image-guided breast intervention procedures such as fine needle biopsy, core biopsy and pre-operative needle localization/ counselling of women with breast cancer/planning and coordinating treatment of women with breast cancer assessment, monitoring and ongoing care of women at high risk such as women who have a family history of breast cancer and those who have previously been treated for breast cancer. Breast Physicians work in consultation with breast surgeons, radiologists, oncologists, geneticists and other members of the Multidisciplinary team.

Breast Care Nurse: Timely access to a breast care nurse can greatly assist women going through treatment for breast cancer. Breast care nurses improve the continuity of care for women, and provide important information, support and referral for a wide range of needs experienced by women. Improving access to breast care nurses was the number one priority identified by women attending Breast Cancer Network Australias (BCNA) 1998 and 2004 national confer-

ences for women with breast cancer. All Australians should have access to a breast care nurse whether they undergo treatment for breast cancer through the public or private health care system. Australians with both early and secondary breast cancer should have access to a breast care nurse. Appropriate training, accreditation and ongoing professional development should be available for breast care nurses to ensure that women receive the best quality care. The role of breast care nurses needs clarification, and should include a focus on psychosocial assessment and support for women. Funding for breast care nurse positions should be ongoing and sustainable. A range of breast care nurse models should be established, including for women in rural and remote areas who may access breast care nurses through the use of telephone and video conferencing calls. Breast care nurses must be included as members of multidisciplinary breast cancer teams. "BREAST CANCER SURVIVORSHIP PROGRAM AND SHARED CARE" is as follows Breast Cancer Survivorship Program aims to improve follow-up care for women who have completed active breast cancer treatment at VCCC hospitals.

The goal is to develop, implement and evaluate a model of survivorship care. This model actively involves women and their GPs, and recognises the specific issues and opportunities that exist at the end of active treatment to support women to live well. This includes developing a follow-up care plan and implementing a shared follow-up care arrangement between the Breast Service and the general practice. This model of care will result in better coordinated and more personal healthcare planning and management.

We would like women to feel more educated and empowered about their ongoing healthcare. This program will identify and address a womans immediate and future needs in terms of her follow-up care, and improve systems that share information between a woman, her GP, other community services and the hospitals in order to improve quality of care.

Although Korea and Australia basically have different medical systems, I think there are things to be introduced in Australia in terms of efficient use of medical resources and active management of breast cancer survivors. It is believed that it is necessary to introduce The Shared care with Survivorship care plan to adapt to the situation in Korea.

HEALTH STATUS AND HEALTHCARE UTILIZATION OF BREAST CANCER SURVIVORS

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Breast cancer survivors experience variable spectrum of complications from cancer treatment. Some symptoms may last longer and described as persistent or late effects, which started during treatment or after the treatment had ended. There are issues that breast cancer survivors are suffered from, such as psychosocial distress, lymphedema, sexual dysfunction, weight gain, cognitive impairment, fatigue, and osteoporosis. Some of them are serious that can influence to patients survival, for example, cardiovascular diseases and secondary cancers. Fear of recurrence is also one of the factors that can influence survivors quality of life. Those late and persistent effects sometimes can be confused with normal aging process.

Cancer survivors presented poorer mental health outcomes than non-cancer controls from a study comparing health status of adolescent/young adult cancer survivors (breast and gynecological). Additionally, hypertension, ulcer, and arthritis were more seen in cancer survivors. Long-term cancer survivors showed high incidence of lymphedema, osteopenia, osteoporosis, and heart diseases such as congestive heart failure, myocardial infarction, or coronary heart disease. In very long-term breast cancer survivors (defined breast cancer survivors whose cancer was diagnosed ≥ 15 years earlier) reported significant higher incidence of arthritis, osteoporosis, cataracts, heart problems, loss of memory, lung problems, and other secondary cancers. On the other hands, a recent report from matched cohort of breast cancer survivors and non-cancer control women showed different results, which showed comparable results between two groups in newly developing diseases after breast cancer treatment reviewed from ICD 9 codes. With 10 years of follow up in this study, distribution of diseases of circulatory system was shifted slightly negative associations in breast cancer survivor, and low incidence of aortic aneurysms were seen.

In Korean population, breast cancer survivors showed more physical and urogenital symptoms than age-matched healthy controls. Impaired cognitive functions were also seen in cancer survivors, such as memory, executive function, concentration, and organizing skills. In another report, breast cancer survivors were less sexually active than general population, with a symptom of dyspareunia. The available data of late effects in Korean breast cancer survivors are limited. In a study from Korean National Health and Nutrition Examination Survey (KNHANES), long-term breast cancer survivors who had been treated more than five years and age-matched

control health women were selected and compared. There were no differences in incidence of cardiovascular disease and osteoporosis. Bone mineral density examination showed no difference between two groups. Vitamin D levels presented deficiency in all women.

The incidence of breast cancer in Korea has been gradually increased and the overall survival has been improved, which reflects growing populations of breast cancer survivors. Careful management of such population should be organized.

ABRCA & HBOC SESSION

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BREAST CANCER GENETICS- HOW IS IT CHANGING OUR PRACTICE

Ava Kwong

Department of Surgery, The University of Hong Kong, Hong Kong

BRCA1 and BRCA2 are the predominant breast cancer susceptibility genes which increase risk of breast, ovarian and a number of other cancers. The leap in the technology advances of Next Generation Sequencing have allowed the creation of multigene panels , which apart from these two dominant genes, a number of moderate penetrance genes have now been identified to have an effect of breast cancer risk. The risk assessment based on genetic testing allows options of high risk surveillance, prevention and may now also guide use of specific therapies for treatment such as targeted therapies and use of specific types of chemotherapy. The choice of management, once an individual has been found to carry the BRCA mutation or other breast cancer related genes may also vary based on clinical and person choices. Moreover the availability of genetic testing, method of testing such as the transition into the use of Next Generation Sequencing techniques may also vary in different parts of the world and still have some limitations in some areas in Asia. The current evidence supporting the choice of management and controversies will be discussed.

PANEL TESTING AND SNP TESTING (POLYGENIC RISK SCORE) IN ASIAN WOMEN

Soo-Hwang Teo

Cancer Research Malaysia, Malaysia

The mean age of breast cancer diagnosis in Asia is younger than that in the majority of populations of women of European descent, suggesting that inherited predisposition to breast cancer may be more significant. In my talk, I will describe the current understanding of major breast cancer susceptibility genes in Asian women, focusing on the challenges of moving from analytical validity and clinical validity, to the clinical utility of these panel tests. I will review the status of our current knowledge of polygenic risk scores in the Asian population and review the opportunities for coming these into risk stratified approaches for screening and prevention in Asian populations.

BREAST CANCER GENETICS AND CANCER POLICY

Steven A Narod

Women's College Research Institute, Dalla Lana School of Public Health, University of Toronto, Canada

The BRCA1 and BRCA2 genes were identified in 1994 and 1995 respectively and since then genetic testing has been in place. There have been many additional genes identified, but of these, only PALB2 has much clinical utility. Genetic testing can be supported by advances in the prevention and treatment of hereditary breast cancer and it is now reasonable to offer testing to all newly diagnosed patients with breast and ovarian cancer. In Canada we have developed the first national program to offer genetic testing direct to consumer to all men and women in Canada who are above the age of 18 at a low price. The rational for population based genetic testing will be discussed

GENETIC SUSCEPTIBILITY TO BREAST CANCER: ROLES OF HIGH- MODERATE- AND MODEST-PENETRANCE ALLELES

David Goldgar

Department of Genetics, University of Utah School of Medicine, U.S.A.

Based on allele frequency and risk, we currently recognize three classes of breast cancer susceptibility genes: (i) high-risk susceptibility genes, such as BRCA1, BRCA2, and TP53, which harbor very rare pathogenic alleles conferring 10- to 20-fold increased risk; (ii) moderate-risk susceptibility genes, such as ATM and CHEK2, which harbor rare pathogenic alleles conferring 2- to 5-fold increased risk; and (iii) more common single nucleotide polymorphisms (SNPs), which generally confer a 1.05- to 1.25-fold increased risk, but have allele frequencies of 1% to 50%. Although these SNPs are not useful for risk prediction when considered individually, theoretical calculations indicate that a combined score based on genotypes at a large number of such loci could have substantial predictive value for risk stratification in the general population, as well as in BRCA1 and BRCA2 carriers.

Recent large case-control studies such as the iCOGS and OncoArray projects have identified nearly 100 additional risk loci which has increased our knowledge about the common loci and when combined into a Polygenic Risk Score (PRS) they now have considerable predictive power in both the population and familial settings as well as providing considerable risk differences in carriers of high-penetrance mutations in BRCA2. At the same time, there have been a number of genes described in which there is some evidence that rare alleles in these genes are associated with increased risk of breast and/or ovarian cancer. However, with the exception of PALB2, these have largely not been independently validated, and the risks (if any) not been determined with sufficient precision. I will show the results of our analysis of cancer in a large series of individuals tested for these genes by a commercial testing laboratory and describe two ongoing large research studies that will definitively define these risks. I will also discuss the clinical implications of specific BRCA1/2 variants that appear to have intermediate penetrance and how we propose that carriers with those variants be counseled in the genetics clinic.

Finally I will show the current state of knowledge about how each of these classes of susceptibility alleles contributes to familial breast cancer and show information about their associated risks.

SATELLITE SYMPOSIUM

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THE ROLE OF FASLODEX IN ADVANCED BREAST CANCER MANAGEMENT PURSUING LONG TERM TREATMENT STRATEGY

Peter Schmid

Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, United Kingdom

DOSE INTENSITY AND THE IMPORTANCE OF FEBRILE NEUTROPENIA PREVENTION

Yeon Hee Park

Department of Hematology-Oncology, Samsung Medical Center, Korea

Myelosuppression is the most important dose-limiting factors in cytotoxic chemotherapy. Patients with severe neutropenia often develop clinically important complications, including an increased risk for opportunistic infections and sepsis. As a result, patients with early stage cancers may receive adjuvant chemotherapy at decreased relative dose intensity (RDI), which compromises treatment efficacy. In patients with advanced or recurrent cancers, severe infectious complications can be a major cause of morbidity and can deteriorate the quality of life. Combination chemotherapy such as AC and TAC (docetaxel, doxorubicin, and cyclophosphamide are standard of care for patients with high-risk early and advanced HER-2 negative breast cancers. However, implementation of these chemotherapeutic regimens in patient care has been limited by the high incidence of febrile neutropenia. Based on the clinical benefit of granulocyte-colony stimulating factor (G-CSF) in the prevention of febrile neutropenia and subsequent intravenous antibiotic treatment or hospitalization in these setting, prophylactic use of G-CSF is recommended by the guidelines of the American Society of Clinical Oncology, the European Organization for Research and Treatment of Cancer, and the National Comprehensive Cancer Network.

Filgrastim, a recombinant methionyl human granulocyte colony-stimulating factor (G-CSF) (rmetHuG-CSF), is efficacious in stimulating neutrophil production and maturation to prevent febrile neutropenia (FN) in response to chemotherapy. Because of its relatively short circulating half-life, daily filgrastim injections are required to stimulate neutrophil recovery. In an effort to develop a long-acting form of filgrastim, fusion of filgrastim to polyethylene glycol (PEG) was selected. Following extensive analysis of conjugation chemistries as well as in vitro and in vivo characterization of a panel of PEGylated proteins, a construct containing a 20 kDa PEG moiety covalently conjugated to the N-terminus of filgrastim was chosen for advancement as pegfilgrastim. Pegfilgrastim is primarily cleared by neutrophils and neutrophil precursors (rather than the kidneys), meaning that clearance from the circulation is selfregulating and pegfilgrastim is eliminated only after neutrophils start to recover. Importantly, addition of PEG did not alter the mechanism of action and safety profile compared to filgrastim.

In this lecture, clinical trials for pefilgrastim FN in patients receiving chemotherapy will be discussed comprehensively. In addition, recent approval of reimbursement of pegylated G-CSF by Korean insurance system will also be discussed.

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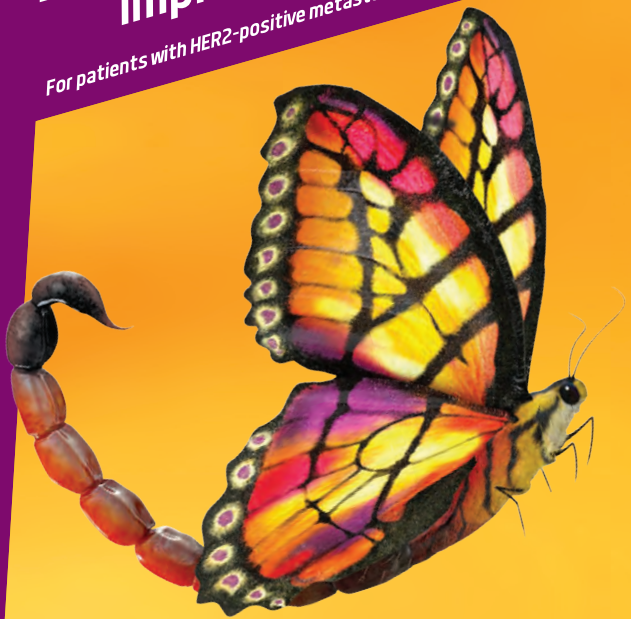

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- Developed disease recurrence during or within six months of completing adjuvant therapy

Reference 1. Barok et al. Trastuzumab emtansine: mechanisms of action and drug resistance. Breast Cancer Research 2014, 16:209 2. Verma S, et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. EMILIA Study Group. N Engl J Med. 2012;367:1783–179

Kadcyla(trastuzumab emtansine) Prescription drug (Ingredients) | Kadcyla 100mg: kwa(4334.8mg) main ingredients: trastuzumab emtansine 100mg, Kadcyla 160mg: kwa(6300.2mg) main ingredients: trastuzumab emtansine 129mg [PHARMACEUTICAL FORM] Powder for concentrate for solution for infusion, White to off-white lyophilised powder. [Therapeutic Indications] Kadcyla, as a single agent, is indicated for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: Received prior therapy for locally advanced or metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy. [Posology] The recommended dose of trastuzumab emtansine is 3.6 mg/kg bodyweight administered as an intravenous infusion every 3 weeks (21-day cycle). Patients should be treated until disease progression or unacceptable toxicity. The initial dose should be administered as a 90 minute intravenous infusion. Patients should be observed during the infusion and for at least 90 minutes following the initial infusion for fever, chills, or other infusion-related reactions. The infusion site should be closely monitored for possible subcutaneous infiltration during administration. If the prior infusion was well tolerated, subsequent doses of trastuzumab emtansine may be administered as 30 minute infusions. Patients should be observed during the infusion and for at least 30 minutes after infusion. The rate and severity of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms. Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions. Medicinal products to treat allergic/anaphylactic infusion reactions, as well as emergency equipment should be available for immediate use. Delayed or missed dose: If a planned dose is missed, it should be administered as soon as possible; do not wait until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The next dose should be administered in accordance with the dosing recommendations. Dose modification: Management of symptomatic adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of Kadcyla as per guidelines. Kadcyla dose should not be re-escalated after a dose reduction is made. Dose reduction schedule: Starting dose is 3.6 mg/kg). First dose reduction 3 mg/kg), Second dose reduction 2.4 mg/kg). Requirement for further dose reduction Discontinue treatment. Method of administration: Trastuzumab emtansine must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. It must not be administered as a bolus or intravenous push or bolus. The use of 0.20 or 0.22 micron in-line polyethersulfone (PES) filter is required for this infusion when the concentrate for infusion is diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion. [Special warnings and precautions for use] 1) In order to prevent medication errors it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Kadcyla (trastuzumab emtansine) and not Herceptin (trastuzumab). 2) Hepatotoxicity: Severe hepatotoxicity including liver failure and fatal outcomes has been reported. Concentrations of serum transaminases and bilirubin should be monitored prior to initiation of treatment and each dose. 3) Left ventricular dysfunction: Patients treated with trastuzumab emtansine are at increased risk of developing left ventricular dysfunction. LVEF should be measured before treatment initiation. The dose should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction. 4) Trastuzumab emtansine can cause foetal harm or death when administered to a pregnant woman. Contraindications: Hypersensitivity to the active substance or to any of the excipients. • Important Usage Notes 1. Administration for pregnant women, lactating women and fertile women 1) Contraception in males and females: Women of childbearing potential should use effective contraception while receiving trastuzumab emtansine and for 7 months following the last dose of trastuzumab emtansine. Male patients or their female partners should also use effective contraception. 2) Pregnancy: There are no data from the use of trastuzumab emtansine in pregnant women. Trastuzumab, a component of trastuzumab emtansine, can cause foetal harm or death when administered to a pregnant woman. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia, have been reported in pregnant women receiving trastuzumab. Animal studies of maytansine, a closely related chemical entity of the same maytansinoid class as DM1, suggest that DM1, the microtubule inhibiting cytotoxic component of trastuzumab emtansine, is expected to be teratogenic and potentially embryotoxic. Administration of trastuzumab emtansine to pregnant women is not recommended and women should be informed of the possibility of harm to the foetus before they become pregnant. Women who become pregnant must immediately contact their doctor. If a pregnant woman is treated with trastuzumab emtansine, close monitoring by a multidisciplinary team is recommended. 3) Breast-feeding: It is not known whether trastuzumab emtansine is excreted in human milk. Since many medicinal products are excreted in human milk and because of the potential for serious adverse reactions in breast-feeding infants, women should discontinue breast-feeding prior to initiating treatment with trastuzumab emtansine. Women may begin breast-feeding 7 months after concluding treatment. 4) Fertility. No reproductive and developmental toxicology studies have been conducted with trastuzumab emtansine. 2. Elderly patients: No dose adjustment is required in patients aged ≥ 65 years. There are insufficient data to establish the safety and efficacy in patients ≥ 75 years due to limited data in this subgroup. Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of trastuzumab emtansine. 3. Renal impairment: No adjustment to the starting dose is needed in patients with mild or moderate renal impairment. The potential need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data and therefore patients with severe renal impairment should be monitored carefully. 4. Hepatic impairment: No adjustment to the starting dose is required for patients with mild or moderate hepatic impairment. Trastuzumab emtansine was not studied in patients with severe hepatic impairment. Treatment of patients with hepatic impairment should be undertaken with caution due to known hepatotoxicity observed with trastuzumab emtansine. 5. Paediatric populations: The safety and efficacy in children and adolescents below 18 years of age have not been established as there is no relevant use in the paediatric population for the indication of metastatic breast cancer. Kadcyla leaflet 2016-04-26-R-4

MC2017001-4-002

- If a patient becomes pregnant while receiving Kadcyla or within 7 months following the last dose of Kadcyla, health care providers and patients should immediately report Kadcyla exposure to Roche Korea (02-3451-3600).
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This will allow Roche to understand more about the safety of Kadcyla and provide adequate information to health authorities, health care providers, and patients.
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RECENT INSIGHT INTO CLINIC FOR HER2+ mBC PATIENTS

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Approximately 1820% of invasive breast cancers are HER2-positive. Trastuzumab, the first developed anti-HER2 targeted agent, is the cornerstone in the treatment of HER2-positive metastatic breast cancer (MBC). In addition to trastuzumab, recently a several kinds of anti-HER2 targeted agents including lapatinib, pertuzumab and T-DM1 have been studied and actively used in real practice. Pertuzumab is also anti-HER2 targeted agent and has a different mode of action from trastuzumab in the point that it binds to epitope 4 and inhibits the dimerization of HER family. The CLEOPATRA, a randomized phase III trial was developed to evaluate the efficacy of pertuzumab combined with docetaxel plus trastuzumab (DH). In patients with HER2-positive MBC, the addition of pertuzumab to DH, significantly improved the median overall survival to 56.5 months, as compared with the addition of placebo (48.3 months, HR 0.68; 95% CI, 0.56-0.84; $P < 0.001$). Based on the CLEOPATRA, pertuzumab in addition to DH has been considered the standard of care in first-line therapy.

T-DM1, an antibody-drug conjugated, a complex compound obtained by the conjugation of trastuzumab and the potent maytansine-derived cytotoxic drug DM1, which is able to inhibit cell division and to induce cell death. In the EMILIA trial, T-DM1 significantly prolonged progression-free (PFS) (9.6 months vs. 6.4 months, HR 0.65; 95% CI, 0.55-0.77; $P < 0.001$) and overall survival (OS) (30.9 months vs. 25.1 months, HR 0.68; 95% CI, 0.55-0.85; $P < 0.001$) in the patients who failed trastuzumab and taxane, compared with lapatinib plus capecitabine. Based on the EMILIA trial, T-DM1 has been recommend in patients with HER2-positive breast cancer who failed trastuzumab and taxane.

Since dual anti-HER2 blockade showed the superiority to single anti-HER2 blockade in the CELOPATRA, the trial for dual anti-HER2 blockade without chemotherapy was studied. The MARIANNE trial was designed to compare T-DM1 vs T-DM plus pertuzumab vs taxane plus trastuzumab (TH) as first-line therapy. However, T-DM1 plus pertuzumab failed to improve OS compared with T-DM1 alone and TH (21.2 months in T-DM+pertuzumab, 20.7 months in T-DM1 and 12.5 months in TH).

The concept of continuum of trastuzumab has been generally accepted and recommended by most experts. Trastuzumab combined with a diverse kind of cytotoxic agents (navelbine, capecitabine and gemcitabine, etc) are used even if the patients previously received trastuzumab-containing chemotherapy. For example, in GBG26/BIG03-05 trial trastuzumab plus

capecitabine significantly improved PFS (8.2 months vs. 5.6 months, $p = 0.0338$) and response rate (48.1% vs. 27.0%, $p = 0.0068$) compared with capecitabine alone in even patients with HER2-positive breast cancer that progresses during treatment with trastuzumab. Besides trastuzumab plus chemotherapy, trastuzumab plus lapatinib also showed improvement of clinical outcomes in patients who had experienced progression on prior trastuzumab-based therapy in EGF104900. The concept of continuum of trastuzumab expanded to the use of continuum of another anti-HER2 targeted agents, T-DM1. The TH3RESA was developed to evaluate the efficacy of T-DM1 in patients who received 2 prior anti-HER2 targeted agents including trastuzumab and lapatinib. T-DM1 showed the prolongation of PFS (6.2 months vs. 3.3 months, HR 0.528; 95% CI, 0.42-0.66; $P < 0.0001$), compared with treatment of physicians choice. The improvement of PFS remained constant in the patients who received physician's choice containing trastuzumab.

Several anti-HER2 targeted agents have been used in various combinations and in various sequences. However, the best combination or the best sequences of anti-HER2 targeted agents have not been yet established. Therefore further clinical trials should be warranted to find the appropriate answers.

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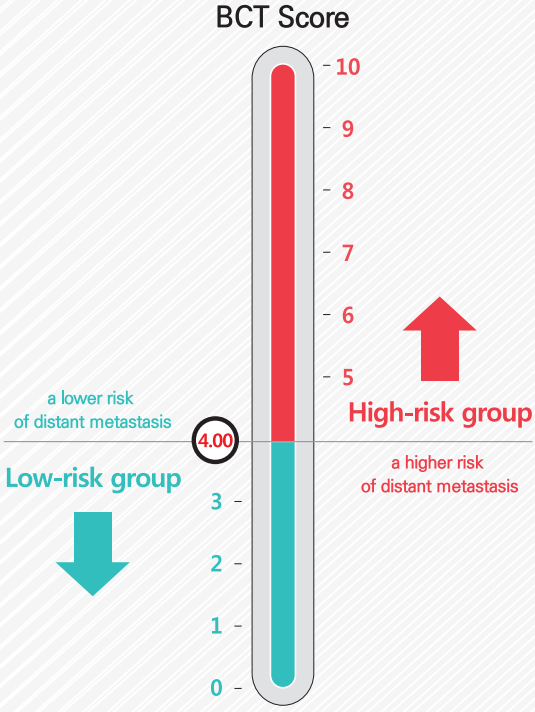

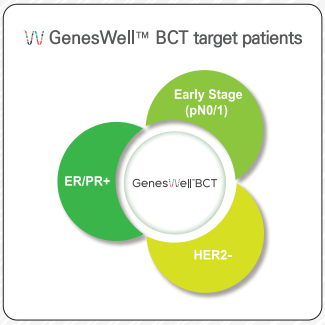

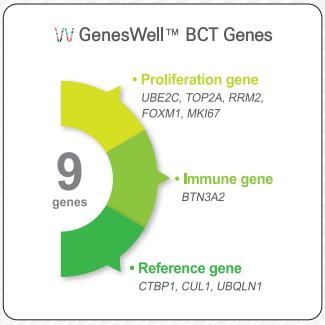

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PROGNOSTIC DIAGNOSIS FOR HR+/HER2- EARLY BREAST CANCER PATIENT BASED ON THE ALGORITHM THROUGH THE GENE EXPRESSION SIGNATURE

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Patients with HR+/HER2- early breast cancer have a higher risk of late recurrence beyond 5 years after primary hormone therapy than those with HR+/HER2+ or HR- breast cancer. For this population, accurate assessment of risk of recurrence beyond 5 years would be useful for decision-making in terms of whether to extend adjuvant hormone therapy or treat with adjuvant chemotherapy. Here, we developed and validated a new prognostic model for predicting the risk of distant metastasis in patients with pN0-N1, hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer treated with hormone therapy alone. RNA was extracted from formalin-fixed, paraffin-embedded (FFPE) tumor tissues and gene expression was measured by quantitative real-time reverse transcription-PCR. The relative expression of six novel prognostic genes was combined with two clinical variables (nodal status and tumor size) to calculate a risk score (BCT score). In the validation cohort treated with hormone therapy alone, the 10 year rate of distant metastasis in the high-risk group (26.3%) according to BCT score was significantly higher than that in the low-risk group (3.8%) ($P < 0.001$). Multivariate analysis adjusted for clinical variables revealed that BCT score is an independent predictor of distant metastasis. The BCT score outperforms prognostic models based on traditional clinicopathological factors (e.g., Nottingham Prognostic Index [NPI], SNAP and PREDICT) and predicts the risk of distant metastasis in patients with HR+/HER2- early breast cancer.

Several commercial assays based on expression of multiple genes in frozen or FFPE samples have been developed: the 70-gene prognostic signature MammaPrint, Oncotype DX, Prosigna (based on the PAM50 gene signature), EndoPredict test (EP). An immunohistochemical score (IHC4 score) based on expression of four markers (ER, PR, Ki-67, and HER2) provides prognostic information. However, these tests produce discordant results when used for risk assignment, and studies show that MammaPrint results are different in Asian breast cancer patients and patients from Europe. This suggests that the performance of the current commercial prognostic assays can be population-specific. Assays such as Oncotype DX or MammaPrint target ER+ breast cancer but do not discriminate between ER+/HER2- and ER+/HER2+ subtypes. Because adjuvant chemotherapy is of little benefit to patients at low risk of recurrence, this treatment is generally used for HR+/HER2- breast cancer patients considered at high risk of re-

currence or for those with an unfavorable prognosis due to low HR expression and high cell proliferation. By contrast, current treatment guidelines based on tumor size and nodal status recommend appropriate adjuvant chemotherapy in addition to hormone therapy and anti-HER2 therapy for many HR+/HER2+ cases. In this context, it is of particular importance to assess the benefit of chemotherapy for patients with HR+/HER2- breast cancer. However, currently available assays such as Oncotype DX are optimized to identify high-risk patients among ER+ early breast cancer cases and do not differentiate those with HR+/HER2- breast cancer. Therefore, there is an urgent clinical need to identify novel prognostic markers to better differentiate high- and low-risk patients with HR+/HER2- early stage breast cancer. (partially modified from Scientific Reports manuscript)

THE FIRST IN CLASS CDK4/6 INHIBITOR[1]

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- Letrozole as initial endocrine based therapy in postmenopausal women or
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Pre/perimenopausal women treated with the combination IBRANCE® plus endocrine therapy should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to local clinical practice standards.

IBRANCE® (palbociclib) + Letrozole[3]

mPFS 24.8 months

IBRANCE® (palbociclib) + Fulvestrant[4]

mPFS 9.5 months

Safety Information: Neutropenia was the most frequently reported adverse event in the clinical study and monitoring complete blood count is needed. Please refer to the Product Information for the dose modification related to neutropenia.

Study Design

• PALOMA2 : In double-blind, phase 3 study, patients were randomly assigned, in a 2:1 ratio, 666 postmenopausal women with ER-positive, HER2-negative breast cancer, who had not had prior treatment for advanced disease, to receive palbociclib plus letrozole (n=444) or placebo plus letrozole (n=222). The primary endpoint was progression-free survival, as assessed by the investigators. Secondary endpoints were overall survival, objective response, clinical benefit response, patient-reported outcomes, pharmacokinetic effects, and safety. Adapted from Finn RS, et al. N Engl J Med 2016;375:1925-36.

• PALOMA3 : In multicentre, double-blind, randomised phase 3 study, 521 women with HR-positive, HER2-negative metastatic breast cancer that had progressed on previous endocrine therapy were stratified by sensitivity to previous hormonal therapy, menopausal status, and presence of visceral metastasis. The primary endpoint was investigator-assessed progression-free survival. Secondary endpoints were confirmed objective response, clinical benefit, safety including type, incidence, and severity of adverse events. Adapted from Cristofanilli M, et al. Lancet Oncol 2016;17:425-39.

References 1. Dhillon S. Palbociclib: first global approval. Drugs 2015;75:543-51. **2.** IBRANCE® PRESCRIBING INFORMATION, 2016.08.29. **3.** Finn RS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375:1925-36. **4.** Turner NC, et al. Palbociclib + fulvestrant versus placebo + fulvestrant for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425-39.

IBRANCE® Capsules [COMPOSITION] Palbociclib 75 mg, 100 mg, 125 mg **[INDICATIONS]** IBRANCE® is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with: • letrozole as initial endocrine based therapy in postmenopausal women, or • fulvestrant in women with disease progression following endocrine therapy **[DOSAGE AND ADMINISTRATION]** The recommended dose of IBRANCE® is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. IBRANCE® should be taken with food. When co-administered with palbociclib, the recommended dose of letrozole is 2.5 mg taken once daily continuously throughout the 28-day cycle (Please refer to the registered information of letrozole). When co-administered with palbociclib, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter (Please refer to the registered information of fulvestrant). Patients should be encouraged to take their dose of IBRANCE® at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. IBRANCE® capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). Capsules should not be ingested if they are broken, cracked, or otherwise not intact. Pre/perimenopausal women treated with the combination IBRANCE® plus endocrine therapy should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to local clinical practice standards. **[PRECAUTIONS FOR USE]** 1. Warnings 1) Neutropenia: Neutropenia was the most frequently reported adverse event in clinical studies. Monitor complete blood counts prior to starting IBRANCE® therapy and at the beginning of each cycle, as well as on Day 14 of the first 2 cycles, and as clinically indicated. Dose interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia. Febrile neutropenia has been reported in about 1% of patients exposed to IBRANCE®. Physicians should inform patients to promptly report any episodes of fever. 2) Pulmonary Embolism: Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate. 3) Embryo-fetal Toxicity: Based on findings from animal studies and its mechanism of action, IBRANCE® can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IBRANCE® and for at least 3 weeks after the last dose. 2. Contraindications 1) Because of lactose contained in this drug, it should not be administered to the patients with hereditary problems of galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption.
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PP-IBR-KOR-0113-Mar 2017

ENHANCING ENDOCRINE THERAPY FOR HORMONE RECEPTOR - POSITIVE ADVANCED BREAST CANCER

Sung-Bae Kim

ASAN Medical Center, University of Ulsan College of Medicine, Korea

Endocrine therapy is the mainstay of treatment for hormone receptor positive (HR+) HER2 negative breast cancer. Patients with this HR+ metastatic disease may experience long disease control across several lines of endocrine therapy. The major limitation of this therapeutic approach is primary or acquired resistance. A better understanding of endocrine resistance has resulted in newer targeted agents to be added to endocrine therapy.

It is believed that the mTOR antagonist everolimus in combination with the AI exemestane and recently, CDK 4/6 inhibitors has evolved to become a valuable addition to the therapeutic options in metastatic breast cancer, based on available data regarding activity and tolerability,

Combining endocrine therapy with agents targeting putative mechanisms of endocrine resistance is a newer treatment paradigm in HR+ breast cancer, including inhibitors of PI3K, Akt, HDAC, Src, IGFR-1, and FGFR. Adding a biologically targeted agent to endocrine therapy results in improved response rate, and clinical benefit rate, and prolonged progression-free survival. A clear advantage in overall survival has not yet been reported. Combination therapy allows to delay chemotherapy but increases toxicities and costs, which are critical factors in decision making in the clinical practice. Appropriate clinical trial design and patient selection based on prior therapy exposure, together with predictive biomarkers derived through real-time molecular profiling, are needed to enrich future trials and maximize any additional benefit that co-targeting may bring to current endocrine therapies for estrogen receptorpositive breast cancer.

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NURSING SESSION

Global Breast Cancer Conference

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SURVIVORSHIP ISSUES OF THE METASTATIC, RECURRENT AND INTRACTABLE BREAST CANCER

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Background: Breast cancer is known for its relatively high survival rate compared to other solid tumors. As the number of breast cancer survivors has increased, their survivorship issues have been highlighted and emphasized. However, only limited information is available for Korean patients, and healthcare providers often miss out on what their actual care needs are. As a healthcare provider, it is important to convey valid information and provide appropriate health education for patients. The purpose of this presentation is to analyze and synthesize survivorship issues of metastatic, recurrent, and intractable breast cancer and to propose directions for patient care.

Methods: The presentation is based on (a) an integrated literature review using multiple databases and (b) publications of official health parties, including the Korean Breast Cancer Society, the American Cancer Society, and the U.S. National Cancer Institute. First, previously reported survivorship issues are concisely summarized. Based on the discussion of these issues, direction for patient encounter and care are proposed.

Result: Three themes were identified: (1) suffering from the lingering symptoms of cancer treatment (e.g., vasomotor symptoms, neuromusculoskeletal pain, fatigue, and impaired sexuality); (2) managing conditions acquired from the treatment (e.g., cardiac toxicity, weight gain, cognitive changes, and increased risk of osteoporosis or other cancers); and (3) experiencing complex emotions (e.g., concerns regarding child bearing, feeling sorry and guilty in relation to family members, becoming obsessive in terms of lifestyle, and fear of disease progression). Based on these themes, five suggestions for breast cancer survivorship care were proposed: (1) providing individualized treatment and a follow-up plan; (2) providing evidence-based health education and preventing follow-up loss; (3) delivering collaborative care with multi-providers (e.g., gynecologist, cardiologist, and psychiatrist); (4) implementing a comprehensive interdisciplinary team approach (e.g., nutritionists and physical therapists); and (5) emphasizing the necessity of further efforts (e.g., qualitative nursing research and utilizing health informatics).

Conclusions: Breast cancer survivors confront complex changes from cancer treatments. These changes affect every aspect of their lives, including the physical, psychological, social, and spiritual domains. This presentation introduced survivorship issues through three themes and made five suggestions for better care. As a healthcare provider, understanding the issues impacting breast cancer survivors as well as the priority concerns will contribute to enhancing communication with survivors, the provision of adequate care, and an improvement in their quality of life.

NURSING CARE IN BONE METASTASIS

Hyejin Cho

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Bone metastasis is the most common site of the recurrence in metastatic breast cancer. About 70% of breast cancer patient who have a relapse disease develop bone metastasis. Mostly bone metastasis occurs at axial skeleton. Osteolytic metastasis occurs more than osteoblastic metastasis in breast cancer. Complication of bone metastasis is pain, pathologic fractures, spinal cord compression, hypercalcemia and bone marrow suppression. Treatment of bone metastasis is anti-tumor agent, radiotherapy, osteopedic surgery and bone-directed therapy. Bone-directed therapy is used bisphosphonates and RANKL inhibitor. They improve patient's quality of life. But side effect is flu-like symptoms, nephrotoxicity, hypocalcemia and Osteonecrosis of the jaw. Therefore, nurses need a understanding of bone metastasis and managing the side effect.

NURSING CARE IN VISCERAL METASTASIS

Seung Hee Seon

Department of Nursing Service, Korea University Guro Hospital, Korea

Breast cancer is the second common in Korean women. Although patients initially diagnosed with metastatic breast cancer account for less than 5% of all breast cancer patients, about 40% of patients receiving curative treatment recur. Major site of metastasis of breast cancer are bone, lung, liver and brain. Visceral metastasis are metastasis to internal organs(liver, lungs, and pleura).

The decision for treatment of metastatic breast cancer is made with regard to the metastasis site (bone or Visceral organs), the performance status of patients, age, Hormone receptor status and Her-2 status. Chemotherapy and combined therapy are given frequently in patients with visceral metastasis. Commonly used chemotherapeutic agents for patients with metastatic breast cancer are Anthracycline, Paclitaxel, Docetaxel, Gemcitabine, Vinorelbine, Eribuline and Capecitabine. Target agents are Trastzumab, Pertuzumab and Lapatinib.

Common side effects of chemotherapy are nausea/vomiting, alopecia, bone marrow suppression and peripheral neuropathy. A Nurse who takes care of MBC patients should actively assess and manage symptoms to relieve symptoms and improve quality of life.

1) Nausea/Vomiting: Nausea and vomiting are two of the most feared side effects of chemotherapy. Prevention of chemotherapy induced nausea and vomiting is the ultimate goal. It is important to use appropriate antiemetics depending on the emetogenicity of the chemotherapeutic agents.

2) Alopecia: Alopecia ranks as one of the most distressing treatment related side effect. It is the responsibility of Oncology Nurses to understand the significance that hair loss has for patients and help them to prepare for this loss. The plan of care must include taking the time to understand the emotional impact and assisting in planning interventions to minimize this emotional impact.

3) Bone marrow suppression: Myleosuppression is a common, complex and often serious consequence of chemotherapy. It includes anemia, thrombocytopenia and neutropenia. Nurses can anticipate the need for potential interventions for developing myelosuppression and proactively intervene through patient education and astute nursing assessment.

4) Peripheral neuropathy: PN is a dysfunction in the peripheral nerve system and can cause pain, numbness, burning, and tingling. Nurses should be well informed of the risk factors, pathophysiology, assessment, prevention, and treatment of PN. Appropriated counseling and teaching patients and care givers about PN will be improve the QOL of them.

SPECIALIST NURSING ROLES FOR THE PATIENT WITH METASTATIC, RECURRENT AND INTRACTABLE BREAST CANCER

Su Jin Lee

Dankook University Hospital, Korea

Breast cancer is the most commonly diagnosed cancer in women and remains the leading cause of death from cancer in women. Early detection and improvements in adjuvant treatments are decreasing mortality rates in women diagnosed with early breast cancer. However, as many as a third of these women will develop and die from metastatic, recurrent and intractable breast cancer. Likewise it has a high survival rate of 91% in Korea, it has been reported that recurrence and metastasis are 20–30% after diagnosis 10 years due to the slow growth rate of cancer cells.

We know that a metastatic, recurrent and intractable breast cancer patients need specific physical and emotional management. In response to needs of these breast patients, special nursing roles have started to emerge. The role requires specialized skills and knowledges about each patients who are in special condition.

In this section, we will overview that the information, and supporting tips you need when you manage special condition breast cancer patients who has diagnosed with recurred or intractable breast cancer. You will find information about treatment options for recurrent and metastatic breast cancer, palliative care, living with metastatic breast cancer. We hope that these information can show you an option when you care these breast cancer patients.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

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Although the mortality rates for breast cancer patients have improved over the last decade, the loss of breast cancer patients as a result of metastatic or recurrent has remained constant. All patients with metastasis or recurrence will likely have problems with symptoms related to organ involvement, treatment, or both that affect their quality of life. The fact that metastatic or recurrent breast cancer can involve virtually any organ and the myriad of treatment options available frequently make management challenging. The goal of any treatment in this situation is disease control, palliation of symptoms, and maintenance of the highest quality of life.

Cancer patients take a wide range of complementary and alternative medicines (CAM). Recently, Complementary and integrative medicine (CIM) is a new term that is now replacing the term CAM. This includes approaches to complement services or alternatives to mainstream health care interventions. Integrative medicine refers to health care that incorporates complementary therapies with more conventional approaches, such as acupuncture or meditation. In other words, it reflects the integration of the best conventional health care with evidence-based complementary modalities such as acupuncture, massage, mind-body medicine, nutrition and nutritional supplements, and other modalities. Therefore, CIM can make regarding the use of relaxation and meditation to improve emotional well being and ease cancer pain, and exercise to reduce fatigue and improve emotional well being among cancer patients.

Currently, metastatic breast cancer is largely considered to be incurable, and the goals of treatment are generally palliative. Palliative care focuses on symptom management regardless of where the patient is in the cancer continuum. Managing symptoms to maintain an optimum quality of life is the major goal of care in the metastatic setting. Moreover, Integrating palliative care has become more important because patients can live with metastatic or recurrent disease for long periods of time.

Many symptoms in the metastatic breast cancer occur based on the site of metastasis or together with fatigue, depression, insomnia, and pain, among the most common. Whereas declining sexual function was the most frequently reported symptom, worry was the most severe symptom and pain was the most distressing symptom. Also, the most reported unmet supportive care needs in patients with metastatic breast cancer were psychological support, counseling, and adequate information concerning: things they could do themselves to help feel better, which member of the health care provider was available for communication, the status of their

cancer, an explanation of test results, the risks and benefits of treatment, and how to obtain access to counseling.

When breast cancer recurs or metastasis, the goals of treatment often shift from one of cure to controlling the disease for as long as possible while palliating symptoms interfering with the patients functional status and quality of life. This requires ongoing discussions with the patient and family about the goals of care. Balancing the side effects of treatment with potential control of the disease and symptom relief must be evaluated with every change in status.

The management of symptoms in women with metastatic breast cancer is challenging and is frequently made even more so by the potentially dire additive effects of tumor-related organ dysfunction and treatment toxicity. Although incurable, maintaining the highest quality of life while optimizing disease control should be the mainstay of care. Complementary and alternative therapies may help patients to cope with treatment side-effects and disease symptoms, and contribute to patients psychological well-being and quality of life.

INVITED ORAL PRESENTATION

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SUBGROUP ANALYSIS OF ASIAN POPULATION AMONG PALOMA-2 TRIALS

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Palbociclib is an orally active selective inhibitor of the CDK 4/6 growth signal that blocks cell proliferation and cellular division. The PALOMA-2 trial assessed the safety and efficacy of the combination of palbociclib and letrozole as first line therapy for postmenopausal women with HR+/HER2- advanced breast cancer. Results showed that the combination of palbociclib and letrozole significantly extended progression-free survival (PFS) by more than 11 months compared with letrozole plus placebo. In the sub-analysis of the PALOMA-2 trial, investigator-assessed the safety, efficacy, and patient-reported outcomes (PROs) of palbociclib plus letrozole in Asians in the study. Of 666 enrolled postmenopausal women with ER+/HER2– breast cancer, 95 were Asian. Patients were randomized 2:1 to receive palbociclib plus letrozole or placebo plus letrozole. Median PFS in Asian patients was significantly longer in the palbociclib plus letrozole vs. the placebo plus letrozole arm (25.7 months [95% CI, 19.2–not estimable] vs. 13.9 months [7.4–22.0]; hazard ratio = 0.55 [95% CI, 0.30–1.00]; $p = 0.0239$). The most common adverse events among patients receiving palbociclib were hematologic which were more common among Asian vs. non-Asian patients: neutropenia (any grade: 95.4% vs. 76.8%; grade 3/4: 89.2% vs. 62.5%), leukopenia (any grade: 43.1% vs. 38.3%; grade 3/4: 32.3% vs. 23.5%), anemia (any grade: 24.6% vs. 24.0%; grade 3/4: 6.2% and 5.3%), and thrombocytopenia (any grade: 27.7% vs. 13.5%; grade 3/4: 4.6% vs. 1.1%). Discontinuations due to adverse events were similar among Asian and non-Asian patients in the palbociclib plus letrozole arm (10.8% and 9.5%). No Asian patients had febrile neutropenia. In Asian patients, there were no significant differences between treatments in changes from baseline in breast cancer-specific quality of life and general health status scores. As observed in the overall study population, addition of palbociclib to letrozole significantly improved PFS in Asian patients enrolled in PALOMA-2, with an increase in myelosuppression manageable with supportive care while maintaining quality of life.

FIRST-LINE RIBOCICLIB + LETROZOLE IN POSTMENOPAUSAL ASIAN WOMEN WITH HORMONE RECEPTOR-POSITIVE (HR+), HER2-NEGATIVE (HER2-) ADVANCED BREAST CANCER (ABC): A SUBGROUP ANALYSIS OF MONALEESA-2

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Background: 23% of breast cancer cases are diagnosed in Asia. Endocrine therapy resistance occurs in most patients with HR+ ABC. In MONALEESA-2 (NCT01958021), ribociclib (LEE011; cyclin-dependent kinase inhibitor) + letrozole significantly improved progression-free survival (PFS) vs. letrozole alone in patients with HR+, HER2- ABC (hazard ratio [HR] = 0.556; 95% CI: 0.429-0.720; $p = 0.00000329$). Here we present results from patients treated in Asia.

Methods: Postmenopausal women (N = 668) with HR+, HER2- ABC with no prior systemic therapy for ABC were randomized 1:1 to ribociclib (600 mg/day; 3-weeks-on/1-week-off) + letrozole (2.5 mg/day; continuous) or placebo + letrozole. Primary endpoint: locally-assessed PFS; subgroup analysis evaluated patients in Asia.

Result: MONALEESA-2 enrolled 68 patients (10%) in Asia (ribociclib vs. placebo; 35 vs. 33) and 600 patients (90%) outside Asia (299 vs. 301). At data cut-off (January 29, 2016), 9 (26%) vs. .21 (64%) patients (ribociclib vs. placebo) in Asia had discontinued treatment, most commonly due to progressive disease (7 [20%] vs. 20 [61%] patients). Grade 3/4 adverse events (≥ 10% patients; ribociclib vs. placebo) in patients in Asia: neutropenia (71% vs. 0%) and leukopenia (14% vs. 0%); in patients outside Asia: neutropenia (58% vs. 1%), leukopenia (22% vs. 1%), hypertension (11% vs. 11%), and liver enzyme elevations (10% vs. 3%). Ribociclib + letrozole significantly prolonged PFS in patients in Asia (HR = 0.298; 95% CI: 0.134-0.662) and outside Asia (HR = 0.602; 95% CI: 0.457-0.792).

Conclusions: Ribociclib + letrozole significantly prolonged PFS vs. placebo + letrozole with an acceptable safety profile in postmenopausal women with HR+, HER2- ABC treated in Asia.

BREAST MRI MONITORING FOR YOUNG BREAST CANCER PATIENTS AFTER BREAST CONSERVATION THERAPY: A MULTICENTER PROSPECTIVE STUDY

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Purpose: To compare outcomes of a combined mammography and magnetic resonance imaging (MRI) or ultrasound screening in women who had received breast conservation therapy (BCT) for breast cancer at age ≤ 50 years.

Methods: In a prospective multi-institutional study, 754 women ≤ 50 years after BCT for breast cancer underwent 3 annual screening rounds using mammography, ultrasound, and MRI with independent interpretation of imaging. Screening outcomes between each image modality and their combinations in the first round and subsequent rounds were compared using Rao and Scott's adjusted chi-square test or generalized estimating equations.

Result: Seventeen (2.3%) cancers were diagnosed, and the majority were stage 0 or 1 (76.5%, 13/17). In the first screening round, sensitivity (100% vs. 58.3%; $p = 0.016$) and cancer detection rate (CDR) (16.0 vs. 9.3 per 1,000; $p = 0.073$) of mammography with MRI was higher than mammography alone. In the subsequent screening rounds, sensitivity (100% vs. 40%; $p = 0.180$) and CDR (3.8 vs. 1.5 per 1,000; $p = 0.158$) were not significantly different from that of mammography alone. After the addition of ultrasound, no difference was found in the sensitivity and CDR compared with mammography alone (all $p > 0.05$). The specificity (83.5% or 82.8% vs. 94.3%; $p < 0.001$ and 90.9% or 93.1% vs. 96.9%; $p < 0.001$) of mammography with MRI or ultrasound was lower than that of mammography alone. No interval cancer was found.

Conclusions: Addition of MRI to mammography screening improved the detection of early-stage breast cancers at an acceptable specificity in women who had BCT at age ≤ 50 years. These results can inform the decision-making process for screening methods after BCT.

A PROSPECTIVE, RANDOMIZED, MULTICENTER, OPEN-LABEL PHASE III NEOADJUVANT STUDY TO COMPARE CHEMOTHERAPY WITH ENDOCRINE THERAPY IN PREMENOPAUSAL PATIENTS WITH HORMONE RECEPTOR POSITIVE, HER2 NEGATIVE BREAST CANCER

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In the next decade, personalized medicine will likely become an important aspect of breast cancer therapy and to include strategies to avoid chemotherapy in an oncologically safe way, which is currently a major challenge for hormone-responsive breast cancer. For younger patients, the fear of breast cancer encompasses not only the breast cancer itself, but also the treatment of breast cancer. Chemotherapy causes changes in appearance and life patterns, and also presents fertility issues to younger women.

For hormone-responsive breast cancer, the question of who can safely be spared adjuvant chemotherapy has been extensively studied. The findings of such studies have formed the basis for decision making when considering systemic adjuvant therapy. For cases of hormone receptor-positive tumors, younger patients show a poorer prognosis than older patients for tamoxifen resistance. However, this finding does not indicate that young patients should receive chemotherapy. The larger impact of chemotherapy in younger patients is likely to be partially explained by the endocrine effects of chemotherapy on ovarian function. Irrespective of the chemotherapy agent administered, iatrogenic amenorrhea can increase the survival rate for ER-positive breast cancer and amenorrhea is a surrogate marker for effective treatment in hormone receptor-positive young breast cancer patients. This finding suggests that irrespective of chemotherapy or endocrine therapy, amenorrhea is important for premenopausal patients who have an ER-positive, HER2-negative tumor. A few well characterized prognostic tests can identify patients with a low risk profile, thereby justifying the omission of chemotherapy based on its potentially low benefit. A number of clinical trials, such as TAILORx, RxPonder, MINDACT, NNBC-3, and WSG plan B, are currently underway to address this question (for example, the Daniel Hofmann et al trials).

Treatment decisions based on demographic characteristics and tumor burden have the potential to over-treat many individuals and under-treat others. The Oncotype DX assay has been studied for lymph node-positive breast cancer patients, and the SWOG 8818 study reported that the low-risk Oncotype DX group showed no additional benefits from chemotherapy. As

presented at the 2014 ASCO meeting, SOFT and TEXT joint analysis showed excellent survival data that included lymph node-positive, ER-positive breast cancer patients who received endocrine therapy alone. These findings suggested that not all lymph node-positive, ER-positive, HER2-negative tumors necessitate chemotherapy. Apart from tumor burden, identifying robust biological predictors of benefit are likely to be informative and useful. It has been shown that endocrine therapy, which can substitute for chemotherapy even though there is a high tumor burden in hormone-responsive breast cancer, is effective. The factors that determine chemotherapy sensitivity remain poorly understood, and might not entirely overlap with negative predictors of endocrine sensitivity or prognostic determinants.

Neoadjuvant treatment has benefits, which include reducing the tumor burden and evaluating the treatment response while the tumor is in the body. The response to neoadjuvant chemotherapy is diverse and varies according to the intrinsic subtype. ER-positive, HER2-negative breast cancer shows a reduced pCR rate, but better survival compared to other subtypes. Moreover, pCR is not related to survival in the luminal A subtype. Therefore, the goal of neoadjuvant treatment for hormone-responsive tumors is to evaluate the treatment effects and to reduce the tumor size prior to treatment, even though it can rarely achieve pathological CR. Neoadjuvant endocrine therapy has been mostly studied for postmenopausal breast cancer patients in comparison with tamoxifen and aromatase inhibitors. Semiglazov et al compared neoadjuvant endocrine therapy and chemotherapy for postmenopausal breast cancer patients and found a similar clinical response between the two groups. Recently, the STAGE study was conducted for premenopausal breast cancer patients that compared GnRHa with tamoxifen and GnRHa with an aromatase inhibitor. However, no clinical trial has yet compared neoadjuvant chemotherapy with neoadjuvant endocrine therapy for premenopausal patients.

We therefore designed and initiated a phase III clinical trial to compare the neoadjuvant response of chemotherapy with endocrine therapy in premenopausal women with ER-positive, HER2-negative, lymph node-positive breast cancer. We constructed this study to determine the response rate and response pattern of both treatments.

Methods/Design

ER-positive, HER2-negative, and lymph node-positive premenopausal breast cancer patients will be randomized to either 24 weeks of neoadjuvant chemotherapy with adriamycin plus cyclophosphamide (AC) followed by taxane (T) or neoadjuvant endocrine therapy with zoladex and tamoxifen. The target patient accrual number is 145 per arm. The primary endpoint is the clinical response rate, as measured by calipers and MRI. Secondary endpoints include the pathological complete response rate, changes in Ki-67 expression, the rate of conservation surgery, and quality of life.

ORAL PRESENTATION

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POTENTIAL APPLICATION OF GUGGULSTERONE AS A NOVEL ANTAGONIST OF CXCR4 EXPRESSION IN TRIPLE-NEGATIVE BREAST CANCER

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Background: Breast cancer is a complex and heterogeneous disease with respect to histology, mutations, metastatic potential, disease progression, therapeutic response and clinical outcome. Triple-negative breast cancer (TNBC), defined as ER-negative, PR-negative and lacking overexpression of HER2, is an aggressive breast cancer subtype with high rate of proliferation and metastasis, as well as poor prognosis for advanced-stage disease. Despite recent advances in targeted therapies, patients with TNBC continue to have poor survival and early metastasis compared to other types of breast cancer, highlighting urgency to identify novel therapeutic targets. Recent studies have suggested antagonists to the chemokine receptor CXCR4 (C-X-C chemokine receptor-4) may abrogate the invasive phenotype of breast cancer. Specifically for TNBC breast cancer, high CXCR4 overexpression in TNBC specimens predicts a worse outcome. Since there is currently no targeted treatment for patients with TNBC, understanding molecular mechanism of the CXCR4 signaling pathway in this subtype of breast cancer may lead to development of target-specific therapy.

Methods: The anti-cancer effects of guggulsterone were analyzed by a wide variety of molecular biology techniques in breast cancer cells as well as in breast cancer mouse model.

Result: Guggulsterone isolated from Commiphoramukul has been demonstrated to reverse MDR (Multi-drug resistance) through inhibiting function and expression of P-glycoprotein and our data suggests that this steroid can inhibit migration, invasion and circumvent chemoresistance in TNBC cells as well as modulate tumor growth in breast cancer mouse model.

Conclusions: Guggulsterone is a novel antagonist for CXCR4 expression that may exert its anticancer effects through modulation of diverse oncogenic signaling cascades in TNBC.

A RADIOSENSITIVITY GENE SIGNATURE AND PD-L1 STATUS PREDICT CLINICAL OUTCOME OF PATIENTS WITH INVASIVE BREAST CARCINOMA IN THE CANCER GENOME ATLAS (TCGA) DATASET

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Background: We investigated the link between the radiosensitivity gene signature and programmed cell death-ligand 1 (PD-L1) status and clinical outcome.

Methods: We validated the identified gene signature related to radiosensitivity and analyzed the PD-L1 status of invasive breast cancer in The Cancer Genome Atlas (TCGA) dataset. To validate the gene signature, 1,065 patients were selected and divided into two clusters using a consensus clustering algorithm based on their radiosensitive (RS) or radioresistant (RR) designation according to their prognosis. Patients were also stratified as PD-L1-high or PD-L1-low based on the CD274 mRNA expression level.

Result: Patents assigned to the RS group had better 5-year recurrence-free survival (RFS) rate than patients in the RR group by univariate analysis (89% vs. 75%, $p = 0.017$) only when treated with RT. The RS group was independently associated with the PD-L1-high group, and CD274 mRNA expression was significantly higher in the RS group ($p < 0.001$) than the RR group. In the PD-L1-high group, the RS group had better 5-year RFS rate compared to the RR group (89% vs. 72%, $p = 0.015$), this difference was also significant by Cox-hazard proportional analysis.

Conclusions: We first evaluated the predictive value of the radiosensitivity gene signature following adjuvant RT for invasive breast cancer patients in the TCGA and described a relationship with this radiosensitivity gene signature and PD-L1. The radiosensitivity gene signature and PD-L1 were important factors for prediction of the clinical outcome of RT in patients with invasive breast cancer and may be used for selecting patients who will benefit from RT combined with anti-PD1/PD-L1 therapy.

INTERPLAY BETWEEN MEVALONATE AND HIPPO PATHWAYS REGULATES DDX20 VIA YAP IN INVASIVE BREAST CANCERS

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Background: Statin, the widely used cholesterol-lowering drug, has been reported to exhibit pleiotropic functions, including anti-tumor activity. Despite notable evidence for statins as an anti-tumor agent, clinical trials have demonstrated controversial results in breast cancer patients. A likely reason is the lack of biomarkers to identify responsive patients. In this study, we investigated using DDX20, an oncogene recently uncovered by our group, as a biomarker for statin response in breast cancer.

Methods: We first assessed correlation between mevalonate pathway genes and DDX20 in 1325 breast tumors and employed various assays to validate DDX20 is a biomarker for statin response. In vivo, a mouse model was used. To examine if statin-induced downregulation of DDX20 is translated to patients, we obtained tissues from a window-of-opportunity clinical trial where breast cancer patients were administered simvastatin.

Result: A positive correlation between DDX20 and the mevalonate pathway genes was observed. All in vitro, in vivo and clinical data showed that simvastatin decreased DDX20 expression and breast cancers with high DDX20 are more responsive to statin. Our immunoprecipitation data indicated a direct interaction between DDX20 and YAP. Moreover, we observed increased DDX20 level upon YAP overexpression and patients with higher YAP expression showed higher expression of DDX20, suggesting DDX20 could be a novel YAP target.

Conclusions: Our study demonstrated that DDX20 is a biomarker for statin response in breast cancer and the mechanism involving crosstalk with hippo pathway. Potential application is a combinatorial therapeutic using statins to suppress DDX20 and a first-line agent to treat invasive breast cancer.

CO-EXISTENCE OF DUCTAL CARCINOMA WITHIN PHYLLODES TUMOR-A REVIEW OF 557 PHYLLODES TUMORS FROM A TWENTY-YEAR REGION-WIDE DATABASE IN HONG KONG AND SHENZHEN, CHINA

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Background: Phyllodes tumor (PT) is an uncommon breast tumor arising from the stromal component of the breast, co-existence of ductal carcinoma in-situ (DCIS) or invasive ductal carcinoma (IDC) is even a rare occurrence. To the best of our knowledge, there were only seventeen reported cases of ductal carcinoma arising from PT in the literature.

Methods: Retrospective review on two prospectively-maintained databases was performed. We identified 557 patients who were treated for PT in five government hospitals in Hong Kong and in Shenzhen, China from January 1997 to February 2016, pathology slides were retrieved for review by two pathologists. Fisher-exact and Chi-square tests were performed to evaluate the statistical correlation.

Result: Three hundred sixty three (65.2%) patients had benign PT, 130 (23.3%) had borderline PT and 64 (11.5%) had malignant PT. Six (1.1%) patients were identified for having co-existing ductal carcinoma within the PT. Four patients were from Hong Kong and 2 were from Shenzhen. Median age was 48 year-old (range 25-54). Ductal carcinoma occurs more frequently in malignant PT than in benign or borderline PT (4.7% vs. 0.6%) ($p = 0.02$). However, malignant PT is not associated with advanced DCIS grade ($p = 0.1$). All patients underwent surgery with clear resection margin. After median follow-up interval of 70 months (Range 2 months 101 months), none of these six patients developed disease recurrence.

Conclusions: This study revealed six additional cases to the current knowledge of ductal carcinoma arising from PT. Malignant PT is associated with the presence of co-existing ductal carcinoma.

RANDOMIZED PHASE III TRIAL OF IRINOTECAN COMBINED WITH CAPECITABINE VERSUS CAPECITABINE IN PATIENTS WITH METASTATIC BREAST CANCER (MBC) PREVIOUSLY TREATED WITH ANTHRACYCLINE AND TAXANES - PROCEED TRIAL -

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Background: We investigated whether the combination of irinotecan plus capecitabine improved progression free survival (PFS) compared with capecitabine alone in patients with HER2 negative MBC previously exposed to anthracyclines and taxanes.

Methods: A total of 211 patients were assigned by randomization strata of hormone receptor status and presence of visceral metastasis to irinotecan (80mg/m^2 on D1 and D8) and capecitabine (1,000 mg/m^2 bid on D1 to D14) or capecitabine alone (1,250 mg/m^2 bid on D1 to D14) every 3 weeks. The primary objective was PFS; secondary objectives included overall response rate, overall survival and safety. Quality of life (QoL) was assessed using EORTC-QLQ-C30 questionnaires both at the baseline and every other cycles of treatment.

Result: Both arms were well balanced. There was no significant difference in PFS between the combination and capecitabine monotherapy arm (median, 6.6 vs. 5.3 months; HR = 0.87; 95% CI, 0.65 to 1.16; $p = 0.33$). In patients with triple negative breast cancer (N = 87), the combination treatment significantly improved PFS (median, 4.8 vs. 2.8 months; HR = 0.59; 95% CI, 0.37 to 0.94; $p = 0.03$). Overall response rate was higher in the combination arm though it did not reach statistical significance (42.7% vs. 29.6%, $p = 0.06$). Overall survival did not differ between two groups (median, 26.4 vs. 20.4 months; $p = 0.47$). Grade 3 or 4 neutropenia occurred in 39.6% in the combination arm and 10% in the monotherapy arm. Hand-foot syndrome (≥

grade 2) was more common in the monotherapy arm (23.0% vs. 12.6%). QoL measurements in global health status was similar between two groups at every time points. However, patients in the combination arm showed significantly worse symptom scales especially in nausea/vomiting and diarrhea ($p < 0.05$).

Conclusions: Irinotecan plus capecitabine did not demonstrate superior clinical activity in heavily treated HER2 negative Metastatic Breast Cancer (MBC) patients. QoL data showed similar global health status in both arms, while several symptom scales were much higher in the combination arm. The role of adding irinotecan to capecitabine in triple negative breast cancer remains to be elucidated.

DETECTION OF SPLICEOMIC SIGNATURES FOR PREDICTING ENDOCRINE RESISTANCE IN ESTROGEN RECEPTOR-POSITIVE BREAST CANCER

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Background: Estrogen receptor (ER)-positive breast cancers are relatively indolent biologically. Yet, up to 25% of these tumors develop endocrine resistance. Alternative splicing events are observed in almost every hallmarks of cancer, implying that dysregulation of splicing and cancer progression are closely related. The purpose of this study was to detect phenotype-specific splice variants and to discover spliceomic signatures related to endocrine resistance in ER-positive breast cancer.

Methods: Whole transcriptome sequencing data from 57 ER-positive invasive breast cancers were analyzed. Splice variants of 96 ESR1 pathway-related genes were detected using a data-mining algorithm recognizing spliceomic heterogeneity. A differential analysis of splice variants between 25 endocrine therapy-resistant and 32 endocrine therapy-responsive patients was performed. Isoforms related to endocrine resistance was analyzed using RNA sequencing data of ER-positive patients (52 resistant, 412 responsive) who received endocrine therapy from TCGA database.

Result: Six isoforms with highest statistical significance were detected in ESR1 pathway-related genes KRAS, CREB1, KCNJ5, PIK3R3, ITPR2, and MAP2K1. KRAS, CREB1, PIK3R3, MAP2K1 are genes known to independently activate the estrogen signaling pathway in the presence of ER blockage. A differential analysis using TCGA database showed significant difference in ITPR2 (4.28% vs. 3.16%, accuracy 0.777, *p*-value 0.041) and MAP2K1 (1.59% vs. 0.21%, accuracy 0.88, *p*-value 0.049).

Conclusions: Phenotype-specific splice variants can be detected using transcriptome sequencing data. Splice variants in KRAS, CREB1, KCNJ5, PIK3R3, ITPR2, and MAP2K1 are potential spliceomic signatures that may be used to predict endocrine therapy-resistant breast cancer. Further investigation is warranted to validate the role of splice variants as a biomarker for endocrine resistance.

INHERITED MUTATIONS IN BRCA1 AND BRCA2 IN AN UNSELECTED MULTI-ETHNIC COHORT OF ASIAN BREAST CANCER PATIENTS AND HEALTHY CONTROLS FROM MALAYSIA

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Background: To ascertain the contribution of germline alterations in BRCA1 and BRCA2 in an unselected cohort of Asian breast cancer patients and healthy controls.

Methods: Two thousand and ninety-two invasive breast cancer patients and 2,815 healthy controls were included into our study. Amplicon-based targeted sequencing of exonic and proximal splice site junction regions of 31 known and probable breast cancer susceptibility genes were performed on Fluidigm Access Array system, with sequencing conducted on Illumina HiSeq2500 platform. Variant calling was performed as per GATK recommended best practices and were validated with Sanger sequencing.

Result: Comparable BRCA1 and BRCA2 carrier rates were observed among breast cancer patients with frequencies of 57 (2.2%) and 66 (2.5%), respectively. Both BRCA1 and BRCA2 conferred increased breast cancer risk with odds ratio 13.0 (95% Cl: 5.2-32.4) and 12.5 (95% Cl: 5.4-28.9), respectively. BRCA1/2 carriers were more likely to be younger, have family history of breast and/or ovarian cancer, have higher grade tumours and for BRCA1 carriers, they were more likely to have hormone receptor negative breast cancers. Notably, 45.7% of breast cancer patients fulfilled the NCCN guidelines for recommendation for genetic counselling and genetic testing, and of these, 80% of BRCA1/2 carriers fulfilled the NCCN guidelines.

Conclusions: Taken together, our results show that approximately 5% of unselected Asian breast cancer patients are carriers of germline BRCA1/2 mutations. Our study could provide a framework for genetic breast cancer risk assessment and calibration, and enable risk assessment and management of Asian breast cancer patients attending clinical genetic services.

CLINICAL APPLICATION OF MULTIGENE PANEL TESTING AND GENETIC COUSELING FOR HEREDITARY/FAMILIAL BREAST CANCER RISK ASSESSMENT: PROSPECTIVE SINGLE CENTER STUDY

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Background: The identification of individuals at elevated risk for hereditary cancers has allowed the development of consensus recommendations for cancer screening and prevention. The introduction of multigene panels may identify more individuals with breast cancer gene mutations than does testing for BRCA1/2 alone. Therefore, the multigenerational panel increase the need for genetic counseling suggesting preventive approach or cancer-specific screening to patients and family members. The rapid clinical introduction of multigene panel testing, however, have several issues such as low- to moderate-risk gene mutations and clinical recommendations. We collect the mutation results and clinical recommendations after testing with multigene panel and giving genetic counseling.

Methods: We had developed multigene panel consisted of 64 genes related to hereditary cancer through previous study and prospectively enrolled 100 individuals who were appropriate candidates for hereditary breast cancer evaluation. The patients were tested with 64-gene panel (Celemics) and results were provided by us 5–10 weeks later. We checked the family history of cancer and made a pedigree before testing. (We enrolled 100 individuals, and the result of 23 patients is pending.)

Result: Among 77 participants, 16 patients harbored deleterious mutations, most commonly in high to moderate-risk breast/ovarian cancer genes (BRCA1/2, RAD51, RAD51D and NBN) and Lynch syndrome genes. We recommended the cancer-specific screening and/or preventive approach for mutation-positive patients and suggested additional genetic test for the family members.

Conclusions: We demonstrate the use of multigene panel testing for hereditary breast cancer and will suggest the process of the genetic counseling including indication and results analysis with multigene panel testing.

GENETIC DETERMINANTS OF SPORADIC BREAST CANCER IN A COHORT OF SRI LANKAN POSTMENOPAUSAL WOMEN

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Background: While a range of common genetic variants have been shown to be associated with sporadic breast cancer risk in several Western studies, little is known about their role in South Asian populations. This study was designed to investigate the association between common genetic variants in breast cancer associated genes and the risk of breast cancer in a cohort of Sri Lankan postmenopausal women.

Methods: A case-control study involving 350 postmenopausal breast cancer patients and 350 healthy postmenopausal women was conducted. Peripheral blood DNA was genotyped using the iPLEX GOLD assay for 56 haplotype-tagging single nucleotide variants (SNV) in 36 breast cancer related genes. Odds ratios and 95% confidence intervals were obtained from adjusted logistic regression models.

Result: Four SNV [rs3218550 (XRCC2), rs6917 (PHB), rs1801516 (ATM), and rs13689 (CDH1)] were significantly associated with breast cancer risk. The rs3218550 T allele and rs6917 A allele increased the risk of breast cancer by 1.5-fold and 1.4-fold, respectively. The CTC haplotype defined by rs3218552|rs3218550|rs3218536 on chromosome 7 ($p = 0.0088$) and the CA haplotype defined by rs1049620|rs6917 on chromosome 17 ($p = 0.0067$) were significantly associated with increased breast cancer risk. The rs1801516 A allele and the rs13689 C allele decreased breast cancer risk by 40% and 30%, respectively.

Conclusions: These findings suggest that common genetic variants in the XRCC2, PHB, CDH1 and ATM genes, are associated with breast cancer risk among Sri Lankan postmenopausal women. The exact biological mechanisms of how these variants regulate overall breast cancer risk needs further evaluation using functional studies.

LUMINAL ANDROGEN RECEPTOR AND ANDROGEN RECEPTOR-HIGH TRIPLE-NEGATIVE BREAST CANCERS ARE GENETICALLY SIMILAR TO LUMINAL BREAST CANCERS

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Background: Triple-negative breast cancers (TNBCs) can be classified into six gene expression subtypes. Among them is the luminal androgen receptor (LAR) subtype, characterized by androgen receptor (AR) expression and AR-pathway activation. We investigated the genomic landscape of LAR-TNBCs and compared their mutational and copy number profiles with those of non-LAR TNBCs and non-TNBCs.

Methods: Gene expression, targeted sequencing and DNA copy number data from METABRIC study (n = 1,972) were reanalyzed. TNBCs were classified into the six subtypes and according to AR mRNA levels. Mutation profiles and large-scale state transition (LST) scores of LAR or AR-high TNBCs were compared to those of other TNBCs, and non-TNBCs subtyped by PAM50.

Result: Of 313 TNBCs, 8% were classified as LAR and 20% as AR-high TNBCs. LAR TNBCs displayed significantly higher frequency of somatic mutations affecting PIK3CA, AKT1, GATA3 and CDH1 than non-LAR TNBCs. Notably, 73% of LAR TNBCs displayed mutations in PI3K pathway members. LAR-TNBCs exhibited significantly higher rate of mutations in TP53 (62% vs. 16%, 11%, 24%) and AKT1 (23% vs. 5%, 5%, 4%) when compared with luminal A/B, luminal A and luminal B. LAR TNBCs displayed significantly lower LST scores than non-LAR TNBCs.

Conclusions: LAR/AR-high TNBCs likely constitute a distinctive triple-negative disease that displays genetic similarities with luminal breast cancers, including a high rate of PIK3CA and AKT1 mutations (69%) and lower frequency of homologous recombination deficient than that found in other TNBCs subtypes. Studies investigating whether LAR/AR-high TNBCs are sensitive to PI3K pathway inhibitors are warranted.

CIRCULATING TUMOR DNA PRESENTS VARIABLE CLONAL RESPONSE OF BREAST CANCER DURING NEOADJUVANT CHEMOTX

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Background: Circulating tumor DNA (ctDNA) is a new biomarker which could guide further treatment. Characterization of tumor mutation profiles is required for informed choice of therapy, given that biological agents target specific pathways and effectiveness may be modulated by specific mutations. Thus, we assess the potency of ctDNA to predict tumor response to neoadjuvant chemotherapy (NAC) in locally advanced breast cancer (LABC).

Methods: We performed targeted deep sequencing of 30 plasma DNAs and 15 matched germline DNAs from 15 LABC patients. Serial plasma DNAs were collected at diagnosis, after 1st NAC and curative surgery. For the target enrichment, we designed RNA baits covering a total of -202kb regions of human genome including a total of 83 cancer-related genes.

Result: Of total, 20 patients were enrolled. In terms of ctDNA, 15 serial samples had been collected because of one withdrawal before 1st sampling and four poor quality samples. TP53 mutation was most commonly detected in primary tumor tissue and plasma. BRCA1 and BRCA2 mutation were also frequently detected. Somatic BRCA1 and BRCA2 mutation was detected in 5 BCs (2 BRCA1 and 3 BRCA2) and germline mutation was in 5 BCs (4 BRCA1 and 1 BRCA2). Of somatic BRCA1 mutation, one case was only detected in plasma DNA without primary tumor. In terms of therapeutic effect of NAC, we found that ctDNA was disappeared after 1st NAC in two samples that achieved pCR.

Conclusions: Plasma single nucleotide variants (SNVs) after 1st cycle NAC represented tumor response of NAC and variation of plasma SNVs also associated with tumor response.

PREDICTIVE ROLE OF FCRR3A-158 POLYMORPHISM AND STROMAL TUMOR INFILTRATING LYMPHOCYTES IN PATIENTS WITH HER2 POSITIVE METASTATIC BREAST CANCER

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Background: Even though trastuzumab has remarkably improved prognosis of HER2+ breast cancer, it is not yet well delineated who get the most benefit from HER2 blockade. This study aimed to evaluate whether the stromal tumor infiltrating lymphocytes (sTILs) or FcrR polymorphisms are associated with the efficacy of trastuzumab in patients with HER2+metastatic breast cancer.

Methods: Between June 2006 and March 2013, a total of 56 women with HER2+ MBC treated with trastuzumab-taxane combination as the first line treatment were included. Single-step multiplex allele-specific real-time PCR technique was employed in FcrR3A genotyping. sTILs were assessed using immunohistochemistry in surgical specimen and biopsy specimen of metastatic lesion. Primary endpoint was progression-free survival (PFS), and secondary endpoints were response rate and overall survival (OS).

Result: In overall patients, median PFS and OS were 20.0 months (95% CI, 9.7-20.2) and 70.0 months (95% CI, 29.8-40.2), respectively. We grouped patients based on the level of stromal TILs (> = 10% [n = 44] and < 10% [n = 12]), and high TILs were more commonly detected in patients with hormone receptor-negative tumor than in hormone receptor positive tumor (31% vs. 6%; $p = 0.02$). High sTIL group showed longer median PFS than low sTIL group (28.0 months [95% CI, 22.9-33.1] vs. 16.0 months [95% CI, 10.6-21.4], $p = 0.03$). In terms of FcrR3A, patients were classified into FF (23 patients, 41%), F/V (23 patients, 41%) and VV (10 patients, 18%) group. However, there was no significant association with clinical outcomes.

Conclusions: This study suggests that high sTILs might be associated with better efficacy of trastuzumab-containing therapy in BC patients.

PHASE II STUDY OF APATINIB PLUS VINORELBINE, A NOVEL COMBINATION OF ALL-ORAL REGIMEN IN HEAVILY PRETREATED PATIENTS WITH METASTATIC HER2-NEGATIVE BREAST CANCER

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Background: Background: Antiangiogenic therapy in combination with chemotherapy is effective in control advanced breast cancer (ABC). Apatinib is an oral, highly potent tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGFR-2). This all-oral phase II study aims to investigate the efficacy and safety of the oral vinorelbine-Apatinib combination in pre-treated metastatic breast cancer (MBC).

Methods: This single arm prospective study enrolled patients with HER2 negative advanced breast cancer, pretreated with anthracycline and taxanes, and who failed in the metastatic setting at least one prior chemotherapy regimen. The primary end point of this study was progression free survival (PFS). Secondary end points included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. Patients were treated with apatinib 500/425 mg daily plus oral vinorelbine 60-80 mg/m^2 day 1, 8, 15 every 21 days.

Result: Results: To date, 16 patients were enrolled with a median age of 59 years and received treatment for a median of 5 cycles. 12 (75.0%) patients experienced dose reduction or interruption during treatment. Median follow-up time was 6.3 months. 11 (68.8%) patients were eligible for efficacy analysis. Median PFS was 4.7 months (95%CI 3.1-6.2). ORR was 36.4% (4/11). DCR was 72.7% (8/11). Median OS was 7.0 months (95%CI 3.9-10.0). The most common adverse events (AEs) of all grade were hypertension (62.5%), gastrointestinal reaction (56.3%), fatigue (56.3%), hand-foot syndrome (37.5%). The most common grade 3/4 AEs were myelosuppression (25%), gastrointestinal reaction (25%) and hypertension (18.8%). Toxicities were tolerable and manageable.

Conclusions: Our results so far indicated that apatinib plus oral vinorelbine exhibited objective efficacy in heavily pretreated, metastatic HER2 negative breast cancer with acceptable safety.

BREAST CANCER TRENDS IN YOUNG WOMEN -A SINGAPOREAN PERSPECTIVE

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Background: The incidence of breast cancer and the incidence of young women (< 40 years of age) with breast cancer is on the rise in the West. In Asia, the incidence of breast cancer is also on the rise, but the incidence of young women with breast cancer is not known.

Methods: A retrospective study was performed on all women who was diagnosed with breast cancer in the Singhealth Institution (largest healthcare cluster in Singapore) from 2005-2014.

Result: A total of 8645 women were diagnosed with breast cancer in our institution from 2005-2014. Over this decade, the number of women diagnosed with breast cancer increased by 33% (626 in 2005 to 838 in 2014). Contrary to international studies, the number and percentage of young women (under 40 years of age) diagnosed with breast cancer in Singapore decreased – from 11.7% (2005) to 5.6% (2014). This was also associated with a concurrent increase in the number and proportion of women above 60 diagnosed with breast cancer (16.3% in 2005 to 28.1% in 2014). In contrast to the West, the histological subtypes are similar in both the under 40s (ER+ 65.1%, Her2 + 8.3%, Triple negative 9.6%) and the 40 and above group (ER+ 67.2%, Her2 + 9.4%, Triple negative 8.8%). Subgroup analysis shows that the Malay women are more likely to present with breast cancer younger, are more likely to have Her2 positive tumours (13.1% vs. 8.7% average), and are more likely to present with a higher stage of breast cancer across all age groups. Overall survival and disease free survival trends is similar in both the under 40s and above 40 age group.

Conclusions: The incidence of breast cancer is on the rise in Singapore. However, in contrast to studies in the West, the incidence of breast cancer in young women is downward trending, have a similar proportion of oestrogen sensitive tumours and have a similar overall survival and disease free survival as the older women in our population. Breast cancer in younger women in Asia is not necessarily more 'aggressive' , as it may be less likely driven by genetic predisposition, but more environmental factors and lifestyle. Racial differences are also noted in their age of presentation and tumour histology, which may be attributed to genetic differences between the different ethnic groups. In a multiracial country like Singapore, breast screening may need to be tailored to cater to the differences races.

RISK STRATIFICATION WITH ENDOPREDICT SIGNATURE FOR LUMINAL SUBTYPE BREAST CANCERS: RE-ANALYZING MICROARRAY EXPERIMENTS WITH HAN CHINESE ORIGIN

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Background: Breast cancer is a heterogeneous disease in terms of molecular aberrations. Luminal breast cancers, most of which are estrogen receptor (ER) positive without human epidermal growth factor receptor 2 (HER2) over expression clinically, constitute the majority of human breast cancers with better prognosis compared with basal-like or HER2-enriched subtype. The aim of the study is to evaluate the prognostication of EndoPredict signature, for which high- and low-risk group is defined based on a multi-gene assay. EndoPredict signature is supposed to guide adjuvant therapy for ER+/HER2- luminal breast cancers with up to three positive lymph nodes, while the test has not been validated for Han Chinese population yet.

Methods: Our microarray experiments (partially published under GSE48391) and two publicly available microarray studies (GSE5460 and GSE20685) constituted the combined dataset of 565 breast cancers with Han Chinese origin, of which 280 were ER+/HER2- by immunohistochemical analysis. Transformation of Affymetrix microarray gene expression values to RT-qPCR-based expression values were conducted with the mathematical formula provided by the EndoPredict investigators, with gene-specific transformation factor and offset. Each enrolled patient was categorized into either high- or low-risk group based on the result of EndoPredict (EP) algorithm.

Result: Direct adaptation of the EP algorithm for microarray gene expression data results in over inflation of EP scores, and most cases were categorized into the high-risk group with the predefined threshold of EP score of 5 and adjustments with rescaling and relocations of microarray-based EP scores were performed. The proportion of disease-free was 88% for low-risk group and 74% for high-risk group during the 10-year follow up period, with disease-free survival advantage reported for those with EP-predicted low-risk group patients. On the other hand, borderline overall survival discrepancy was observed (89% for low-risk and 80% for high-risk group). In addition, patients with high-risk EP scores were associated with larger tumor size, higher nuclear grade, and more involved lymph nodes.

Conclusions: The study provides a solution to enhance the comparability between the FFPE/

RT-qPCR based EP algorithms and fresh frozen microarray gene expression data. The statistical framework presented here provides an "in-silicon" validation for EP algorithm and further studies taking clinical parameters into consideration will augment the clinical applicability of EP scores and EPclin scores to ascertain the prognostic power of multi-gene assay for luminal breast cancers in Taiwan.

INTRODUCING THE JAPANESE BREAST CANCER REGISTRY AND THE ACTIVITY

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Background: We herein introduce a Japanese breast cancer registry and the activity using these big data.

Methods: Since the Japanese Breast Cancer Society (JBCS) launched breast cancer patient data registry and combined with the National Clinical Database (NCD) from 2012, a total of 480588 cases from 925 institutes were registered from 2004 to 2014.

Result: In addition to the trend of treatment and clinicopathological characteristics, prognostic analysis of Japanese breast cancer patients is periodically reported. Large retrospective studies using the database with over 50 demographic and clinicopathological factors of newly-diagnosed primary breast cancer patients has annually been invited and were conducted after taken an inspection by Scientific Committee and Ethics Committee of JBCS. In 2016, 4 papers were published using the big data. One study showed that young age at onset was an independent negative prognostic factor. Second study demonstrated that low-risk tumors account for a substantial proportion of clinical screening-detected cancers. Third study showed that being obese or underweight is associated with a higher risk of death in Japan. Fourth study confirmed that loss of HER2-positivity could occur after neoadjuvant treatment and strongly supported the need for retest biomarker status on surgical sample.

Conclusions: Not only for the clinical studies, this database system would be useful for quality indicator analysis and improvement of diagnosis and treatment guideline.

EXOSOMAL DEL-1 AS A POTENT DIAGNOSTIC MARKER FOR BREAST CANCER: A PROSPECTIVE COHORT STUDY

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Background: We previously demonstrated a diagnostic role of exosomal del-1 with two separated groups of breast cancer patients. In the current study, we aimed to confirm the diagnostic role in a prospective study with breast cancer by measuring plasma exosomal del-1 before and after surgery.

Methods: To identify the optimal time of sampling after surgery, serial blood at day 1, 3, 5, and 7 after surgery was collected from 22 patients with early breast cancer. Thereafter, one hundred fifteen patients with breast cancer who underwent curative surgery were enrolled in the prospective cohort study to compare difference in plasma exosomal del-1.

Result: Among all 22 patients, exosomal del-1 was higher than 0.5 at the time of diagnosis and then normalized at Postoperative day 1 (POD 1). Among 115 patients for the confirmatory set, 109 (94.8%) showed a normalization of del-1 lower than 0.5 after surgery and 10 patients showed del-1 > 0.4. Median f/u duration of 22 months, 9 patients experienced relapse (4 locoregional and 5 distant), where 3 out of 6 in high group (> 0.5), and 2 out of 4 in borderline group (0.4-0.5), and 4 out of 105 in normalized group (< 0.4). In particular, patients who relapsed in higher del-1 group showed relatively earlier relapse compared to lower del-1 group.

Conclusions: In a prospective cohort study, we confirmed that exosomal del-1 has a potent diagnostic role in breast cancer. Furthermore, del-1 was also identified to dramatically decrease after curative surgery. Our current findings suggest its potential prognostic role as well as diagnostic role in breast cancer patients.

ADJUVANT CARBOPLATIN-CONTAINING REGIMEN WAS NON-INFERIOR TO EPIRUBICIN-CONTAINING REGIMEN IN EARLY TRIPLE-NEGATIVE BREAST CANCER: RESULTS OF A MULTICENTER, RANDOMIZED CONTROLLED PHASE 2 TRIAL

Peng Yuan[1], Feng Du[2], Yong Sheng Wang[3], Ming Li[4], Anjie Zhu[1], Jiayu Wang[1], Ruigang Cai[1], Fei Ma[1], Ying Fan[1], Qing Li[1], Pin Zhang[1], Binghe Xu[1]

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Withdrawn

A SINGLE CENTER STUDY OF RISK REDUCING MANAGEMENT IN BRCA MUTATION CARRIERS AFTER DIAGNOSIS OF BREAST CANCER

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Background: The best strategy of risk management for BRCA mutation carriers relies on personal decision. The aim of study is to evaluate clinico-pathological characteristics and check management patterns with BRCA mutation carriers after diagnosis of breast cancer.

Methods: Study group consisted of 523 breast cancer patients who visited to genetic counseling clinic of National Cancer Center, Korea from 2008 to 2015. BRCA mutation was detected in 63 patients (12.0%) with 30 of BRCA1 gene and 33 of BRCA2 gene.

Result: Among 63 carriers, 55 had familial history of breast or ovarian malignancies (24 in BRCA1 and 31 in BRCA2 mutation [$p < 0.01$]). At diagnosis 87% of patients had stage I or II disease. Most common subtype was basal-like in BRCA1 (76.7%) and luminal-A in BRCA2 mutation (48.5%) ($p < 0.01$). Ten had bilateral breast cancer (3 in BRCA1 and 7 in BRCA2 mutation). About 40% of patients with BRCA mutation chose intensive surveillance, 8% received chemoprevention, and 62% had risk-reducing surgeries (RRSs) (3 cases of prophylactic mastectomy and 38 cases of prophylactic bilateral salphingo-oophorectomy [BSO]). There were no clinico-pathological differences between surveillance/chemoprevention vs. RRS group. The numbers of detected BRCA mutation and RRSs increase annually since year 2013 ($p < 0.01$).

Conclusions: After diagnosis of breast cancer, prophylactic BSO is the most preferred management for BRCA mutation carriers. Results might be contributed by reimbursement from National Insurance Plan and high risk perception of patient for ovarian cancer. Additional education and efforts about risk reducing management are needed to Korean breast cancer patients with BRCA mutations.

DNA METHYLATION PATTERNS OF CANCER TISSUES ASSOCIATED WITH BREAST CANCER SURVIVAL

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Background: Estimation of cancer patients survival is important for planning the treatment. DNA methylations reflect the activities of the genes and they can surrogate the functional differences between cancer tissues. DNA methylation patterns combined with epidemiological factors and the characteristics of cancer may provide more precise survival estimation of breast cancer patients.

Methods: Clinical information and DNA methylation profiles of 1,082 female breast cancer patients registered in the Cancer Genomic Atlas (TCGA) were downloaded from TCGA database. The associations between the intensity of DNA methylation and breast cancer survival were evaluated by Cox proportional hazard model. The model was adjusted with clinical and epidemiological variables including diagnosis of age, other cancer, race, cancer status, histologic type, menopause status, estrogen receptor status, progesterone receptor status, human epidermal growth factor receptor 2 status, TNM stage, chemotherapy, immunotherapy and hormone therapy.

Result: DNA methylation intensity from 397,665 sites remained after we removed the DNA methylation sites with missing values. There were 378 DNA methylation sites with $p < 5e\text{-}8$ and 735 DNA methylation sites with $p < 1e\text{-}5$.

Conclusions: This study found 378 DNA methylation sites associated with breast cancer survival. Further evaluation of the functions and pathways of the DNA methylation sites and Multi-omics survival analysis will be continued.

MYBL1 REARRANGEMENTS AND MYB AMPLIFICATION IN BREAST ADENOID CYSTIC CARCINOMA LACKING THE MYB-NFIB FUSION GENE

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Background: Breast adenoid cystic carcinoma (AdCC), a rare type of triple-negative breast cancer (TNBC), is driven by the MYB-NFIB fusion gene through MYB pathway activation. Alternative genetic mechanisms, such as MYBL1 rearrangements, have been reported in MYB-NFIB fusion-negative salivary gland AdCCs. Here we perform molecular analyses of four breast AdCCs lacking the MYB-NFIB fusion.

Methods: Four FISH-proven MYB-NFIB fusion-negative breast AdCCs were subjected to RNA sequencing (RNA-seq, n = 3) and/or whole-genome (n = 2) sequencing. MYBL1 FISH was done subsequently and qRT-PCR to assess expression levels of MYB and MYBL1. Single sample gene set enrichment analysis (ssGSEA) was performed to examine enriched pathways with RNA-seq data.

Result: In AdCC1 and AdCC2, RNA-seq revealed translocations of MYBL1, fused to NFIB or ACTN1 respectively, accompanied by MYBL1 overexpression while lacking MYB overexpression. MYBL1 rearrangements were confirmed by FISH and/or whole-genome sequencing. AdCC3 harbored a high-level MYB gene amplification, which resulted in overexpression of MYB at the mRNA and protein levels. No definite alternative driver was found in AdCC4, despite its high levels of MYB expression. ssGSEA revealed AdCC4, akin to AdCC1 and AdCC2, displayed activation of similar pathways as in a MYB-NFIB fusion-positive AdCC.

Conclusions: We demonstrate that MYBL1 rearrangements and MYB amplification are alternative genetic drivers of breast AdCCs, functioning through activation of pathways similar to those activated by MYB-NFIB rearrangement. These observations emphasize that breast AdCCs likely constitute a convergent phenotype, whereby activation of MYB/MYBL1 and their downstream targets can be caused by MYB-NFIB fusion, MYBL1 rearrangements, MYB amplification and other yet to be identified mechanisms.

PREDICOTRS FOR COSMETIC OUTCOME IN ONCOPLASTIC MASTOPEXY TECHNIQUES

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Background: By advancing locally available breast tissue along the chest wall and mastopexy closure, oncoplastic breast-conserving surgery achieves widened surgical margin and preserve the shape of breast. The impact of patient characteristics on their postoperative cosmetic outcome need further study.

Methods: From 2009 to 2015, there were 101 women of breast cancer who underwent breast-conserving surgery by oncoplastic mastopexy techniques. The ages of patients are between 30 and 80, with median age of 55 years. All of the patients received postoperative radiotherapy. The cosmetic outcome was evaluated by scar visibility, skin depression, and breast retraction assessment (BRA). Skin depression less than 5 mm was defined as good result. The cut-off value of BRA was specified as 5 cm. Breast volume was estimated by each patient's mammogram according to modified Katariya method.

Result: Patients of invisible surgical scars were at significant older ages compared with those of visible scars (58 years vs. 51 years, $p = 0.0039$). There were 89 women (88%) of skin depression less than 5 mm at surgical sites. Women of larger breast volumes had significant retraction of breast (BRA > 5 cm) compared with those of smaller breasts (938 mL vs. 681 mL, $p = 0.0003$). Comparing women of good cosmetic outcome and women of unsatisfactory results, tumor size, percentage of resected breasts, tumor location, and body mass index were not significant predicators to outcome.

Conclusions: Oncoplastic mastopexy techniques can maintain the breast's shape. Scar may be more common in young patients. Larger breast volume may result in significant BRA and breast asymmetry.

RANDOMIZED PHASE 2, OPEN-LABEL, DOSE-RANGING STUDY OF A NOVEL, LONG-ACTING G-CSF, EFLAPEGRASTIM (SPI-2012, ROLONTISTM) OR PEGFILGRASTIM FOR THE MANAGEMENT OF NEUTROPENIA IN PATIENTS WITH BREAST CANCER

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Background: SPI-2012 is a novel investigational biologic that uses innovative proprietary long-acting protein/peptide discovery (LAPSCOVERY™) technology with potentially unique distribution to areas rich in FcRn receptors. This Phase 2 study evaluated three SPI-2012 doses versus pegfilgrastim in patients with BC receiving myelosuppressive chemotherapy. The preliminary data was presented at San Antonio Breast Cancer Symposium, 2015.

Methods: This was an open-label, global, dose-ranging study designed to compare the safety and efficacy of SPI-2012 relative to a standard dose of pegfilgrastim as an active control. The study included 3 dose levels of SPI-2012 (45 μg/kg, 135 μg/kg, and 270 μg/kg) vs. fixed dose pegfilgrastim (6 mg). The primary objective was Duration of Severe Neutropenia (DSN) during Cycle 1.

Result: In 147 evaluable patients enrolled, median age was 59 years (range 32-77 years); most patients were < 65 years (68%), female (98%) and White (95%). The DSN for the 135 μg/kg and 270 μg/kg was non-inferior to pegfilgrastim during all cycles. In addition, the DSN for 270 μg/kg was superior to pegfilgrastim in Cycle 1 ($p = 0.023$). The common adverse events observed in ≥ 20% of patients were similar across all groups and included fatigue, nausea, alopecia, diarrhea, and bone pain.

Conclusions: All doses of SPI-2012 administered were well tolerated. Most reported adverse events were mild and similar to those reported with G-CSF drugs in patients receiving myelosuppressive chemotherapy. The 135 μg/kg dose of SPI-2012 was non-inferior and the 270 μg/kg dose was superior to pegfilgrastim and the efficacy sustained in all 4 cycles. Phase 3 studies are ongoing.

WNT-DP103-GSK3Bβ CASCADE PROMOTES WNT/β-CATENIN SIGNALING IN PARENTAL AND STEM CELLS FROM TRIPLE NEGATIVE BREAST CANCER

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Background: Despite recent advances in breast cancer therapeutics, mortality of highly metastatic triple negative breast cancer (TNBC) subtype remains high. Therefore, there is a pressing need to identify new prognostic markers and therapeutic targets for this group of breast cancers. Aberrant activation of Wnt/β-catenin signaling has been associated with breast cancers.

Methods: A series of in vitro assays were used in this study.

Result: The link between DP103 and Wnt/beta-catenin signaling was further validated using in vivo Zebrafish models, where disruption in DDX20 gene splicing mechanisms resulted in deformities, which phenocopies loss of Wnt/beta-catenin signaling. Interestingly, we also show DP103 drives breast cancer stem cell (CSC) formation, a process regulated by the Wnt/beta-catenin pathway. Depletion of DP103 led to a marked reduction in the percentage of CSC-enriched mammospheres with reduced tumor-initiating ability. Mechanistically, we show DP103's role in driving Wnt/beta-catenin pathway is highly dependent on GSK3β activity. More interestingly, from molecular docking data, we found DP103 protein has to be phosphorylated at threonine residue 552, when it interacts with GSK3β. Surprisingly, induction of Wnt/β-catenin signaling also significantly increased DP103 expression, indicating a possible positive feedback loop.

Conclusions: Collectively, our data suggest a novel regulatory role of DP103 in the Wnt/β-catenin signaling pathway in parental and CSC derived TNBC-a study which has attracted Pharma company, Rexahn Pharmaceuticals Inc., USA to further develop their Phase I Wnt drug with our group here in Singapore.

POSTER EXHIBITION

Global Breast Cancer Conference

GBCC 2017

10th ANNIVERSARY

TRENDS OF BREAST CANCER IN ETHIOPIA

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Background: The essence of this study is to illustrate the trends of breast cancer among women living in different regions of Ethiopia and to offer suggestions about some measures to put in place to control the disease and reduce its morbidity and mortality.

Methods: Data were collected from October 2014 to April 2015. Data on new cases of breast cancer registered annually at the cancer registry of the Tikur Anbessa Specialize Hospital over a period of sixteen years were obtained retrospectively and analysed using MS office and SPSS Version 20.

Result: There were 3,460 new cases of breast cancer registered at the cancer registry during the 16-year period. The peak age of incidence was the 4th and 5th decade. Most of the cases were found in Addis Ababa, where the hospital is situated. An increase in trend of breast cancer case was observed in the hospital.

Conclusions: Non-declining incidence of breast cancer in this study indicates; the awareness of people to be diagnosed is improved and more cancerous patients and inadequate control measure to stem its morbidity due to diversion of the health care systems attention to HIV/AIDS and malaria. Screening programs and training such as mammography, clinical and self-examination. In addition, it will be important to open breast cancer diagnosing center in each region to know the number of cases, will be affected by being undiagnosed due to far from diagnosing center and researches on breast cancer post treatment survival rate, risk factors assessment, patient quality of life and others recommended in future.

EVALUATION OF BRCA1/2 MUTATIONS IN KOREAN WOMEN WITH TRIPLE-NEGATIVE BREAST CANCER: RESULTS FROM KOHBRA STUDY

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Background: NCCN guideline recommends genetic testing for women less than 60 years with triple-negative breast cancer (TNBC). However, BRCA1/2 mutation rates of TNBC patients were evaluated among limited ethnicities. Our aim was to determine the prevalence and distribution of BRCA1 and BRCA2 mutations in Korean women.

Methods: We performed a retrospective review of TNBC patients from the Korean Hereditary Breast Cancer study. Clinical and demographic data were collected including genetic testing results of BRCA1/2 mutations and risk categories.

Result: A total of 532 TNBC patients who underwent BRCA1/2 genetic testing were identified. Mean age was 39.0 years (range 20-73). Overall mutation rate was 32.1% (n = 171); BRCA1 (n = 122), BRCA2 (n = 46), and both mutations (n = 3). BRCA mutation prevalence according to age at diagnosis was as follows: < 30 years (20.3%), 30-39 years (31.2%), 40-49 years (39.4%), 50-59 years (25.7%), and ≥ 60 years (56.5%). In patients aged between 20 and 59, the proportion of BRCA1 mutations was higher than that of BRCA2. However, BRCA2 mutation prevalence was the highest in patients over 60 years old. BRCA mutation prevalence differed by presence of risk categories: patients with a family history of breast or ovarian cancer (45.0%), bilateral breast cancer patients (21.4%), and isolated young breast cancer patients (13.3%).

Conclusions: We observed high BRCA mutation rates among Korean TNBC patients. Although this study has a limitation to target the high risk individuals, our results will help to refine the BRCA mutation risk among Korean TNBC patients. Evaluation considering BRCA1/2 mutation in TNBC should be continued based on general populations.

BRCA1, BRCA2 MUTATIONS AND THE ASSOCIATION WITH THE CLINICOPATHOLOGICAL CHARACTERISTICS OF WOMEN WITH EARLY-ONSET BREAST CANCER

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Background: BRCA1 and BRCA2 mutations have been associated with early-onset breast cancers and adverse clinico-pathological features.

Methods: Seventy females aged 40 or less with confirmed breast cancer diagnosis that underwent follow-ups at Seberang Jaya Hospital were recruited into this study. Clinical and pathological (ER, PR, HER2 status, triple negativity, tumour grades and stages) characteristics of the breast cancers were obtained by reviewing medical records. Three ml of blood was taken from each subject, subjected to DNA extraction and then screened for germline mutations of BRCA1 gene (exons 11, 13, and 16) for BRCA2 gene (exons 10 and 11) using allele-specific PCR.

Result: The prevalence of BRCA2-only and combined BRCA1 and BRCA2 mutations were 28.6% (95% CI: 18%, 39.2%) and 71.4% (95% CI: 60.8%, 82.0%), respectively. Three BRCA1 mutations (3232A > G (rs16941, exon 11), 3667A > G (rs16942, exon 11) and 4427T < C (rs1060915, exon 13) were significantly associated with a more advanced tumour size group (p values = 0.032, 0.049, and 0.043, respectively). Besides, 3232A > G (rs16941, exon 11) mutation was also significantly associated with higher risk of HER2-negative (OR 7.50 (95% CI: 1.439, 39.089), p value = 0.017) and triple negative breast carcinoma (OR 4.375 (95% CI: 1.193, 16.038), p value = 0.042).

Conclusions: Three BRCA1 germline mutations were found to be significantly predictive of a more advanced tumour size group whilst only one BRCA1 mutation was significantly associated with HER2-negative and triple negative breast tumours. Nevertheless, further studies are warranted to address the unresolved issues encountered by this study.

PILOT STUDY ON THE RELATIONSHIP OF P53 MUTATION WITH CLINICOPATHOLOGICAL CHARACTERISTIC IN BREAST CANCER

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Background: p53 is a tumour suppresor gene. In breast cancer, p53 gene mutation were noted with frequency of about 30% (range 15 to 71%) and associated with poor prognosis.

Methods: This study conducted in Hospital Seberang Jaya and Institut Perubatandan PergigianTermaju, Universiti Sains Malaysia. Sixty four breast cancer patients with available fresh breast cancer tissue that been kept under -80°C and with complete clinicopathological data involve in this study. These fresh breast tissues DNA extracted and 10 sampels sent for DNA sequencing. Total 19 mutations found and only four randomly run for test due to limitation of time. The remaining 54 samples proceeded with Polymerase Chains Reaction analysis based on the result from DNA sequencing.

Result: The mean age of the patients in this study was 52.45 ± 9.51 years. 51.6% of these patients undergone CT scan staging and 14.1% has distant metastases. p53 gene mutation prevalence showed rs1042522 only has 15.7% mutation. There was 54.7% Deletion A and 45.3% Wild Type A detected in rs59758982, 87.5% Deletion A and 12.5% Wild Type A in rs35069695 and 92.2% recorded for Deletion GAA in rs376546152. There was no significant result between these mutation with breast cancer molecular classification and breast cancer aggressiveness except for rs59758982 shows significant result with p value 0.04 ($p < 0.05$) with metastases.

Conclusions: In this pilot study, these four mutation site no significant association with clinicopathological characteristic of breast cancer. The remaining fifteen mutations site is in progress.

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DOES THE ONCOLOGIC OUTCOME OF BREAST CANCER WITH BRCA 1/2 (-/-) WITH HEREDITARY BREAST CANCER RISK FACTORS WORSE THAN SPORADIC BREAST CANCER?: A CASE CONTROL MATCHED STUDY

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Background: As most patients who examined BRCA 1/2 mutation have risk of hereditary breast and ovarian cancer (HBOC), patients have psychological distress even though BRCA 1/2 mutation was negative. We hypothesized that negative BRCA 1/2 mutation with risk of HBOC may show a similar oncological outcome with sporadic breast cancer without risk of HBOC.

Methods: A retrospective review was conducted between 2002 and 2014 at a tertiary single institution in Korea. The criteria for HBOC risk was defined as follows: family history of breast or ovarian cancer, early onset breast cancer less than 35 years old, bilateral breast cancer, and personal history of breast or ovarian cancer. Patients were matched maximally 1:3 to patients who identified BRCA 1/2 mutation negative with HBOC risk (Study group) and not examined BRCA 1/2 mutation without risk for HBOC (Control group). Matched variables were pathologic stage, estrogen receptor status, progesterone status, human epidermal growth factor-2 status, and operation date.

Result: 470 patients were identified for the study group and matched to 1,350 patients for the control group. All matching variables were matched successfully. Median follow-up duration was 51.1 and 60.1 months for the study and control groups, respectively ($p > 0.005$). Disease-free survival did not differ significantly between the two groups ($p = 0.197$). Control group shows worse breast cancer specific survival (BCSS) than study group ($p < 0.0001$). In multivariate analysis, hazard ratio to BCSS was 0.469 (95% confidence interval, 0.252-0.870) ($p = 0.042$).

Conclusions: BRCA 1/2 negative breast cancer with HBOC risk may have a similar prognosis comparing to sporadic breast cancer.

THE PREDICTING FACTORS FOR NEOADJUVANT ANTI-HER2 THERAPY RESPONSE IN LOCALLY ADVANCED HER2 POSITIVE BREAST CANCER

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Background: HER2 targeting receptor tyrosine kinase (RTK) inhibitors show clinical efficacy in HER2 positive breast cancer, its use was expanded to neoadjuvant therapy. To lower the treatment failure rate, predicting drug response became more important in each patient. This study aims at identifying new potential biomarker genes and druggable signal pathways with different response to neoadjuvant anti-HER2 therapy.

Methods: We identified 64 women with locally advanced HER2-positive breast cancer who underwent surgical resection after neoadjuvant anti-HER2 systemic therapy at our institution between July 2005 and January 2014. Genechip microarray was performed with 20 samples collected from paraffin embedded tissue. We compared two groups by the response to neoadjuvant chemotherapy, complete response (11 cases) or partial response (19 cases). Gene expression data was analyzed using David Bio-informatics Resource Tool and Ingenuity Pathway Analysis (IPA).

Result: In the pathway analysis results, the function of most commonly and strongly showed 10 pathways were related with cell cycle and cell signaling. It was consistent with our previous frozen tissue study. Especially, eIF signaling pathway that is related with PI3k pathway was highly shown.

Conclusions: In this study, the possibility of our subpathway identification approach is once more proven. The pathways related cell cycle or cell activity are strongly related with drug response to anti-HER2 therapy. It could be highly effective for accurate pathologic biomarker and pathway discovery.

A PILOT STUDY OF MOLECULAR-GUIDED NEOADJUVANT CHEMOTHERAPY (NAC) IN PATIENTS WITH TRIPLE NEGATIVE BREAST CANCER (TNBC)

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Background: Patients with TNBC have higher risk to be carriers of BRCA1/2 mutation. BRCA1/2 carriers have been reported to derive more clinical benefit from platinum-containing neoadjuvant chemotherapy (NAC). Identifying patients at risk could also impact surgical plan. Although next generation sequencing (NGS) allows multi-gene panel testing at a lower cost, there are limitations in accuracy of mutation detection and interpretation of variants of unknown significance (VUS). The availability of technology, bioinformatics and resource support is also variable. This pilot study evaluated the feasibility of a molecular-guided approach in TNBC patients planning for NAC.

Methods: TNBC patients planned for NAC were invited for fast track genetic testing for germline mutation. NGS on a four-gene panel detecting mutation in BRCA1, BRCA2, TP53, and PTENs was performed including Multiplex ligation-dependent probe amplification assays. All positive results were validated by Sanger sequencing.

Result: From January 2015 to November 2016, 17 patients with early-stage TNBC recruited for fast track genetic testing. The average age was 45 years. The average turnaround time for the test was 24 days. 1 BRCA pathogenic variant and 2 VUS were identified (17.6%) which is comparable with data from Hong Kong Hereditary Breast Cancer Family Registry (non selected 17.6%, with Family history and young age 48.3%).

Conclusions: Molecular-guided NAC in early-stage TNBC using expedited NGS is feasible with multidisciplinary effort. Resource support to genetic testing among Asian countries varies. Local guideline for molecular-guided NAC should be established according to resources to screen out patients who are more likely to benefit from this approach.

THE NEGATIVE EFFECT OF YOUNG AGE ON LOCO-REGIONAL CONTROL HAS DECREASED OVER TIME AS SYSTEMIC TREATMENT EVOLVED IN BREAST CANCER

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Background: Young age has been well known to be a negative prognosticator for breast cancer. The purpose of this study is to investigate whether young age still remains to be the powerful prognosticator related to loco-regional recurrence (LRR) in breast cancer over time as systemic treatments have been evolved.

Methods: We reviewed 4,629 patients with breast cancer who received primary surgery followed by adjuvant treatment between 2000 and 2012. The cohort was divided into 2 treatment period groups, the early period (EP; 2000-2004, n = 1,232) and late period (LP; 2005-2011, n = 3,397) cohorts according to the active use of modern therapies.

Result: LRR for EP and LP developed 81 (6.5%) and 64 (1.9%) patients, respectively within 69 months after diagnosis. The EP group had more patients with adverse features compared to LP group: larger tumor ($p < 0.001$); involvement of lymph node ($p < 0.001$); lower proportion of luminal type ($p < 0.001$). In the EP cohort, the 10-year LRR of patients aged < 35 years vs. ≥ 35 years were 17% and 6.9%, respectively ($p = 0.003$). Also, young age was significantly associated with an increased LRR (< 35 years vs. ≥ 35 years, HR 2.158; 95% CI 1.061-4.390; $p = 0.034$) by multivariable analyses. Whereas, 5-year LRR of younger patients was not significantly higher compared to those of older patients by multivariable analyses (HR 1.289; 95% CI 0.464-3.583; $p = 0.627$) in the LP cohort.

Conclusions: The prognostic power of young age on LRR has decreased as effective chemotherapy and targeted therapy reduced overall LRR of breast cancer.

THE BASIC FACTS OF KOREAN BREAST CANCER IN 2014: A 10 YEAR PROGRESS

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Background: In Korea, breast cancer is the second most common female cancer, and the incidence is increasing continuously. The Korean Breast Cancer Society (KBCS) made a nationwide breast cancer registry since 1996, the database have been used for various studies on breast cancer. The aim of this study was to investigate the characteristics of Korea breast cancer in 2014 and trends over 10 years period.

Methods: Data on newly diagnosed breast cancer patients` information were collected for the year 2014 from KBCS registry database and Korean Central Cancer Registry (KCCR) database.

Result: In 2014, there were 21,484 patients who were newly diagnosed with breast cancer. The crude incidence rate and age-standardized incidence rate (ASR) of female breast cancer including carcinoma in situ in 2014 were 84.3 and 63.9 per 100,000 women, respectively. ASRs for female breast cancer increased 6.1% annually between 1999 and 2014. According to annual percentile change of all breast cancer (invasive and DCIS) incidence, the ASRs increase had slowed since 2008. The proportion of early breast cancer (stage 0, 1) has steadily increased and accounted for more half of total cases of breast cancer since 2011. Breast - conserving surgery was performed in 64.9% and mastectomy in 34% during 2014. The total number of breast reconstruction surgeries increased rapidly over the 12 years. The 5-year and 10- year overall survival rate of female breast cancer were 91.2% and 84.8%, respectively.

Conclusions: Analysis of nationwide registry data will contribute to a better understanding of changing patterns in the characteristics of Korean breast cancer.

LONG NONCODING RNA SNAR REGULATES PROLIFERATION, MIGRATION AND INVASION OF TRIPLE-NEGATIVE BREAST CANCER CELLS

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Background: We evaluated the role of long noncoding ribonucleic acid (lncRNA) in breast cancer cell lines by quantitative reverse transcription polymerase change reaction.

Methods: The effects of small NF90-associated RNA (snaR) with RNA interference on proliferation, migration and invasion of MDA-MB-231 cells were observed by 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide, wound healing and transwell assay.

Result: Among 90 lncRNAs, E2F transcription factor 4, p107/p130-binding (E2F4) antisense, Insulin-like growth factor 2 antisense (IGF2AS), snaR, and small nucleolar RNA host gene 5 (SNHG5) were up-regulated in MDA-MB-231 and 7SK, antisense noncoding RNA in the INK4 locus (ANRIL), IGF2AS, Nespas, p53 mRNA, and snaR were up-regulated in MCF-7 cells. Downregulation of snaR inhibited the proliferation, migration, and invasion of MDA-MD-231 breast cancer cells.

Conclusions: LncRNAsnaR was found to be up-regulated in breast cancer cells, and the cancer progression of MDA-MB-231 cells was significantly suppressed by down-regulation of snaR. Therefore, snaR knockdown has potential as a treatment modality for triple-negative breast cancer.

REACTIVE OXYGEN SPECIES MODULATOR 1 (ROMO1) IS A POTENTIAL CLINICAL PARAMETER IN BREAST CANCER : IN VITRO STUDY USING BREAST CANCER CELL LINES

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Background: Reactive oxygen species modulator 1 (Romo1) is a novel protein that has been reported to be crucial for hepatic cancer and lung cancer cell proliferation and invasion. However, its oncologic effect in breast cancer cells are not well-known. We investigated the association between Romo1 and the breast cancer cells behaviors.

Methods: We grew the breast cancer cell lines (MCF-7, MDA-MB-231) and transfected with Romo1 siRNA or control siRNA. After 24 hours transfection, we examined the association between Romo1 expression and cell invasion, cell motility using Matrigel invasion assay, cell viability assay, wound healing assay in breast cancer cell lines. We confirmed Romo1 knockdown by western blotting.

Result: Cell invasiveness decreased in the Romo1 knockdown breast cancer cells in contrast to the controlled cells. Compared with controlled breast cancer cells, invasive activity decreased by approximately 40% in MDA-MB-231 transfected with Romo1 siRNA and approximately 32% in MCF-7 transfected with Romo1 siRNA. However, cell motility was not changed in the Romo1 knockdown cells.

Conclusions: Romo1 expression in breast cancer cell lines was associated with cancer cell invasion. This suggesting Romo1 expression as a potential adverse prognostic marker. Further study to investigate the correlation between Romo1 expression and clinical outcome is needed.

CLINICAL APPLICATION OF NK CELL ACTIVITY IN BREAST CANCER PATIENTS

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Background: Natural killer (NK) cells play a key role in the inhibition and elimination of malignant tumor cells. IFN-γ is a major cytokine secreted from activated NK cells and exerts immune responses against tumor cells. The aim of this study is to evaluate the NK cell activity (NKA) in breast cancer patients and to assess the relationship between NKA and disease severity.

Methods: We reviewed the clinical data and NKA of newly diagnosed 98 breast cancer patients between June 1, 2015 and December 31, 2016. NKA was represented by IFN-γ levels after stimulation of the peripheral blood using NK VueTM assay.

Result: NK cell-specific IFN-γ level was significantly lower in patients with positive lymph node (LN) metastases compared to those with negative LN metastasis (n = 34, 503.9 pg/mL vs. n = 64, 990.1 pg/mL; $p = 0.0026$). NK cell-specific IFN-γ level tended to gradually decrease according to disease progression (stage 0, n = 13, 1203.88 pg/mL vs. stage I&II, n = 67, 840.16 pg/mL vs. stage III&IV, n = 18, 475.41 pg/mL; $p = 0.0313$). There were no significantly statistical differences in histologic grade, hormonal receptor status, HER2 status.

Conclusions: These findings revealed the possibility that the NKA was related with breast cancer severity. Therefore, we suggest that the NKA could be utilized as a supportive diagnostic marker for breast cancer.

CHARACTERIZATION TUMOR-INFILTRATING LYMPHOCYTES FOCUSED ON IMMUNE CHECKPOINT EXPRESSIONS IN HUMAN BREAST CANCER

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Background: The expression of immune checkpoint receptors in breast cancer remains poorly understood. We aimed to investigate the expression pattern of multiple immune checkpoint molecules on tumor-infiltrating and peripheral blood (PB) lymphocytes in breast cancer.

Methods: We isolated lymphocytes from fresh breast tumor and paired PB from 33 patients who underwent surgery. Multi-color flow cytometry was performed primarily focusing on expression of PD-1, TIGIT, LAG3, and TIM3 on CD8+ T cells and regulatory T cells (Tregs).

Result: PD-1 was most frequently expressed among the CD8+ T cells in tumor-infiltrating lymphocytes (TILs) (median 62%), followed by TIGIT, LAG3, and TIM3. In the CD8+ T cell subset, PD-1 was highly expressed in CCR7-CD45RA- effector memory T cells (TEM) ($p = 0.001$). Moreover, CD8+ T cells in TILs showed significantly higher level of PD-1, LAG3, and TIM3 than those in PB ($p = 0.0001$, $p = 0.002$, and $p = 0.009$, respectively). In the CD4+ T cell subset, the proportion of CD25+FoxP3+ Tregs was higher in tumor than that in PB (16.60% vs. 7.86%; $p = 0.002$). CD4+CD25+FoxP3+ Tregs in TILs showed higher expression levels of PD-1, TIGIT, and CTLA-4 compared to those in PB ($p < 0.05$). There was no noteworthy correlation between immune checkpoint expression and clinical features including stage and subtype.

Conclusions: We show that the major immune checkpoint receptors are highly expressed in breast tumor-infiltrating CD8+ T cells CD4+CD25+FoxP3+ Tregs. Our data provide an understanding of comprehensive phenotypes of immune checkpoint expressions on T cells in breast cancer. Functional changes of CD8+ T cells and Tregs by blocking of immune checkpoint receptors are being investigated.

THE STRENGTH OF ESTROGEN AND PROGESTERONE RECEPTOR EXPRESSION AND PROGNOSTIC MARKERS IN LOW PROLIFERATIVE HER2 NEGATIVE BREAST CANCER

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Background: Breast cancer is very heterogeneous and human epidermal growth factor receptor 2 (HER2) amplification is related with aggressive clinical features in breast cancer. We investigated the clinical characteristics and prognostic factors of less aggressive HER2 negative and low proliferative breast cancer.

Methods: We collected 279 breast cancer data with low Ki 67 proliferation index ($\leq 20\%$) and HER2 negative. We divided them into three subgroups such as strong luminal, weak luminal, and triple negative group based on hormonal receptor expression status using Allred score. We analyzed the clinical and pathological data including age at diagnosis, TNM stage, estrogen receptor (ER), progesterone receptor (PR), and Bcl-2 of all subgroups. Recurrent or metastatic characteristics as well as disease free survivals and overall survivals of each subgroup was evaluated.

Result: Strong luminal group was associated with younger age (≤ 50 years) ($p = 0.0497$), higher nuclear grade ($p = 0.0206$), higher Bcl-2 expression ($p < 0.0001$). Weak luminal group was associated with more frequent lymphatic ($p = 0.0005$) and neural invasion ($p = 0.0165$), brain ($p = 0.0133$), liver ($p = 0.0156$), lung ($p = 0.0455$) metastasis than strong luminal and triple negative groups. Disease free survival was best in strong luminal group and worst in triple negative group. Overall survival was best in triple negative group but worst in weak luminal group.

Conclusions: Weak luminal subgroup showed worse prognosis than strong luminal and triple negative group in HER2 negative low proliferative breast cancer. We could consider weak ER or PR expression as poor prognostic factor in HER2 negative low proliferative breast cancer.

CHARACTERIZATION OF HUMAN CATHELICIDIN ANTIMICROBIAL PROTEIN (CAMP) IN BREAST CANCER

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Background: It is well-established that tumor associated macrophages (TAMs) play important role in breast cancer development. Accumulating evidence suggested that human cathelicidin antimicrobial protein (CAMP), which is mainly expressed in host defense cells such as macrophages, is crucial not only in combating microorganisms but also promoting tumor growth. Our study aims to elucidate the interaction of CAMP with TAMs in breast cancer.

Methods: MTT, migration/invasion assay, cell cycle analysis, apoptosis assay were performed in MCF-7 and T47D cells (estrogen receptor, ER positive) breast cancer cells. Gene expression was investigated by real-time PCR and detection of CAMP in serum was evaluated by ELISA. Co-culture assay of breast cancer cells and macrophages was carried out by using the 0.4m pore transwell. Immunofluorescence staining was introduced to investigate the cellular expression in macrophages and cancer cells.

Result: CAMP was overexpressed in cancer tissues and serum of breast cancer patients. CAMP knockdown led to decreased cell proliferation, inhibited migration/invasion ability, which was associated with G1 phase cell cycle arrest, increased early apoptosis and alteration in epithelial mesenchymal transition (EMT)-related genes. CAMP expression was altered during macrophage M1/M2 polarization and was released predominantly in M2 phenotype. In addition, breast cancer cells co-cultured with macrophages showed upregulated CAMP expression and also increased cancer cell viability.

Conclusions: Our data implicated that CAMP confers oncogenic role in breast cancer and it plays important role in the tumor microenvironment between TAMs and breast cancer cells. These findings provide novel therapeutic options for this malignant disease.

CARDIAC ARRHYTHMIA IS ASSOCIATED WITH BREAST CANCER COMPARED TO BENIGN BREAST DISEASE

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Background: There have been reported that cancers and the cardiovascular system share common pathways, however we do not fully understand the mechanism. Breast cancer also has been known to associate with cardiovascular disorders, including heart failure or cardiotoxicity related to chemotherapy. We evaluated whether breast cancer is associated with cardiac disorder.

Methods: Six hundred sixty eight patients who underwent sonography guided breast core biopsy from 2011 to 2013 were studied. All baseline 12-lead electrocardiogram (ECG) were assessed in 467 patients diagnosed with breast cancer (right, n = 225; left, n = 242) compared to 201 patients diagnosed with benign breast disease, as a control group. Twenty-four hours Holter ECGs were conducted in patients with abnormal ECG and/or symptom.

Result: All of patients were women and mean age of patients was 50.7 years. PR interval was significantly prolonged in the cancer group compared to benign group (155 ms vs. 149 ms, $p = 0.001$), however there was no significant difference in PR interval between patient with right breast cancer and those with left breast cancer (155 ms vs. 154 ms, $p = 0.768$). In ECGs, ventricular premature complex (VPC) and atrial premature complex (APC) were documented only in breast cancer group (VPC, 0.64%; APC, 0.64%). Occasional APCs occurred more often in cancer group (66.7%, vs. 12.5%, $p = 0.05$).

Conclusions: This study showed that PR interval was significantly prolonged and APCs was more prevalent in patients with breast cancer. These findings suggest that breast cancer may be associated with the increase risk of arrhythmia. Therefore, clinicians carefully evaluate the cardiac function from diagnosis to treatment.

ANTAGONISTIC EFFECTS OF COMBINATION BETWEEN EMODIN AND ENODIXIFEN IN ESTROGEN RECEPTOR POSITIVE BREAST CANCER CELL LINES

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Background: Study aimed to investigate combination effect between endoxifen and emodin in estrogen receptor (ER) positive breast cancer cell lines and explain to mechanism of combination effect.

Methods: We determined this study using MCF-7 (ER+/human epidermal growth factor receptor-2; HER2-), T47D (ER+/HER2-), ZR 75-1 (ER+/HER2+), and BT474 (ER+/HER2+) cell lines, which confirmed drug combined effect between endoxifen and emodin. Optimal combined concentration decided to study cell proliferation in MCF-7 and ZR 75-1 cell lines. Analysis of combination effect was used by CompuSyn software. Combination of downstream mechanism, and combination effect for other similar compounds were analysis in the MCF-7 and ZR 75-1 cell lines.

Result: Combination with endoxifen/emodin induced antagonistic effect in MCF-7 and ZR75-1 cell lines (combination index > 1). We validated an antagonistic effect in T47D and BT474 cell lines. When combination, the results showed elevation of pAKT and phosphoryl-extracellular signal-regulated kinase (pERK) expression. Drug interaction showed antagonistic effect between endoxifen and similar chemical compounds such as chrysophanol or rhein in MCF-7 and ZR 75-1 cell lines.

Conclusions: Combination treatment with endoxifen/emodin had antagonistic effect via pAKT and pERK overexpression in ER positive breast cancer cell lines.

IMPACT OF CLINICAL AND MOLECULAR PARAMETERS ON RECURRENCE OF PATIENTS DIAGNOSED WITH BREAST PHYLLODES TUMORS

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Background: Although the prognoses of breast phyllodes tumors (PTs) were excellent, they have recurrent and even metastatic potentials. This study investigated the impact of clinical characteristics and possible molecular parameters on recurrence.

Methods: Data of 319 patients diagnosed with PTs who received surgical intervention at National Taiwan University Hospital (NTUH) from 1991 to 2013 were retrospectively reviewed.

Result: Of the 319 patients, 8 (2.5%) developed metastasis. All but 1 died of metastasis and metastasis was associated with poor prognosis. Forty patients (12.5%) developed local recurrences. Among them, 18 were diagnosed with benign, 13 with borderline and 9 with malignant PTs. Patients who received partial mastectomy without free margin were positive associated with recurrence by using Cox stepwise regression analysis ($p = 0.035$). Using direct sequencing, we analysed MED12 exon 2 mutations for the 13 recurrent patients diagnosed with benign PTs initially. Somatic mutation of MED12 was observed in 7 patients (53.8%). The mutation patterns were similar (6/7, 85.7%) between initial and recurrent PTs, with codon 44 being involved for all 6 patients.

Conclusions: Besides histology and clinical parameters, more parameters (including molecular parameters) should be investigated to predict recurrence of PTs.

MAP3K1 EXPRESSION AND STROMAL CD10 EXPRESSION WERE CLOSELY ASSOCIATED WITH HIGHER IPSILATERAL RECURRENCES OF DUCTAL CARCINOMA IN SITU OF BREAST

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Background: Previous studies suggested that stromal CD10 expression was closely associated with the risk of recurrence. We recently reported that MAP3K1 rs889312 (C/C) was associated with poor prognosis in early breast cancer patients who receive adjuvant hormonal therapy alone. In this study, we assessed whether MAP3K1 expression as well as stromal CD10 expression were closely associated with the high-risk recurrences of breast DCIS.

Methods: Between 2004 and 2009, 18 cases with breast DCIS had IBE events, whereas 49 cases had compared clinicopathologic and treatment characteristics but without IBE were included in this study. The expression of CD10 and MAP3K1 in tumor cells were evaluated by the immunohistochemistry. The association between the expression patterns of CD10 and MAP3K1, University of Southern California/Van Nuys Prognostic Index (USC/VNPI) score, estrogen receptor (ER) status, and tamoxifen use, and the ipsilateral breast event (IBE)-free survival were calculated using the Kaplan-Meier method and log-rank tests.

Result: Patients with stromal CD10 expression had a lower 7-year IBE-free survival rates than those without (62.1 % versus 88.2%, $p = 0.003$). The expression of MAP3K1 was closely associated with the poor 7-year IBE-free survival rate (63.2% versus 85.7%, $p = 0.015$). In the multivariate analysis, stromal CD10 expression ($p = 0.024$) and MAP3K1 expression ($p = 0.005$) were closely associated with the unfavorable IBE-free survival, where ER status, tamoxifen use, and USC/VNPI) score lost significances.

Conclusions: Our results indicate that stromal CD10 expression and MAP3K1 expression are closely associated with the higher IBE of patients with breast DCIS.

PHASE-DEPENDENT VARIATION IN COSMETIC OUTCOME AFTER POSTOPERATIVE RADIOTHERAPY FOR BREAST CANCER

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Background: To compare characteristics of immediate and long term cosmetic outcomes of the breast after postoperative radiotherapy (RT) for breast cancer.

Methods: From 2002 to 2007, 125 non-selected breast cancer patients who had photographic data of breasts just before RT (phase 1), just after RT (phase 2), and at the last follow-up day (phase 3) were retrospectively reviewed and each cosmetic factor was scored on 4-point scale by one clinician. s

Result: Median follow-up of phase 3 was 48 months. The rate of excellent/good cosmetic outcomes of phase 1, 2, and 3 was 84%, 81%, and 60% for size; 74%, 73%, and 45% for shape; 78%, 71%, and 52% for nipple position, respectively. While edema, pigmentation, and erythema were predominantly aggravated between phase 1 and 2, then improved between phase 2 and 3 ($p = 0.024$, < 0.001, and < 0.001, respectively). The sum of cosmetic scores of edema, pigmentation, and erythema at phase 2 was not correlated with the sum of scores of size, shape, and nipple position at phase 3 ($p = 0.086$). The slope of cosmetic score using Harvard scale was +0.055 per 1 month between phase 1 and 2 ($p = 0.077$), and +0.009 per 1 month between phase 2 and 3 ($p < 0.001$).

Conclusions: Acute reactions after postoperative RT did not impact on long term cosmetic results. Morphological changes such as size, shape, and nipple position were major factors that determine long term cosmetic outcomes.

ONCOLOGIC OUTCOMES AFTER IMMEDIATE BREAST RECONSTRUCTION FOLLOWING TOTAL MASTECTOMY IN PATIENTS WITH BREAST CANCER: A MATCHED CASE-CONTROL STUDY

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Background: Immediate breast reconstruction (IBR) has been increased markedly. As the indication of IBR has been broadened and more patients who eligible BCS underwent IBR, it is more difficult to compare the oncologic safety. This study aimed to analyze oncological outcome between total mastectomy (TM) only and IBR following by matching.

Methods: A retrospective review was conducted to identify all patients who TM between 2008 and 2014. We divided into two groups, which are TM only (Control group) and IBR following TM (Study group). Both groups were matched by propensity score maximally 1:2. Matched variables concluded age, pathologic stage, estrogen receptor, progesterone receptor status, HER-2 status and year at operation.

Result: After matching, 878 patients included in the control group and 580 patients (197 underwent nipple-sparing mastectomy (NSM) and 383 underwent non-NSM (NNSM) included in the study group. The median follow-up duration was 43.4 (11-100) months for the control group and 41.3 (12-100) months for study group, respectively ($p = 1.000$). The mean age was 47.3 ± 8.46 for the control group and 43.9 ± 7.14 year-old for the study group, respectively ($p > 0.05$). The matching was considered successful not only matching variables but also other factors which associated factors such as family history, histology, multiplicity and lymphovascular invasion. There was no significant difference in overall survival (log-rank $p = 0.4538$), disease free survival (log-rank $p = 0.1861$), local recurrence free survival (log-rank $p = 0.1137$), and distant metastasis free survival (log-rank $p = 0.5368$).

Conclusions: Our results suggest that IBR following NSM or NNSM is a feasible treatment option in breast cancer patients.

BILATERAL SALPINGO-OOPHORECTOMY COMPARED TO GONADOTROPIN-RELEASING HORMONE AGONISTS IN PREMENOPAUSAL HORMONE RECEPTOR-POSITIVE METASTATIC BREAST CANCER PATIENTS TREATED WITH AROMATASE INHIBITORS

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Background: Although combining aromatase inhibitors (AI) with gonadotropin-releasing hormone agonists (GnRHa) is becoming more common, whether GnRHa is as effective as bilateral salpingo-oophorectomy (BSO) remains debatable.

Methods: We retrospectively analyzed the data of 66 premenopausal patients with HR-positive, HER2-negative recurrent and metastatic breast cancer (MBC) who had been treated with AIs in combination with GnRHa or BSO between 2002 and 2015.

Result: The median patient age was 44 years; 24 (36%) patients received BSO and 42 (64%) received GnRHa. The clinical benefit rate (CBR) was higher in the BSO group than in the GnRHa group (88% vs. 69%, $p = 0.092$). Median progression-free survival (PFS) was longer in the BSO group, although statistical significance was not reached (17.2 months vs. 13.3 months, $p = 0.245$). When propensity score matching was performed, median PFS was 17.2 months for the BSO group and 8.2 months for the GnRHa group ($p = 0.137$). In multivariate analyses, the luminal B subtype (HR 1.67, 95% confidence interval [CI] 1.082.60, $p = 0.022$) and later-line treatment ($\geq$ third line vs. first line, HR 3.24, 95% CI 1.596.59, $p = 0.001$) were found to be independent predictive factors for a shorter PFS. In a subset of GnRHa-treated patients, whose disease showed progression, incomplete ovarian suppression was observed, with E2 levels higher than 21 pg/mL.

Conclusions: Both BSO and GnRHa were found to be effective, although BSO treatment was characterized by numerically higher CBR and longer PFS in our AI-treated premenopausal MBC patient cohort. Whether BSO is superior to GnRHa warrants further studies in larger populations.

CLINICAL OUTCOME AFTER OMISSION OF POSTOPERATIVE RADIOTHERAPY AFTER BREAST CONSERVING SURGERY FOR DUCTAL CARCINOMA IN SITU OF THE BREAST: A MULTICENTER, RETROSPECTIVE STUDY IN KOREA (KROG 16-02)

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Background: The potential indication for omitting adjuvant radiotherapy (RT) after breast conserving surgery in low risk ductal carcinoma in situ (DCIS) of the breast is controversial. We evaluated the loco-regional recurrence (LRR) rate in DCIS patients treated with breast conserving surgery without postoperative RT, and investigated the potential risk factors influencing LRR rate.

Methods: Between 2000 and 2010, 311 DCIS patients from 9 institutions were analyzed retrospectively. The median age was 47 (range, 20-82). The median tumor size was 7 mm (range, 0.01-76). Margin width was < 1 cm in 85 patients (27.3%), and nuclear grade was high in 37 patients (11.9%). Two hundred and three patients (65.3%) received tamoxifen.

Result: With a median follow-up of 74 months (range, 5-189), there were 11 local recurrences (invasive carcinoma in 6 and DCIS in 5) and 1 regional recurrence. The 7-years LRR rate was 3.8%. On univariate analysis, age and margin width were significant risk factors influencing LRR ($p = 0.017$ and 0.014, respectively). When age and margin width were combined, the 7-years LRR rates were as follows ($p < 0.001$): (1) 0% in patients with age > 50 years and any margin width status (n = 104), (2) 1.2% in age ≤ 50 years and margin width ≥ 1 cm (n = 93), (3) 5.5% in age ≤ 50 yrs and unknown margin width status (n = 60), (4) 13.1% in age ≤ 50 years and margin width < 1 cm (n = 54).

Conclusions: The LRR rate was very low in selected DCIS patients treated with breast conserving surgery without postoperative RT. However, adjuvant RT should be considered for those with age ≤ 50 years and margin width < 1 cm.

COMPARISON OF TWO DIFFERENT TYPES OF OXIDIZED REGENERATED CELLULOSE FOR PARTIAL BREAST DEFECTS

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Background: A defect after breast conserving surgery, sometimes, is hard to fill with patients own breast tissue. Two different types of oxidized regenerated cellulose (ORC) for filling of partial defects in small-sized breasts were compared with respect to clinicopathologic factors and outcomes.

Methods: A total of 45 patients with breast cancer underwent conventional breast-conserving surgery with insertion of an ORC filling material. The two filling materials used were a hemostasis-purposed ORC and an adhesion barrier-purposed ORC. Clinical factors were compared between these two ORC materials. Both surgeon and patient assessed the cosmetic outcomes using the Harvard/NSABP/RTOG Breast Cosmesis Grading Scale.

Result: Most of the clinicopathologic factors showed no significant difference between the two groups. However, the mean operation time was significantly shorter in the hemostasis-purposed ORC group ($p = 0.027$). Additionally, the infection rate was significantly higher in the adhesion barrier-purposed ORC group ($p = 0.040$).

Conclusions: Reconstructive surgery using a hemostasis-purposed ORC was associated with a shorter operation time and lower incidence of postoperative infection than that using an adhesion barrier-purposed ORC. However, both types of ORC were feasible as filling compounds for partial defects of the breast.

SHOULDER FUNCTION AND STRENGTH AFTER BREAST RECONSTRUCTION: QUANTITATIVE ANALYSIS OF POSTOPERATIVE ISOKINETIC MUSCLE PERFORMANCE TESTING

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Background: Immediate breast reconstruction after mastectomy is proven to affect patients various aspects, including quality of life, psychologic well being and also maintaining functional capacities. In present study, we investigated the effect of breast reconstruction on postoperative shoulder function and muscle performance by evaluating isokinetic muscle performance tests.

Methods: From July 2013 to March 2015, retrospective study was designed to evaluate objective muscle function tests with isokinetic muscle performance testing to patients that received immediate breast reconstruction after mastectomy. Four groups of patients were enrolled to the study; control group without reconstruction, tissue expander insertion, latissimus dorsi (LD) flap, and transverse rectus abdominis muscle (TRAM) flap group. Isometric Muscle Performance Test (IMPT) was measured on four different time intervals after the operation.

Result: By intragroup analysis that compared the results from 3, 6, 9, 12, and 18 months after the surgery, significant shoulder function improvement in tissue expander and TRAM groups were measured by analysis with linear regression. Compared to control group, patients that received immediate reconstruction with expander and TRAM flap showed statistically significant improvement of shoulder function after mastectomy.

Conclusions: Immediate breast reconstruction with TRAM flap and tissue expander insertion were beneficial for shoulder rehabilitation and regaining function compared to mastectomy alone and reconstruction with LD flap.

A SINGLE INSTITUTE ANALYSIS OF ERIBULIN EFFICACY FOR REAL WORLD METASTATIC BREAST CANCER

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Background: The European Medicines Agency (EMA) approval of the usage of eribulin in the treatment of patients with MBC was limited to patients who exposed to a minimum of two previous chemotherapy regimens including anthracyclines and taxanes in the adjuvant or metastatic setting. On the other hand, in Japan we do not have to care this strict limitation. This retrospective analysis was aimed to evaluate effective usage of eribulin in pretreated metastatic breast cancer patients in daily practice.

Methods: Patients treated with chemotherapy, which included at least paclitaxel or eribulin, for metastatic breast cancer between October 2012 and April 2016 were retrieved in this retrospective observational study in our single institute. One hundred and fifty patients were included in the study. The primary efficacy measure assessed overall survival (OS).

Result: Women with estrogen receptor (ER)-positive human epidermal growth factor receptor 2 (HER2)-negative (ER+/HER2), ER+/HER2+, ER-/HER2+ and ER-/HER2- were include 84, 19, 14 and 33, respectively. Of the patients analyzed, among HER2-negative patients, 51 received eribulin (eribulin arm) and 66 received conventional chemotherapeutic agents excluding eribulin (noneribulin arm). The median OS from MBC diagnosis in the eribulin arm was 39.0 months (95% CI 32.0-45.9) compared with 22.7 months (95% CI 14.3-31.1) in the noneribulin arm [hazard ratio (HR): 0.46, 95% CI 0.29-0.73; $p = 0.001$]. This significant difference was not detected amongst ER-/HER2- population.

Conclusions: Eribulin therapy may have a survival benefit in Japanese women with ER+/HER2 MBC, but may not have significant benefit in ER-/HER2- population in routine clinical practice.

COMPARISON OF SKIN SPARING MASTECTOMY USING LIGASURE

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Background: Skin-sparing mastectomy (SSM) is increasingly used in patients with breast cancer. We compared the differences between use of electrocautery and LigaSure™ Small Jaw in patients with breast cancer who underwent SSM.

Methods: Between January 2012 and December 2015, 81 patients with breast cancer who underwent SSM were selected and the LigaSure™ Small Jaw Group based on the devices that were used. Clinicopathological characteristics, removed breast were obtained from medical records. Total amount and days of drain use, until removal, and postoperative skin necrosis, requiring debridement, were also analyzed.

Result: The study population consisted of 50 patients in the Electrocautery Group and 31 in the LigaSure™ Small Jaw Group. The latter group has significantly shorter operative time (117.5 ± 16.9 vs. 104.0 ± 23.6 min, $p = 0.004$). The mean total volume of drainage was less (805 ± 278 vs. 694 ± 131 mL, $p = 0.017$) and mean duration of drainage was also significantly shorter in the LigaSure™ Small Jaw Group (11.3 ± 2.5 vs. 10.1 ± 2.0 days, $p = 0.029$).

Conclusions: The use of LigaSure™ Small Jaw during skin-sparing mastectomy shortened the operative time and duration of drainage, and reduced the total volume of drainage.

EVALUATION OF CARDIAC-VALVES REGURGITATION IN HER2-POSITIVE BREAST CANCER PATIENTS TREATED WITH TRASTUZUMAB

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Background: Investigate the probability, location and time of cardiac-valve regurgitation occurred in HER2-positive breast cancer patients when treated with trastuzumab, analyze the correlations between cardiac-valve regurgitation, Left ventricular ejection fraction (LVEF) as well as the inner diameters of atrial and ventricular, and assess the risk of cardiac toxicity caused by Trastuzumab treatment.

Methods: Retrospective analysis of 338 cases of HER2-positive breast cancer patients confirmed by pathological examination and treated with trastuzumab from November 2010.11 to November 2014.11 in our hospital, Observe the occurrence of cardiac-valve regurgitation in these patients before and after trastuzumab treatment.

Result: Twenty five patients experienced cardiac-valve regurgitation after trastuzumab treatment, and the percentage of cardiac-valve regurgitation caused by trastuzumab is 7.4%. Among these patients, the probability of mitral regurgitation is 44% (11/25), tricuspid regurgitation 8% (2/25), aortic regurgitation 4% (1/25), pulmonary regurgitation 4% (1/25), mitral regurgitation combined with tricuspid regurgitation 24% (6/25), tricuspid regurgitation combined with pulmonary regurgitation 4% (1/25), mitral regurgitation and tricuspid regurgitation combined with pulmonary regurgitation 12% (3/12). There is no statistically significant difference in LVEF or left atrial or ventricular inner diameter in patients experienced cardiac-valve regurgitation after trastuzumab treatment, but the LVEF has the decreasing tendency and the inner diameter of left ventricular has the increasing tendency.

Conclusions: Trastuzumab treatment may cause cardiac-valve regurgitation in patients with HER2 -positive breast cancer, which mainly are mitral regurgitation and tricuspid regurgitation. Among patients experienced cardiac-valve regurgitation, the LVEF has the decreasing tendency, which may be an early indicator of cardiotoxicity caused by trastuzumab

SINGLE INCISION APPROACH FOR BREAST CONSERVATION SURGERY AND SENTINEL LYMPH NODE BIOPSY

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Background: Breast conserving surgery (BCS) have placed greater emphasis in optimizing aesthetic outcomes for breast oncological surgery. In keeping with this placement of incisions is an important consideration. In this study we review a series of breast conservation surgery cases performed via a single incision in the axillary fold evaluate the oncological safety and aesthetic outcomes in an Asian population.

Methods: Patients who underwent BCS with sentinel lymph node (SLN) biopsy using blue dye tracer through a single axillary fold incision at the National Cancer Centre Singapore from October 2012 to October 2016 were retrospectively reviewed. Early breast cancer, defined as tumour up to 5 cm in the upper outer quadrant with clinically node negative disease, were selected for this procedure. After harvesting the SLN, wide excision was done through the same incision by raising a skin flap.

Result: Thirteen cases were identified, median tumor size was 2.5 cm, average age was 51.8 years old. Ten patients had invasive ductal carcinoma, 1 had invasive lobular carcinoma and 2 had mixed invasive ductal and lobular carcinoma. Two (15.4%) had positive margins requiring completion mastectomy, 2 (15.4%) patient had SLN positive for metastases requiring axillary clearance. There were no post-operative complications and patient reported aesthetic outcomes were excellent. At median follow-up of 25 months, there is no loco-regional recurrence or systemic disease.

Conclusions: Single axillary fold incision is an oncologically safe option for women with tumours in the upper outer quadrant and produces aesthetically superior outcomes by avoiding a scar in the breast without the need for additional oncoplastic surgery.

SEROMA CHANGES DURING MAGNETIC RESONANCE IMAGING-GUIDED PARTIAL BREAST IRRADIATION AND ITS CLINICAL IMPLICATIONS

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Background: To investigate the patterns of post-lumpectomy seroma volume (SV) change and related clinical factors to determine the benefits of adaptive planning in patients treated with magnetic resonance imaging (MRI)-guided partial breast irradiation (PBI).

Methods: MRI data obtained from 37 women with early breast cancer acquired at simulation and at the 1st, 6th, and 10th fractions were analyzed. The planning target volume (PTV) was defined as unequal margins of 10-15 mm added according to the directional surgical margin status of each seroma. Treatment was performed using a 0.35T MRI-guided radiotherapy system. Univariate analysis was performed to assess the correlations between SV change rate and clinical factors. Seroma and PTV for adaptive planning were based on the images obtained at the 6th fraction.

Result: The average time intervals between surgery-simulation, simulation-1st, 1st-6th, and 6-10th fractions were 23.1, 8.5, 7.2, and 5.9 days, respectively. Of the 37 patients, 33 exhibited decreased SV over the treatment period. The mean SV of these 33 patients decreased from 100% at simulation to 60%, 48%, and 40% at each MRI scan. In most cases (26/33), the logarithm of SV was inversely proportional to the elapsed time from surgery ($R^2 > 0.90$, Pearsons correlation test). The volume of spared normal tissue from adaptive radiotherapy was proportional to the absolute change in SV ($R^2 = 0.89$, Pearsons correlation test).

Conclusions: Seromas exhibit exponential shrinkage over the course of PBI. In patients receiving PBI, frequent monitoring of SV could be helpful in decision-making regarding adaptive planning, especially those with a large seroma.

TREATING BREAST CANCER IN THE VERY ELDERLY (>80 YEARS): OUTCOME OF SURGERY

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Background: The optimal treatment of breast cancer for elderly patients (Aged >80 years) is debatable. With an aging population, management of this group of patients will be increasingly common. This study aims to compare the survival outcomes of very elderly women against younger patients, following different treatment modalities within each stage. We also examined how treatment patterns and outcomes differ across different stages.

Methods: Singapore Citizens and Permanent Residents who were diagnosed with breast cancer from 2003-2014 were identified from the Singapore Cancer Registry. Patients were divided into 2 age groups, below and above 80 years of age, and categorized into 3 main treatment groups, namely surgery, non-surgical treatment, and no treatment. Analysis was made on their survival outcomes.

Result: 19,314 patients were diagnosed with breast cancer during the 11-year study period. 1,482 patients were excluded due to unknown stage. 673 patients were aged 80 years and above, while 17,159 patients were aged below 80. Elderly women presented with later stages of disease, and were less likely to have surgery. When performed, surgery provided the greatest survival benefit in those with Stage II disease. In Stage I and II, the 5-year breast cancer specific outcome following surgery, was not significantly different between patients from the 2 age groups. Those who did not have surgery performed better with endocrine therapy than with no treatment.

Conclusions: Elderly patients, especially those with Stages I and II breast cancer do not fare worse than younger patients, and should be offered surgery if they are fit.

IMPROVEMENT OF SURVIVAL OUTCOMES WITH ENDOCRINE TREATMENT OF HORMONE RECEPTOR POSITIVE YOUNG BREAST CANCER PATIENTS

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Background: We investigated the oncologic outcomes by intrinsic subtype and age in young patients with invasive breast cancer and whether survival differences were related to treatment changes over time.

Methods: A retrospective analysis was performed on 9,633 invasive breast cancer patients treated at Asan Medical Center from January 1989 to December 2008. We also enrolled a matched cohort adjusting for tumor size, lymph node metastasis, subtypes, and tumor grade. Patients aged < 35 years were included in the younger group ($n = 602$) and those aged ≥ 35 years were included in the older group ($n = 3,009$).

Result: The younger patients showed a significantly higher T stage, a more frequent axillary node presentation, higher histologic grade, and higher incidence of triple negative subtype tumors than older patients and also received more chemotherapy and were less likely to undergo hormone therapy. The younger patients with HR-positive tumors showed significantly poorer disease-free survival (DFS), loco-regional recurrence free survival, distant metastasis free survival, and breast cancer-specific survival outcomes than older patients. Younger patients with HR positive and HER2 negative (HR+/HER2-) tumor subtypes had a significantly improved DFS over time ($p = 0.032$). Within the HR+/HER2- subtype, more women received gonadotropin releasing hormone (GnRH) agonist and tamoxifen treatment from 2003-2008 compared with 1989-2002 ($p = 0.001$ and $p = 0.075$, respectively).

Conclusions: Hormone receptor positive young breast cancer patients have a poorer survival compared with older patients, even with more frequent chemotherapy, but more recent use of tamoxifen and ovarian suppression might improve this outcome in these patients.

THREE DIMENSIONAL DOSIMETRIC VALIDATION OF THE EUROPEAN ORGANIZATION FOR CANCER RESEARCH AND TREATMENT 22922 TRIAL USING KOREAN RADIATION ONCOLOGY GROUP 0806 PATIENTS

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Background: European Organization for Cancer Research and Treatment (EORTC) 22922 is one of the landmark trials to prove the efficacy of regional nodal irradiation using two-dimensional radiotherapy for breast cancer patients. The purpose of this study was to perform three-dimensional dosimetric validation of the EORTC trial using the Korean Radiation Oncology Group (KROG) 0806 patients.

Methods: Two most commonly used treatment plans according to the EORTC protocol were analyzed for 12 patients with left-sided breast cancer each. The junction between the lateral edge of internal mammary (IM) field and the tangential fields were matching exactly and overlapping 1 cm in plan A and B, respectively. Target volume delineation and normal organ contouring were based on the European Society for Radiotherapy and Oncology guideline for early breast cancer.

Result: IM nodes received an average of 95.1 ± 1.6 % and 105.2 ± 3.3 % of prescription dose in plan A and B, respectively. No significant dosimetric differences were seen for supraclavicular nodes, axillary nodes and ipsilateral lung. However, plan B delivered higher doses to the breast or chest wall as well as to the heart and the left anterior descending coronary artery as compared with plan A.

Conclusions: The two most commonly used RT treatment techniques in the EORTC trial provided reliable three-dimensional dosimetric coverages of IM nodes based on three-dimensional planning in the KROG 0806 patients, with a higher dose to the heart when in the case of overlapping field borders.

RE-EXCISION RATE IN BREAST CONSERVATION SURGERY AFTER NEOADJUVANT CHEMOTHERAPY

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Background: The purpose of this study was to compare the re-excision rate and breast conserving surgery (BCS) success rate of patients who received and who did not received neoadjuvant chemotherapy.

Methods: In this retrospective cohort study, between January 2009 and December 2012, total 256 women were included who had clinical T2 breast cancer and were planned to receive BCS as initial operation(197 pts) or neoadjuvant chemotherapy (59 pts). The data were collected including age, initial tumor size, mammographic microcalcifications, ultrasound multifocality and axillary nodal status. And we reviewed the pathologic tumor size, multifocality, histologic type, ER, PR, HER-2, ki67, DCIS, and EIC. The re-excision rate and BCS success rate were investigated. Univariate analysis and regression model were used. To reduce the effect of selection bias, propensity score matching-based anaylsis was also performed.

Result: Of the 256 patients, 178 patients (90.4%, 178/197) received BCS finally in neoadjuvant group and 56 patients (94.9%, 56/59) in non-neoadjuvant group ($p = 0.406$). In propensity-matched cohorts (N = 118), the re-excision rate was same in two groups (35.6%) in neoadjuvant group vs. 35.6%) in non-neoadjuvant group, $p = 1.000$). BCS success rate was higher in neoadjuvant group (94.9% 56/59) than non-neoadjuvant group (86.4% (51/59), $p = 0.205$). Clinicopathologic factors associated with re-excision were pathologic multifocality (OR = 4.56, $p = 0.0142$), high ki67 ($\geq 50\%$) (OR = 0.7, $p = 0.0243$) and DCIS component (OR = 2.67, $p = 0.0261$) in logistic regression model.

Conclusions: This study showed neoadjuvant chemotherapy could increase the BCS success rate but could not decrease the re-excision rate. The re-excision rate is more associated with pathologic finding rather than effect of neoadjuvant chemotherapy.

SECOND SENTINEL LYMPH NODE BIOPSY IN PATIENTS WITH LOCAL RECURRENCE AFTER BREAST CANCER SURGERY

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Background: We evaluated feasibility and pathologic outcomes of second sentinel lymph node biopsy (SLNB) in patients with locally recurrent breast cancer and their follow-up results.

Methods: From July 2008 to June 2016, second lymphatic mapping was performed in 47 patients for locally recurrent breast cancer. When sentinel lymph node (SLN) was visualized in lymphangiography, SLNB was performed. In the cases which SLN metastasis was confirmed, axillary lymph node dissection (ALND) was performed. Follow-up studies were performed every 6 months for 5 years and then annually.

Result: In 43 patients (91.49%), lymphatic mapping was successfully performed. Aberrant lymphatic pathway which was usually drained to contralateral axillary lymph node (LN), ipsilateral internal mammary LN(IMLN) or chest wall was observed in 15 patients (34.9%). The rate of aberrant lymphatic pathway was higher in patients who underwent ALND previously then in patients who underwent SLNB only (81.8% vs. 18.8%, $p < 0.001$). In 6 patients who previously underwent ALND followed by radiation therapy, all their lymphatic pathway was altered. Among 42 patients who underwent SLNB, SLNs were identified in 36 patients (85.7%). 4 patients (11.11%) had tumor metastasis in their SLNs which were identified at ipsilateral axilla, contralateral axilla or ipsilateral internal mammary lymphatic chain. The mean follow-up period after second operation was 33.70 ± 26.25 months. There were 10 cases (21.28%) of loco-regional recurrence or distant metastasis. One patient whose second SLNB was failed had ipsilateral axillary recurrence solitary.

Conclusions: Second SLNB for locally recurrent breast cancer should be considered because occult LN metastasis could be identified in the ipsilateral axilla or other site through aberrant lymphatic pathway.

FACTORS ASSOCIATED WITH NONADHERENCE TO ADJUVANT ENDOCRINE THERAPY FOR BREAST CANCER VARY DEPENDING ON WHETHER NONADHERENCE REASONS ARE INTENTIONAL OR UNINTENTIONAL

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Background: Adherence to adjuvant endocrine therapy (AET) greatly increases the survival rate of patients with estrogen receptor-positive breast cancer. However, the reasons for nonadherence, as well as the associated factors, are not known. The purpose of this study was to investigate whether the factors associating with intentional nonadherence are different from those associating with unintentional nonadherence.

Methods: Two hundred ten patients with estrogen receptor-positive breast cancer undergoing AET were enrolled in this cross-sectional study. Adherence to AET was self-reported on the Morisky Medication Adherence Scale-8 (MMAS-8) questionnaire, and each query was scored as either intentional or unintentional. Patients adhering to AET (n = 54, subgroup 1, control) had a MMAS-8 score of 8. By contrast, patients nonadhering to AET were categorized as unintentional (n = 62, subgroup 2), intentional (n = 9), or mixed-type (n = 85, subgroup 3). Information on sociodemographic and clinical variables, including AET beliefs and symptoms of menopause and depression, was also collected and compared among subgroups.

Result: Nine variables were evaluated by multivariate logistic regression analysis. An unfavorable balance in AET beliefs and mild or severe symptoms of depression were independent predictors of mixed-type nonadherence vs. adherence [adjusted odds ratio (OR) = 5.89 (95%CI, 1.80-19.25) and 4.30 (95%CI, 1.41-13.09), respectively], but not of unintentional nonadherence vs. adherence (all $P > 0.05$). Age (< 50 years old) was the only independent predictor of unintentional nonadherence vs. adherence [adjusted OR = 3.49 (95%CI, 1.09-11.17)].

Conclusions: The factors associating with intentional nonadherence to AET are different from those associating with unintentional nonadherence. These findings can be applied to clinical protocols to improve adherence to AET by breast cancer patients.

TECHNICAL ASPECTS OF BREAST-CONSERVING SURGERY FOR PARTIAL BREAST IRRADIATION WITH MULTICATHETER BRACHYTHERAPY BASED ON EXPERIENCE WITH 367 CASES

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Background: In adjuvant radiotherapy after breast-conserving surgery, whole breast irradiation (WBI) requires daily for up to 3 weeks or longer. Partial breast irradiation (PBI) is a more convenient that can be performed in 5 days or less. The GEC-ESTRO conducted a large randomized phase 3, non-inferiority trial to compare the efficacy of multicatheter brachytherapy (MCB) with WBI. Although this trial has demonstrated that MCB-PBI showed an equivalent efficacy to WBI, limited data are available for Japanese patients.

Methods: Patients aged ≥40 years, with a maximum tumor diameter of ≤3.0 cm, and with sentinel nodes negative were eligible for MCB-PBI. After removal of the tumor, surgical clips were placed. Insertion of catheters was performed under direct visualization of the tumor cavity. Interstitial brachytherapy was performed with a dose of 32 Gy in 8 fractions over 56 days. Post-treatment follow-up included an annual mammography and contrast-enhanced breast MRI.

Result: Between 2008 and 2016, 367 consecutive patients underwent MCB-PBI. The mean age was 56.8 years, and the median follow-up time was 4 years. Ipsilateral breast tumor recurrence (IBTR) was observed in 7 (true: 3, elsewhere: 4) patients (1.9%, 95% CI: 0.5%3.3%). Complications occurred in 24 patients, of which 18 (4.9%), 5 (1.4%), and 2 (0.5%) were infection, bleeding, and fat necrosis, respectively, which were not considered serious complications.

Conclusions: Although there was a relatively small number of patients and a short follow-up period, MCB-PBI had an adequate clinical efficacy in Japanese patients.

CLINICAL AND ONCOLOGICAL OUTCOMES AFTER A NIPPLE-AREOLA COMPLEX SPARING MASTECTOMY AND IMMEDIATE POSTOPERATIVE RECONSTRUCTION IN PATIENTS WITH BREAST CANCER

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Background: Recently, nipple-areola complex (NAC) sparing mastectomy (NSM) and immediate reconstruction are gaining popularity with better cosmetic outcomes compared to traditional method for breast cancer patients. This study aims to report our clinical and oncological outcomes after NSM.

Methods: This study is a retrospective review of prospectively collected data. Seventy four patients with breast cancer without metastasis underwent NSM and immediate reconstruction from April 2010 to September 2015. Surgical complications and cancer recurrences after reconstruction following NSM were analyzed.

Result: Following NSM, implant (n = 70, 94.6%) or transverse rectus abdominis myocutaneous flap (n = 4, 5.4%) was used for reconstruction. During the follow-up period (36.2 ± 21.5 months), NACs were failed in seven patients (9.5%) due to necrosis and implants were removed in three patients (4.1%) due to infection. Patients with NAC failure had a significantly higher body mass index (26.0 ± 2.6 kg/m^2 vs. 21.9 ± 2.6 kg/m^2, $p < 0.001$). Patients with radiation therapy showed a higher NAC failure rate compared to patients without radiation therapy; however the difference was not significant (28.6% vs. 7.5%, $p = 0.255$). Two patients (2.7%) and six patients (8.1%) suffered loco-regional recurrence (LR) and distant metastasis, respectively; there was no recurrence on NAC among LRs. No significant difference was observed in LR rate as well as in distant metastasis rate between patients with NAC failure versus without NAC failure (14.3% vs. 1.5%, $p = 0.446$; 14.3% vs. 7.5%, $p = 1.000$). There was no mortality.

Conclusions: NSM and immediate reconstruction can be performed safely in selected patients. Further studies with long-term follow-up are needed for verifying long-term oncologic safety.

IS OBESITY A FACTOR THAT AFFECTS DURATION OF SEROMA DRAINAGE AFTER MASTECTOMY?

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Background: The duration of seroma drainage after mastectomy is the most influential factor in the patient hospital length. The purpose of this study was to investigate the relationship between prolonged seroma drainage and obesity.

Methods: We reviewed medical records and calculate Obesity index (BMI, Broca index) in 104 female mastectomy patients performed by one breast surgeon from January 2014 to December 2016.

Result: A drain was removed when the amount of drainage was less than 20 cc. And the average duration of seroma drainage was 8.64 ± 0.33 days. There was a slight correlation between the duration of drainage and BMI ($p = 0.044$) and Broca Index ($p = 0.046$). Age, height, weight, and number of axillary nodes removed were not correlated with drainage duration. However, there was no significant difference in BMI ($p = 0.247$) and Broca index ($p = 0.270$) between the two groups when the patients were divided into two groups: drainage removal within 7 days ($n = 43$) and drainage removal after 7 days ($n = 61$). And there was no difference in the composition of obesity - altitude obesity among the two groups ($p = 1.0$). Immediate breast reconstruction with implant resulted in significant long-term seroma drainage ($p = 0.000$).

Conclusions: Although there is a slight correlation between BMI and seroma drainage, it is difficult to see the factors affecting the duration of hospitalization. In addition, obesity was not a significant factor for long-term seroma drainage in this study. Immediate breast reconstruction with the implant was the only significant factor in prolonged seroma drainage.

S-PHASE KINASE-ASSOCIATED PROTEIN 2 IS A NOVEL TARGET OF CARVACROL TO EXERT ANTI-PROLIFERATIVE EFFECT IN BREAST CANCER CELLS

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Background: S-phase kinase-associated protein 2 (Skp2), an oncogenic protein, plays an important role in cell cycle progression, cell proliferation, and anti-apoptosis. In this study, we examined the effect of carvacrol, a monoterpenoid phenol found in oregano, on Skp2 expression and its downstream effectors such as p21 and/or p27 in breast cancer cells.

Methods: 1) Carvacrol was obtained from Sigma-Aldrich. MCF-7 and MDA-MB 231 cells were purchased from the ATCC. 2) For Western blot analysis, specific antibodies against Skp2, p21, p27 and GAPDH, as well as secondary antibodies were obtained from Santa Cruz Biotechnology. 3) For modulation of Skp2 expression, the recombinant plasmid, pcDNA3- Skp2, or siRNA against Skp2 was used. 4) To observe anti-proliferative activity of carvacrol, cell viability and zlonogenic assay was conducted.

Result: Carvacrol treatment of MDA-MB 231 cells was found to induce a dose dependent decline of Skp2 protein levels. RT-PCR assay also showed that Skp2 mRNA level was reduced by carvacrol, suggesting the transcriptional down-regulation of Skp2 expression by carvacrol. It was further observed the synergistic anti-proliferative effect of carvacrol in cells transfected with Skp2 specific siRNA, while the cytotoxic effect of carvacrol was attenuated in Skp2 overexpressing cells. In addition, carvacrol was found to result in apoptotic cell death as well as the increase of p21 and p27, cyclin-dependent kinase inhibitors, in MCF-7 and MDA-MB 231 cells.

Conclusions: Taken together, our data indicate that Skp2 seem to be novel targets of carvacrol to inhibit cell proliferation and to induce apoptotic cell death in breast cancer cells.

PO041

TRENDS OF IMMEDIATE BREAST RECONSTRUCTION FOLLOWING TOTAL MASTECTOMY AFTER KOREAN NATIONAL HEALTH INSURANCE SYSTEM COVERING IN PATIENTS WITH BREAST CANCER: A TERTIARY SINGLE CENTER EXPERIENCE

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Background: To improve access to breast reconstruction for patients with breast cancer, immediate breast reconstruction (IBR) was covered by the insurance system in Korea from April 2015. We analyzed the changes after the Koran national health insurance system covered IBR for patients with breast cancer.

Methods: A retrospective study conducted from a tertiary single institution. Patients who underwent IBR following mastectomy for primary breast cancer between April 2011 and June 2016 were included. Based on insurance coverage, the patients were divided into before and after insurance coverage groups.

Result: Proportion of IBR among total mastectomy (TM) increased from 30.1% (625 IBR following TM of 2079 TM only) to 40.4% (325 IBR following TM of 804 TM only) ($p < 0.0001$). Patients who have more age (median age (range); 43 (38-48) vs. 45 (40-50), $p < 0.0001$), more patients who planned adjuvant radiotherapy (RT) (n (%); 100 (16.0) vs. 65 (20.0), $p < 0.0001$), more patients who previously treated RT patients (n (%); 6 (1.0) vs. 19 (5.8), $p < 0.0001$), and more patients who underwent neoadjuvant chemotherapy (n (%); 28 (4.5) vs. 17 (5.2), $p = 0.0105$) underwent IBR after insurance coverage. The proportion of stage I and II patients with breast cancer underwent IBR increased between two groups ($p = 0.0006$, $p < 0.0001$, respectively) and the proportion of stage III breast cancer patients underwent IBR showed no significantly difference between two groups ($p = 0.0751$).

Conclusions: The proportion of IBR following mastectomy has significantly increased and the indication of IBR has expanded after the Korean national health insurance system covering IBR for the breast cancer patients.

IMPACT OF TIMING FOR BRCA MUTATION ON SURGICAL DECISION IN BRCA CARRIERS WITH BREAST CANCER

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Background: The first aim of our study was to evaluate the surgical decision making of BRCA mutation carriers based on timing of knowledge of BRCA mutation status. The second was to evaluate outcome of breast cancer following surgical treatment.

Methods: This was a retrospective study of 823 patients diagnosed with invasive breast cancer, tested for BRCA mutation and treated with primary surgery at Samsung Medical Center between 2004 and 2015. We reviewed timing of the BRCA test results and types of surgery. Types of initial surgery were classified by breast conserving surgery (BCS), unilateral mastectomy, or bilateral mastectomy and we established whether contralateral mastectomy and risk reducing mastectomy.

Result: Among 823 patients, a total of 164 BRCA mutation carriers were identified. Only 15 (8.2%) patients had known the BRCA test results before their surgery whereas 149 (90.9%) had known the results after the surgery. In patients with unilateral cancer, there was a significantly difference between groups whose BRCA mutation status known before surgery and groups whose BRCA status unknown before surgery regarding choice of surgery ($p = 0.017$). There was no significant difference across surgery types for ipsilateral breast tumor recurrence (IBTR) ($p = 0.924$), and there was no significant difference for risk of contralateral breast cancer ($p = 0.69$).

Conclusions: Identification of a BRCA mutation status can influence surgical decision making for breast cancer treatment. Thus, it is important to provide genetic counselling and genetic testing before surgical choice and development of treatment strategies needs for patients with a high risk of breast cancer.

PO043

12-YEAR SINGLE-INSTITUTE EXPERIENCE WITH POSTMASTECTOMY BREAST RECONSTRUCTION

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Background: Various surgical options exist for reconstructing the breast following mastectomy. Data on patients receiving breast reconstruction at a single institute may reflect changing trends regarding methods and materials used in breast reconstruction. We introduce our experience of post-mastectomy breast reconstruction.

Methods: A retrospective chart review was conducted of patients diagnosed with breast cancer, carcinoma in situ, or breast deformity undergoing breast reconstruction from 2005 to 2016 at Seoul National University Bundang Hospital. Timing and method of reconstruction, type of mastectomy, vascular pedicle, artificial dermis usage, microsurgical success, and contralateral procedures were noted. Patients were divided into four chronological groups: group 1, 2005–2007; group 2, 2008–2010; group 3, 2011–2013; and group 4, 2014–2016.

Result: A total of 471 patients were evaluated, including 93 delayed and 378 immediate reconstructions. There was an abrupt increase in the number of reconstructions in 2015, when national insurance began providing coverage for breast reconstruction. Use of free TRAM flap increased while that of tissue expanders decreased significantly from group 3 to 4. Type of recipient pedicle consisted entirely of thoracodorsal vessels in groups 1, but use of internal mammary vessels increased significantly over time. 74.5% of breast conserving surgery cases received pedicled Latissimus dorsi (LD). Alloderm use for TRAM donor site increased significantly in group 4. Microsurgical success rate was 95%.

Conclusions: Increase in demand for breast reconstruction is reflected in our data. Type of mastectomy had an influence on method of reconstruction. Artificial dermis is increasingly being used for prevention of abdominal bulging or hernia in TRAM patients.

COMPARISON OF 9-WEEK AND 1-YEAR ADJUVANT TRASTUZUMAB THERAPY IN HER2-POSITIVE BREAST CANCER: A RETROSPECTIVE STUDY

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Background: Adjuvant trastuzumab has become established as the standard treatment for HER2-positive breast cancer, on the basis of the results of randomized controlled trials (RCT) since 2005. Even now, the optimal duration remains debatable because of inconsistency between the treatment protocols of each RCTs. The aims of this study are comparing of oncologic outcomes and adverse events between patients receiving trastuzumab once weekly for 9 weeks and once every 3 weeks for 1 year.

Methods: We reviewed the medical records of total 118 patients who received adjuvant trastuzumab therapy from January 1, 2008 to October 31, 2011 at Chungnam national university hospital and patients are subgrouped by intended duration of treatment. Patients of 9 week protocol is group 1 and those of 1 year is group. Oncologic outcomes and cardiac toxicity were primary end points.

Result: Five year survival were 92.5% and 88.5% in group 1 and 2, respectively ($p = 0.709$). Five year disease free survival were 76.7% and 79.4% in group 1 and 2, respectively ($p = 0.896$) There were no significant differences of 5 year OS and DFS between each groups regardless of hormone receptor status or axillary lymph node status. Cardiac toxicity were no significant differences between each groups, also.

Conclusions: Our results suggest that 9-week adjuvant therapy can be as effective as 1-year therapy in HER2 positive breast cancer patients. We did not verify a correlation between shorter treatment duration and lower cardiac dysfunction and early termination rates but 9-week therapy could be an alternative method in patients with poor compliance for longer treatment period.

THE USEFULNESS OF ONCOPLASTIC BREAST SURGERY WITH ROTATION FLAP IN PARTIAL MASTECTOMY DEFECT

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Background: With advancements in screening and radiotherapy, breast conserving surgery (BCS) is becoming a safe option in the treatment of early breast cancer patients. Rotation flap is a type of oncoplastic breast surgery that involves transposition of tissue from the lateral aspect of the partial mastectomy defect. The outcomes of the rotation flap in various locations over the past 10 years are reviewed.

Methods: We performed a retrospective study of 54 patients who underwent rotation flap between 2007 and 2016. We analyzed patient information such as breast size, tumor weight, defect size, complications using medical charts review, and classified patients into groups according to the location of the defect.

Result: The mean BMI was 23.85, and the mean tumor weight was 86.26 g. A defect was a moderate size as it was 25.22% of a total breast volume. In terms of defect locations, the most common was superomedial (9–11 oclock) in 23 patients, followed by superocentral (11–1 oclock) in 20 patients, superolateral (13 oclock) in 7 patients, and 4 patients in inferior. Complications included partial necrosis and wound dehiscence.

Conclusions: The results shows that rotation flap can cover most moderate sized defects after BCS. Among these, for the superomedial aspect, volume displacement techniques are insufficient to cover moderate sized defects, while donor morbidity is an issue for volume replacement. Conversely, rotation flap could be a useful method for such cases, since it is a relatively simple procedure, shows fewer complications and lower donor morbidity, and shows excellent aesthetic outcomes.

CLINICAL ANALYSIS OF REDUCTION MAMMAPLASTY IN COMBINATION WITH BREAST CANCER SURGERY

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Background: Although reduction mammaplasty is a well-described technique for aesthetic purposes, there are few previous reports regarding its clinical outcome following breast cancer operation. The aim of this study is to investigate the advantages of reduction mammaplasty and the satisfaction of breast cancer patients who are capable of reduction mammaplasty.

Methods: Oncologic data and patient demographics were collected. Reconstructed and opposite breast complications were evaluated. Reduction mammaplasty surgery was performed to correct ptosis and obtain symmetry of both breasts immediately after breast cancer operation. We performed periodic follow-up to investigate postoperative aesthetic evaluation and complication.

Result: 24 patients underwent immediate reduction mammoplasty. In 95.8 percent they were located in the upper portion of breast. Breast complications occurred in 6 patients (25.0 percent). Obese patients (BMI > 25) and large amount reduction volume (volume > 400) patient had a significantly higher rate of reconstructed breast complications compared with the normal/overweight patients ($p < 0.05$) and non-large amount reduction volume patients ($p < 0.05$). No significant association between complications and old age, or axillary lymph node dissection was found.

Conclusions: Reduction mammaplasty is a useful technique as reconstruction for ptotic and larger breast patients. Complications are more often observed in the reconstructed breast, and obese patients and smokers are higher risk patients.

PATHOLOGICAL AND IMAGING FEATURE OF 15 CASES OF METAPLASTIC BREAST CANCER INCLUDING RECURRENT HEMATOMA FORMING METAPLASTIC BREAST CANCER

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Background: Metaplastic carcinoma of the breast is a rare pathologic entity accounting for about 1% of breast carcinomas. The aim of this study was to analyze the pathological and imaging feature of 15 cases of metaplastic breast cancer including one unusual case of metaplastic breast cancer with forming recurrent hematoma.

Methods: We retrospectively reviewed the chart and pathological reports of 15 cases with metaplastic carcinoma of the breast treated at the Konkuk medical hospital between January 2011 and December 2016.

Result: The pathological findings were obtained as follows: 7 patients were diagnosed with squamous cell carcinoma, 3 patients with chondroid differentiation, 3 patients with mixed metaplastic carcinoma and 2 patients with spindle cell carcinoma. The median age was 61yeras with 2 patients older than 80years. Of the available receptor status, 4 patients were ER positive with PR negative, the majority of patient were triple negative (10/15) and one patient was Her2/neu positive. Of the available Ki-67 data, expression levels of all the patients are higher that 20%. Features of VI and LI are absent in all the patients. The imaging features of majority of the patients were ill-defined hypoechoic mass in US findings and irregular round mass in Mammographic findings, 3 patients were accompanied by microcalcification which were squamous cell carcinoma. The most common MRI findings are rim-enhanced cystic pattern in 7 out of 15 patients.

Conclusions: Metaplastic carcinoma is a rare pathologic subtype of breast cancer. Such pathologic, imaging and clinical specialties are essential in distinguishing metaplastic carcinoma from other type of breast cancer.

ANALYSIS OF CLINICOPATHOLOGICAL FEATURES OF MALE BREAST CANCER COMPARED WITH FEMALE BREAST CANCER PATIENTS IN THE SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) DATABASE

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Background: Male breast cancer (MBC) is a rare malignant tumor compared with female breast cancer, accounting for 1% of all breast cancers and it has showed a significant increase in recent years. However, there is low attention on MBC. The purpose of the present study is to compare the clinicopathological features between male and female breast cancer patients.

Methods: We retrospectively investigated Surveillance, Epidemiology, and End Results (SEER) population-based data and identified 5,015 male and 764,246 female cases respectively between 1998 and 2013. We used Pearson chi-square test to compare the clinical diagnosis of breast cancer between male and female patients.

Result: Age at diagnosis, TNM stage, lymph node involvement, tumor size, and SEER stage were measured in this study. In our results, we found that male and female patients above 60 years old accounted for 67.96% and 51.63%, respectively ($p < 0.0001$), showing that the male patients were more likely to be older when diagnosed for breast cancer. Male patients also demonstrated more lymph node involvement than female patients ($p < 0.0001$). In addition, tumor size of male patients was found to be larger than female patients ($p < 0.0001$). Furthermore, SEER stage of male patients was higher compared with female patients ($p < 0.0001$). Additionally, the difference between male and female patients on TNF stage didn't show statistical difference during the analysis ($p = 0.6146$).

Conclusions: The results of our study showed that male patients condition was more critical when diagnosed with breast cancer. This warranted that further future researches should put more attention on early diagnostic and effective preventive measures.

ONCOLOGIC OUTCOME OF MARGIN NAGATIVE NIPPLE SPARING MASTECTOMY WITHOUT ADJUVANT BREAST RADIATION THERAPY

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Background: Oncologic safety and cosmetic effect are the important consideration in making a surgical decision. Nipple sparing mastectomy (NSM) is a method of preserving nipple-areola complex (NAC) and has gradually received more attention from healthcare professionals as well as patients with breast cancer. However, the standard guideline for safety and eligibility criteria is not established yet. This study is to describe the effect of NSM without adjuvant radiation therapy (RTx) on the oncologic outcome.

Methods: This is a retrospective study which includes 80 patients undergoing NSM and immediate breast reconstruction from 2010 to 2015 in a single center. We obtained clinical data through medical record review.

Result: The average follow-up was 30.61 months after surgery (range, 2-78 months). All subjects had ductal carcinoma in situ (33.75%) or breast cancer (66.25%) and were diagnosed as early stage cases (0-I, 97.5%; II, 2.5%). We confirmed that all patients did not have cancer cell on subareolar tissue through frozen biopsy performed in operation. Ductal carcinoma in situ on peripheral margin on postoperative biopsy was found in 2 cases. According to postoperative subareolar biopsy, 2 cases had atypical cell, 1 case had intraductal papilloma, and 2 cases had carcinoma in situ. Two of all patients received additional nipple excision because of inconsistency between subareolar frozen section and permanent biopsy. No recurrent cases were found during the follow-up period.

Conclusions: Our finding revealed that NSM without adjuvant RTx is clinically useful for patients diagnosed with cancer cell negative for peripheral margin and nipple areolar complexes (NAC) at permanent biopsy.

TIME TRENDS OF ADJUVANT CHEMOTHERAPY IN HORMONE RECEPTOR-POSITIVE BREAST CANCER AFTER ADOPTION OF THE 21-GENE ASSAY

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Background: In node-negative, hormone receptor-positive breast cancer patients, 21-gene assay is useful to decide adjuvant chemotherapy. Since the use of 21-gene assay, adjuvant chemotherapy rate has declined in patients with 21-gene assay results. The aim of this study is to investigate the time trends of adjuvant chemotherapy in hormone receptor-positive breast cancer patients without results of 21-gene assay.

Methods: We identified all consecutive 2,038 hormone receptor-positive, HER2-negative breast cancer patients with 0-3 node metastasis who were diagnosed at National Cancer Center in Korea between 2010 and 2015. Among the 2,038 patients, 1,560 patients (76.5%) did not receive 21-gene assay. These patients were categorized into subgroups according to nodal status (N0/N1mi vs. N1). We analyzed the time trends of adjuvant chemotherapy between these subgroups.

Result: Adjuvant chemotherapy rate decreased gradually from 76.8% to 40.6 in all groups between 2010 and 2015 ($p < 0.001$). In the subgroup analysis, the rate decreased from 71.6% to 31.4% in N0/N1mi group ($p < 0.001$) and 97.9% to 78.3% in N1 group ($p = 0.002$) respectively. Because we started to perform 21-gene assay from 2012, we analyzed the trend of adjuvant chemotherapy before and after 2012. Adjuvant chemotherapy rate significantly decreased in the whole group (72.9% vs. 48.6%, $p < 0.001$), N0 / N1mi group (66.7% vs. 42.2%, $p < 0.001$) and N1 group (94.4% vs. 79.3%, $p < 0.001$).

Conclusions: After adoption of the 21-gene assay, adjuvant chemotherapy rate decreased over time even in the patients without 21-gene assay. Biologic behavior as well as stage of hormone-receptor positive breast cancer influenced decision making about adjuvant chemotherapy.

PO051

PRELIMINARY CLINICAL OUTCOME AND SAFETY AFTER ACELLULAR DERMAL MATRIX VOLUME REPLACEMENT SURGERY IN BREAST CONSERVING PROCEDURES

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Background: Acellular dermal matrix (ADM) are soft tissue matrix grafts created by a process that results in decellularization but leaves the extracellular matrix intact. This matrix provides a scaffold upon and within which the patient's own cells can repopulate and revascularize the implanted tissue. Its utility has been demonstrated in various reconstructive techniques, particularly in burn, abdominal wall, and breast reconstruction. With increasing frequency, surgeons are electing to use acellular dermis to assist with tissue expander or implant-based primary breast reconstruction. However, ADM is rarely used in breast conserving procedure. We here by present preliminary clinical outcomes including histologic and radiologic findings after ADM volume replacement surgery in breast conserving procedures to address clinical safety of Human ADM (Megaderm).

Methods: From July, 2015 to December, 2016, 26 patients were treated with breast surgery using ADM (Megaderm). Collected clinical information were initial diagnosis, extent of disease, type of surgery, type of adjuvant treatment and size of ADM used. Radiologic image findings of implanted ADM were also reviewed. Clinical complication and cosmetic outcomes were assessed.

Result: Breast conserving surgery was done in 11 patients. Total mastectomy was performed in 15 patients. Adjuvant radiation therapy was done in 7 patients. ADM related complication such as infection, red breast syndrome, and adverse reaction after radiation or chemotherapy was not reported. Cosmetic outcome among BCS patients were excellent (82%), good (9%), and fair (9%).

Conclusions: ADM (Megaderm) volume replacement surgery in breast conserving procedures is safe and clinically useful in cosmetic aspect.

IMMEDIATE CHEST WALL RECONSTRUCTION USING EXTERNAL OBLIQUE MYOCUTANEOUS FLAP FOR LARGE SKIN DEFECT AFTER EXTENSIVE MASTECTOMY IN ADVANCED OR RECURRENT BREAST CANCER PATIENT : SINGLE CENTER EXPERIENCE

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Background: We report single-stage chest-wall reconstructions using external oblique myocutaneous flap (EOMCF) for large chest-wall skin defects following resection of advanced or recurrent breast tumors at the Pusan National University Hospital over a 7-year period.

Methods: Between January 2007 and October 2015, dermographic and clinicopathologic data of 75 women, who had underwent extensive mastectomy with immediate chest wall reconstruction using EOMCF, were reviewed retrospectively. They were unable to perform primary chemo-radiation therapy because of poor general condition, comorbidities, and preference of patients.

Result: Mean age of the study population was 50.5 years and mean follow-up period was 36.7 months. 59 patients (78.7%) were stage III and 16 patients (21.3%) were stage IV. 56 cases (74.7%) were inflammatory cancer and 19 cases (25.3%) were non-inflammatory cancer. On the final pathologic report, surgical margin was negative in all patients and mean tumor size was 6.9 cm. Mean excised breast tissue weight was 687.6 g (range, 120.3-2,797.1). The mean chest wall skin defect measured 228.3 cm^2 (range, 31.9-1,369.0), which corresponded to about 15 × 15 cm defect. Mean total operative time including mastectomy and chest wall reconstruction was 163.7 minutes. 14 patients (18.7%) experienced minor postoperative complications. In terms of locoregional recurrence, 9 out of 75 patients (12%) including stage IV breast cancer have experienced recurrence. In 59 non-stage IV patients, locoregional relapse occurred in 5 (8.5%).

Conclusions: EOMCF can effectively cover the large chest wall defect with few minor complications and reliable local disease control, especially in patients with a poor general condition or recurrent and/or advanced tumor which is not responsive to primary chemotherapy or radiotherapy.

COMPARISON OF 5-YEAR ONCOLOGIC OUTCOMES BETWEEN AXILLARY LYMPH NODES DISSECTION AND PARTIAL AXILLARY LYMPH NODES DISSECTION IN N1 BREAST CANCER

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Background: Axillary lymph node status is one of the important prognostic factors in breast cancer. However, because of the radiation role is increasing for local control in axillary area, the surgical role for axillary lymph node metastasis is decreasing. The authors compared the actual 5-year oncologic outcomes of conventional axillary lymph node dissection (ALND) and partial axillary lymph node dissection (PALD) in pathologically N1 breast cancer.

Methods: Two hundred and thirty eligible patients with breast cancer who underwent axillary lymph nodes excision were included in this retrospective study. PALD is generally performed anatomically between axillary vein, lateral border of pectoralis major muscle and latissimus dorsi muscle as level 1 dissection. We defined PALD when the number of removed axillary lymph nodes was 5-10 and ALND when the number is more than 10. The comparison was performed between ALND (n = 171) vs. PALD (n = 59) and PALD only (n = 38) vs. PALD with radiotherapy (n = 21) about clinicopathologic factors and locoregional recurrence, distant metastasis, and death.

Result: The mean follow-up period was 65 months (SD, 15.54 months). There was no statistical significance between ALND group and PALD group in local recurrence rate ($p = 0.3875$), distant metastasis rate ($p = 0.5574$) and overall survival ($p = 0.4716$). In comparison between PALD versus PALD with radiotherapy, there were two cases of local recurrence (5.4%) in PALD only group. However, no statistical significance was shown in local recurrence, distant metastasis and expire rate.

Conclusions: During 5-year of follow-up period, there was no statistical difference of oncologic outcomes between ALND and PALD, PALD only and PALD with radiotherapy.

HOW TO DEAL WITH THE MEDIAL QUADRANT AFTER BREAST CONSERVING SURGERY?

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Background: Tumor size and location are important factors for determining the surgical technique for oncoplastic breast surgery after breast conserving surgery (BCS). BCS is especially challenging in medially located breast cancer, particularly in terms of achieving satisfactory aesthetic coverage. Thus, we aimed to investigate reconstructive surgery techniques for filling medial defects resulting from BCS to improve patient satisfaction and aesthetic outcomes.

Methods: 68 patients with medially located breast cancer were retrospectively evaluated from 2007 to 2016. We analyzed patient informations such as breast size, resection volume, tumor weight, complications and aesthetic results with the KNUH breast reconstruction satisfaction questionnaire.

Result: Mean patients BMI, tumor weight were 23.63, and 86.30 g, respectively. The tennis racket (n = 16), round block technique (n = 5) were chosen for small defect (< 10-15%) in small to moderate sized breasts. The rotational flap technique (n = 19) was selected for moderate defect. The TDAP flap (n = 7), mini LD flap (n = 18) were used for large defect (> 40%) in small to moderate sized breasts, and for cases with a resection volume greater than moderate in large breasts (volume > 500 cc). For latter cases, the oncoplastic reduction technique (n = 2), extended LD flap (n = 1) were also performed. There were 1 hematoma, 3 seroma in mini LD flaps, and 2 fat necrosis in rotational flaps. The mean KNUH satisfaction score was 51.4 (total 55), indicating that most of the patients were satisfied with their aesthetic results.

Conclusions: In medially located breast cancer, our technique considering breast size and resection volume in this study can produce superior aesthetic outcomes with great convenience and few complications.

PATIENT SATISFACTION AFTER BREAST CONSERVING THERAPY

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Background: 76% of newly diagnosed Breast Cancer patients in Singapore are early stage. Most would be eligible for breast conserving therapy (BCT). However, rates of BCT are low at 35%. No Patient-Reported Outcome Measures (PROMs) are available at present in Singapore. In this retrospective study, we assessed patient satisfaction among post-BCT patients in terms of cosmetic, body image and psychosocial outcomes and determined the factors influencing them.

Methods: The study was conducted in the National Cancer Centre Singapore (NCCS) Specialist Outpatient Clinic from August 2014 to October 2015. Women who had BCT with completion of radiotherapy at least six months before the administration of study were included. An interviewer-administered questionnaire was performed in the form of a validated Hopwood Body Image Scale and a Post-BCS Patient Satisfaction Survey. Tumor parameters were obtained from medical records. The relationships of these variables with patient satisfaction post-BCT were then analysed.

Result: 147 patients were recruited, with a median age of 54 years old. The median follow up for this cohort was 45 months (range: 6.5 months to 258 months). 77% had bra size of cups A and B. Patients were satisfied with their body image based on the Hopwood Body Image Scale. Good patient-reported cosmetic outcomes positively correlated with increased confidence by patients with a significance p value of 0.03. Better patient-reported cosmetic satisfaction was noted in the older age groups and with increased bra size.

Conclusions: BCT is the standard of care in managing early stage Breast Cancer. In Singapore, despite a relatively low rate of BCT, good patient-reported satisfaction was demonstrated in this questionnaire survey. A good cosmetic outcome is important in boosting the patient's confidence. Better satisfaction with cosmetic results was noted in older patients and those with larger breast sizes.

USE OF FLUORESCENCE WITH INDOCYANINE GREEN (ICG) FOR SENTINEL LYMPH NODE BIOPSY AFTER NEOADJUVANT CHEMOTHERAPY IN INFLAMMATORY BREAST CANCER

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Background: In earlier studies, we and others demonstrated that dye and/or isotope methods for sentinel lymph node biopsy (SLNB) procedure after neo adjuvant chemotherapy (NAC) for patients with inflammatory breast cancer (IBC) carries low identification rates and high unacceptable false-negative rates. Fluorescence using Indocyanine green (ICG) is an emerging method for SLNB detection. The aim of this study was to assess its use in this particular setting.

Methods: Thirteen consecutive patients with clinically negative nodes after NAC for IBC (T4d) and who underwent SLNB using ICG method followed by systematic axillary lymph node dissection by the same operator were assessed.

Result: The SLN identification rate was 92.3% (12/13), the median of SLN removed per patient was 3 (range 1 to 4); Three (25%) had positive SLN and in one of those 3 patients the SLN was the only positive node. On the Nine patients with negative SLNB, one has a positive axillary node at axillary clearance with a false negative rate of 11% (1/9).

Conclusions: To the best of our knowledge, this is the first and only report of SLNB with fluorescence method using ICG for inflammatory breast cancer. Identification rate and more importantly false negative rate are very promising with this technique on the contrary to other SLNB detection methods (isotope/dye). This opens large area of research.

CORRELATION OF HYPOXIA INDUCIBLE TRANSCRIPTION FACTOR-1α, GLUCOSE TRANSPORTER-1, CARBONIC ANHYDRASE IX AND FDG UPTAKE IN INVASIVE DUCTAL BREAST CANCER

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Background: Multiple biomarkers related to tumor hypoxic microenvironment have been discovered and offered as targets for cancer detection, treatment and monitoring, such as hypoxia-inducible transcription factors alpha (HIF-1α), glucose transporter-1 (GLUT1) and carbonic anhydrase IX (CA IX). We studied the immunohistochemical expression of HIF-1α, GLUT1 and CA IX in patients with Invasive Ductal Carcinoma (IDC) and the correlation with SUVmax of the primary tumor (pSUVmax). Prognostic significance of pSUVmax, HIF-1α, GLUT1 and CA IX for the prediction of progression-free survival (PFS) was also assessed.

Methods: One-hundred seventy four female patients with IDC who underwent pretreatment F-18 FDG PET/CT were enrolled. The pSUVmax was compared with clinicopathological parameters including ER, PR, HER2, axillary lymph node metastasis (LNM), stage, GLUT1, CA IX and HIF-1α. The prognostic value of pSUVmax, GLUT1, CA IX and HIF-1 α for PFS was assessed using the Kaplan-Meier method.

Result: PSUVmax was significantly higher in patients with HIF-1α ≥ 2, GLUT1 ≥ 5 and CA IX ≥ 3 compared to patients with HIF-1α < 2, GLUT1 < 5 and CA IX < 3 (4.9 ± 4.1 vs. 3.9 ± 3.2, $p = 0.02$; 6.1 ± 4.2 vs. 3.5 ± 3.0, $p = 0.003$; 5.9 ± 4.5 vs. 3.8 ± 3.2, P = 0.003). Kaplan-Meier analysis identified pSUVmax ≥ 6.8 ($p = 0.0004$), GLUT1 ≥ 5 ($p = 0.0005$) and CA IX ≥ 3 ($p < 0.0001$) as predictors of recurrence. Cox proportional-hazards analysis showed that pSUVmax ≥ 6.8 ($p = 0.0338$, relative risk 2.636), HIF-1α ≥ 2 ($p = 0.0194$, relative risk 0.331), GLUT1 ≥ 5 ($p = 0.0379$, relative risk 3.139) and CA IX ≥ 3 ($p = 0.0064$, relative risk 3.829) significantly predicted recurrence.

Conclusions: SUVmax on pretreatment F-18 FDG PET/ CT reflect expression of HIF-1α, GLUT1 and CA IX and can be used as a good surrogate marker for the prediction of progression in patients with IDC.

A PREDICTION MODEL FOR THE MEASUREMENT OF HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2 (HER2) STATUS IN BREAST CANCER WITH EQUIVOCAL IMMUNOHISTOCHEMISTRY RESULTS

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Background: Accurate human epidermal growth factor receptor-2 (HER2) status is important to predict prognosis and to apply appropriate treatment to HER2 positive breast cancer patients. The measurement of HER2 is most commonly starting with immunohistochemistry (IHC) and progressing to in situ hybridization (ISH) testing if IHC is 2+ (equivocal). However, performing ISH can be an economical burden to the community or patient in devolving countries. The aim of this study is to predict HER2 status of breast cancer patients with equivocal IHC results.

Methods: We retrospectively reviewed clinical data of 15,535 consecutive patients who underwent curative surgery for breast cancer between February 2005 and April 2015 at Samsung Medical Center. Univariate and multivariate analyses were performed to identify clinicopathologic factors that are related to silver in situ hybridization (SISH) status.

Result: 523 patients showed equivocal HER2 IHC results. High nuclear grade (odds ratio [OR], 1.653; 95% confidence interval [CI], 1.164-2.347), high Ki-67 (OR 1.017, 95% CI 1.008-1.027), low pathological tumor stage (OR 0.675, 95% CI 0.498-0.915) and low progesterone receptor Allred score (OR 0.922, 95% CI 0.864-0.983) showed as predictors of positive SISH results in equivocal HER2 IHC patients.

Conclusions: Positive HER2 status by SISH had a relationship with high nuclear grade, high Ki-67, low pathological tumor stage and low progesterone receptor Allred score. By this result, we can predict which patient will show a positive SISH result who are IHC equivocal. This information can help making diagnosis of HER2 positive breast cancer who are in devolving countries or individuals who needs financial support.

URINE-METABOLITE ANALYSIS FOR BREAST CANCER IDENTIFICATION METHOD USING URINES - PRELIMINARY RAMAN STUDY

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Background: Imaging study is an essential tool for breast cancer diagnosis. However, it has a limitation to detect cancers which exist in the very small mass or non-mass form. The objective of this preliminary study is to introduce the rapid label-free optical analysis of urine metabolite with Raman spectroscopy for the detection of breast cancer to overcome this problem.

Methods: Three breast tumor patients' urines were collected, one benign tumor (control) and two invasive carcinomas. The drop-coating deposition surface-enhanced Raman scattering was selected for analyzing the whole urine fluids. A 50-nm Au/2.5-nm Ti-coated glass substrate was used to enhance the Raman signals. All Raman spectra (n = 10, each) were collected with the range of 417–1,782 cm–1 with a 5-cm–1 spectral resolution and twice 10-s acquisition time. The measured signals were normalized to 1004 cm–1 peak corresponded to v (C–C) aromatic ring breathing of phenylalanine. Each Raman spectrum was analyzed by using the computational algorithms.

Result: All Raman spectra showed a prominent intensity at 1,004 cm–1 corresponded to symmetrical C–N stretch vibrational mode (urea peak). The control group showed the flat spectral patterns except the urea peak while the cancer groups showed difference in the intensities of several peaks. The semi-automatic multivariate statistics-assisted classification method yielded high performances such as 94% sensitivity and 97% specificity.

Conclusions: Urine-metabolite analysis with Raman spectroscopy could be a good diagnostic option, which compensates the limitation of conventional imaging studies for breast cancer diagnosis.

PULMONARY SCLEROSING HEMANGIOMAS MIMICKING LUNG METASTASIS FROM BREAST CANCER; A CASE REPORT

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Background: Pulmonary sclerosing hemangioma (PSH) is a rare benign neoplasm. Most patients are asymptomatic, with less than one third experiencing hemoptysis, cough or chest pain. Most cases present as solitary mass on radiologic imaging studies and only 4% of cases are multiple nodules.

Methods: We report a case of PSH initially misdiagnosed as lung metastasis from breast cancer. The patient was a 31-year-old female who had bilateral breast cancer. We identified multiple pulmonary nodules on chest CT and PET-CT showed increased uptakes in the left breast and left axillary lymph nodes, however, no pulmonary uptake. Patient underwent video-assisted thoracoscopic biopsy of one of lesions and biopsy confirmed PSH. The patient got neoadjuvant chemotherapy for the breast cancer.

Result: PSH is derived from primitive respiratory epithelial cells that express TTF-1. PSH is a benign tumor with low prevalence and typically presents on chest radiograph as a peripheral, solitary, well defined, homogenous nodule and frequently be falsely interpreted as malignant by FDG-PET-CT due to increased FDG uptake. Correct diagnosis as the first impression at the preoperative CT reading before tissue conformation occurred in only 30.3% of the patients. Primary lung cancer and metastasis were the most radiologic misdiagnosis, followed by harmatoma. It is quite challenging to make a differential diagnosis when multiple lung nodules are seen on chest CT especially when there is an underlying malignancy.

Conclusions: Clinician should be aware of possibility of various lesions including PSP when lung nodules on chest CT or FDG PET with underlying malignancy and should do tissue confirmation.

SYNCHRONOUS GASTRIC METASTASIS OF INVASIVE LOBULAR CARCINOMA; A CASE REPORT

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Background: Distant metastasis of breast cancer mostly is known as bone, lung and liver. However, very rarely is the metastasis to gastrointestinal tract, and most of the cases was reported in invasive lobular carcinoma. This case is suspected of having cancer in the synchronous double primary malignancy on breast and stomach, but is confirmed by the metastasis of stomach form breast cancer.

Methods: In January 2016, a 44-year-old female patient was diagnosed with advanced gastric cancer after gastric endoscopy and was hospitalized for surgery. PET scan showed hypermetabolism of both breast area. Invasive lobular carcinoma was reported as a result of biopsy of both breast. And post total gastrectomy pathology was reported to signet ring cell carcinoma.

Result: In march 2016, Modified radical mastectomy was performed on both breast, and as a result, multicentric mass (total 6 site, ER/PR positive, HER2 negative, lymph node 19/19). We discussed the possibility of gastric metastasis of breast cancer through a meeting and requested comparative analysis of two specimens through pathologist. ER/PR positive findings were reported in gastric specimens, and diffuse strong findings were reported in GCDFP-15, which was subsequently concluded to be a metastasis to the stomach of breast.

Conclusions: Clinical manifestations of Gastrointestinal tract metastases from breast cancer have been quite diverse with nonspecific symptoms usually mimicking primary GI malignancies. The immunohistochemical diagnosis was primarily emphasized in order to distinguish gastric metastasis from primary gastric cancer (ER/PR/HER2,CK7, GCDFP-15 etc.). Among them, the use of GCDFP-15 marker, is applied for a more accurate pathologic diagnosis of metastatic breast cancer.

COMPREHENSIVE IN SILICO VALIDATION OF GENE PANEL NEXT-GENERATION SEQUENCING WITH SUPERCOMPUTER

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Background: Germline mutation screening by next-generation sequencing (NGS) has been widely adopted for hereditary breast and/or ovarian cancers. Technical performance evaluation based on positive control samples is a key component for quality assurance. Although gene panel is expanding over time, available DNA controls (actual patient samples or synthetic reference materials) are inadequate. In silico simulation of positive control NGS data is gaining traction as a complement to the conventional approach solely based on DNA controls.

Methods: We applied the in silico simulation approach to the evaluation of QIAseq Targeted DNA Panels (Qiagen), namely Human BRCA1 and BRCA2 Plus Panel (BRCA1, BRCA2, TP53, PTEN, PALB2 and CDH1; total length 28 kb) and Human Breast Cancer Panel (93 genes). An updated version of the bioinformatics algorithm Mutation Engineer was developed and optimized for high-throughput simulation in a Cray XC30 supercomputer. Based on real NGS dataset of a DNA control sample, a total of 367,900 samples were simulated for the BRCA1/2 Plus Panel to evaluate the in-house bioinformatics analysis pipeline.

Result: We simulated 367,900 mutation control samples and tested variant calling performance in 62 hours. The mutations included all possible single-nucleotide variants (n = 84,970), insertions and deletions (length range 2 to 10 bp; n = 282,930). The in-house analysis pipeline maintained high overall sensitivity and specificity for the new QIAseq gene panels.

Conclusions: In silico simulation by supercomputer is a feasible, efficient and comprehensive approach to evaluate technical performance of NGS-based germline mutation screening.

A PILOT STUDY OF THE FLUORESCENCE ICG METHOD SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER PATIENTS USING THE MEDICAL IMAGING PROJECTION SYSTEM

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Background: Sentinel lymph node biopsy (SLNB) using fluorescence ICG (flCG) method showed equal or better detection rate (DR) compared with dye or radioisotope (RI). When we perform flCG, we have to turn off operating light and look at the monitor to detect the fluorescence signal. Medical imaging projection system (MIPS) can project the fluorescence image to operating field directly and illuminate the field (Panasonic AVC Networks Company, Japan). The aim of this pilot study was to evaluate the clinical utility of the MIPS.

Methods: Patients with cN0 breast cancer underwent the SLNB using MIPS. We checked additional SLNs using handheld camera (PDE) and RI following MIPS. Primary endpoint was DR of SLNs using MIPS. The MIPS was unapproved medical device. The study protocol was approved by institutional review board at Kyoto University Hospital.

Result: A total of eight patients participated in this study in March 2016. Median age was 59 years (range 45-74), and BMI was 20.6 kg/m^2 (18.2-23.7). Six had cT1 and two had cTis tumor. The DR of SLNs using MIPS was 100%. We could perform SLNB without operating light. Although additional SLN was detected using PDE in two patients, they could be detected by the MIPS, retrospectively. The median number of SLNs identified was 3 (2-5) for MIPS, 3 (2-5) for PDE, and 2 (2-3) for RI.

Conclusions: The SLNB using MIPS showed comparable DR with conventional methods. The MIPS will reduce task during the SLNB and allow us to perform a real-time image-guided surgery.

POSITRON EMISSION MAMMOGRAPHY IN ASSESSMENT OF THE CLINICOPATHOLOGICAL CHARACTERISTICS OF BREAST CANCERS

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Background: Breast cancer is the most prevalent malignant neoplasm in women. Early detection and personalized treatment are very important to decrease mortality. Positron emission mammography (PEM) is a newly developed breast imaging technology using the positron emission tomography (PET) radiopharmaceutical 18F-fluoro-deoxy-D-glucose (18FDG). We investigated the correlation between PEM and known prognostic markers, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER2) status, tumor histology, nuclear grade, and the Ki67 labeling index.

Methods: Ninety-two patients were included in this study. PEM imaging was performed on a commercially available PEM unit. Maximum PEM uptake value (PUVmax) and lesion-to-background (LTB) ratio were determined. All resected specimens were evaluated by our institution pathology department. PUVmax and LTB ratios were compared with ER and PR status, tumor histology, and nuclear grades. The correlation coefficients between maximum PEM uptake value or LTB and the Ki67 labeling index were calculated.

Result: PUVmax values were significantly different between ductal carcinoma in situ and invasive ductal carcinoma ($p = 0.033$). PUVmax and LTB showed significant differences between nuclear grade 1 and nuclear grade 3 (PUVmax: $p = 0.027$, LTB: 0.0043). PUVmax, LTB, and Ki67 labeling index correlated significantly; PUVmax and Ki67: correlation coefficient = 0.558, $p = 0.000125$; LTB and Ki67: correlation coefficient = 0.572, $p = 0.000075$.

Conclusions: PUVmax and LTB showed remarkable correlation with nuclear grades and the Ki67 labeling index, suggesting utility of PEM in assessing the clinicopathological characteristics of breast cancer.

PROBABILITY OF N 2 OR 3 STAGE IN T1-2 INVASIVE BREAST CANCER PATIENTS WITH NO PALPABLE LYMPHADENOPATHY

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Background: Axillary lymph node status is the most influential prognostic factor. After ACOSOG Z0011, axillary lymph node dissection is tending to be omitted in clinical T1-2N0M0 breast cancer patients undergoing systemic therapy. We investigated real percentage of N2 or 3 in clinically T1-2N0M0 and developed a nomogram to predict the possibility of N2 or N3 in these patients.

Methods: Retrospective chart review was performed. Chi-square test, logistic regression were used for statistical analysis. Variables with $p < 0.05$ in multivariable analysis were included in the nomogram. Internal validation was estimated with the 5 fold cross validation method.

Result: Among total 1,437 patients, N1 was 1,355 cases (94.3%) and N2 or 3 was 82 cases (5.7%). Proportion of N2 or 3 was higher (14.3%) when the number of metastatic LNs were 2 than 1 (3.2%)and this tendency was clear only in luminal A. In multivariate logistic regression analysis, lymphovascular invasion ($p = 0.0084$), perinodal extension ($p < 0.0001$), T2 ($p = 0.0260$) and metastatic LN rate ($p < 0.0001$) were independent predictors for N2 or 3 stage. We made the nomogram based on four variables. For the receiver operating characteristics (ROC), the area under curve (AUC) was 0.8050 in the model set and 0.8246 in the test set.

Conclusions: Although there is growing tendency to omit axillary lymph node dissection (ALND) in clinical T1-2N0M0 patients undergoing systemic therapy, no one is sure exactly that omitting ALND in stage IIA or IIIC is safe. Our data suggest that patients with lymphovascular invasion, perinodal extension, $0.5 \leq$ metastatic LN rate and T2 consider cALND than omitting ALND although they fulfill ACOSOG Z0011 criteria.

THE SPECIMEN MARGIN ASSESSMENT TECHNIQUE (SMART) TRIAL: A NOVEL 3D METHOD OF IDENTIFYING THE MOST ACCURATE METHOD OF BREAST SPECIMEN ORIENTATION

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Background: Achieving negative margins remains one of the most important determinants for local recurrence following breast-conserving therapy. Inaccuracies in margin orientation during surgery translates into additional unnecessary surgery or wrong margin re-excision. We report the results of the world's first prospective clinical trial that evaluates the accuracy of intra-operative specimen inking versus suturing on the same lumpectomy specimen using a novel 3 D technique.

Methods: A prospective clinical trial was performed using sham lumpectomies within the prophylactic mastectomy or breast reduction tissue. The specimen was inked using special phospholuminescent inks that dry clear but glow under black light. Specimen suturing using two labeled sutures was performed by the surgeon as per usual. A third mystery suture was placed; the location of which is known only to the surgeon but blinded to the pathologist.

Result: 72 patients were accrued for the study. There was a 42% discordance between the pathologist and surgeon in identification of the mystery suture and a 76% discordance in identification of surface area of each margin. Using 3D imaging, we demonstrated how the specimen center of gravity and volume changes en-route to the pathology department.

Conclusions: Discordance between the surgeon and the pathologist in margin orientation would influence the accuracy of margin identification, subsequent directed re-excisions, as well as subject patients to unnecessary surgeries or prevent them from having necessary re-excisions. Intraoperative specimen inking by the surgeon is a more accurate method of margin assessment. Results of this trial can be extended to other cancers in which a negative margin is prognostic.

STABILITY OF SERUM IgG Fc N-GLYCOSYLATION PROFILING, A PROMISING BIOMARKER FOR BREAST CANCER DIAGNOSIS

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Background: An earlier diagnosis improves the prognosis for breast cancer. Accordingly, an easier, faster, and less-painful test is needed. Immunoglobulin G (IgG) crystallizable fragment (Fc) region N-glycosylation, which affects the function of antibodies, can be analyzed in detail. Previously, we reported that breast cancer patients (N = 55) can be distinguished from cancer-free controls (N = 51) by using a prediction model based on serum IgG Fc N-glycosylation profiling by matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) with good sensitivity and specificity. Stage 0 diseases were also predicted correctly by this model. Here, we analyzed the stability of serum IgG Fc N-glycosylation profiling, a promising biomarker for breast cancer diagnosis.

Methods: Differences in IgG Fc N-glycosylation profiling between serum and plasma, effects of processing and storage conditions, and effects of repeated freezing and thawing of samples were assessed. IgG was isolated from serum or plasma by using Protein G beads. Following SDS-PAGE, gel containing heavy chains was excised, and glycans were extracted by peptide-N-glycosidase F digestion and analyzed by MALDI-MS. The intensity of 32 glycans was normalized by the sum of their intensity.

Result: IgG Fc N-glycosylation profiling was not significantly different between plasma and serum. Neither processing and storage conditions nor continuous freezing and thawing affected serum IgG Fc N-glycosylation profiling.

Conclusions: Serum IgG Fc N-glycosylation profiling was sufficiently stable in various conditions encountered in clinical practice.

ASSESSMENT ON THE QUALITY OF LIFE OF BREAST CANCER PATIENTS UNDERGOING RADIATION TREATMENT IN GHANA

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Background: World statistics show that, 1.1 million women are diagnosed annually with breast cancer and 410,000 women die from the disease. In Ghana, breast cancer is the leading malignancy which accounts for 15.4% of all malignancies and appears to be on the increase. World Health Organization defines quality of life (QoL) as an individual's perceptions of their position in life, in the context of the cultural and value systems in which they live and in relation to their goals, expectations, standards and concerns make up their QoL. The primary aim of the study was to assess factors that contribute to the quality of life of breast cancer patient undergoing treatment to determine the overall quality of life and to suggest ways and methods to improve the situation.

Methods: Ninety breast cancer patients referred to the Oncology Unit were conveniently sampled within a three month period. Quality of life assessment was performed using the Functional Assessment of Cancer Therapy (FACT-B) - Specific Scale for breast cancer version 4. Data was analyzed using Statistical Package for Social Sciences (SPSS) version 16.

Result: The peak incidence age was between (56-65) years, 60% had triple modality treatment; thus had undergone surgery and were on chemotherapy and radiotherapy. Seventeen percent had surgery and were on chemotherapy only, 10% had surgery and were on radiotherapy only, 10% had surgery and only one patient was on chemotherapy and radiotherapy. The scores for the quality of life domains were General Emotional (GE) well-being (18.8 ± 8.4), General Physical (GP) well-being (16.5 ± 6.1), General Social (GS) well-being (14.3 ± 7.0) and General Functional (GF) well-being (10.9 ± 5.7). Seventy percent of the patient had stable quality of life, 10% had poor quality of life and 20% had good quality of life.

Conclusions: Considering the quality of life domains or subscale scores and the overall quality of life scores of the patients, it can be concluded that there is no significant difference ($p > 0.05$) in the quality of life of breast cancer patients who receive treatment at the Unit.

PROGNOSTIC IMPLICATION OF THE TUMOR LOCATION ACCORDING TO MOLECULAR SUBTYPES IN AXILLARY LYMPH NODE-POSITIVE INVASIVE DUCTAL CANCER IN A KOREAN POPULATIONT

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Background: Previous studies have not considered the axillary lymph node status when investigating the prognostic role of tumor location according to each molecular subtype. The present study aimed to investigate the prognostic implication of tumor location according to each molecular subtype in Korean invasive ductal carcinoma (IDC) patients with axillary lymph node metastasis.

Methods: Data from 7856 Korean IDC women with axillary lymph node metastasis were retrospectively analyzed. According to tumor location, patients were divided into the following groups: upper-outer quadrant (UOQ), lower-outer quadrant (LOQ), upper-inner quadrant (UIQ), lower-inner quadrant (LIQ), and central group. Overall survival (OS) and breast cancer-specific survival (BCSS) were evaluated according to tumor location and molecular subtype. A subgroup analysis based on tumor size categorization was also performed.

Result: The patients mean age was 47.97 ± 9.64 years, and the median follow-up time was 90 months. The LIQ group showed significantly worse prognosis in OS and BCSS (76.4 and 83.3 %, respectively) compared with the other groups, which was only significant in human epidermal growth factor receptor 2 (HER2) overexpression and triple-negative (TN) subtypes. In the subgroup analysis according to tumor size, the LIQ group showed a significantly worse prognosis in OS and BCSS compared with the other groups, in HER2 and TN subtypes, and only in patients with more than T2 stage.

Conclusions: In Korean IDC patients with axillary lymph node metastasis, LIQ tumor location was associated with poor prognosis among those with HER2 and TN molecular subtypes and especially in those with more than T2 stage.

MIR-137 AND MIR-496 TARGET DEL-1 AND AFFECT TRIPLE NEGATIVE BREAST CANCER PROGRESSION

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Background: Although Del-1 was recently proposed as a new biomarker for early breast cancer in our previous studies, the mechanisms of Del-1 expression are barely understood. In the current study, we selected two microRNAs (miR-137 and - 496), potentially affecting Del-1 expression in breast cancer and examined their impact on Del-1 expression in a variety of breast cancer cell lines to identify their potential role in Del-1 expression and thereby breast cancer development or progression.

Methods: Del-1 mRNA and miR-137/496 levels were measured by qRT-PCR among breast epithelial (MCF10A) and cancer cells (MDA-MB-231, MCF7, SK-BR3 and T-47D). The effects of miR-137/ 496 on cell proliferation and invasion were detected using MTT, wound healing and Transwell assays. Furthermore, luciferase reporter assay was used to identify the direct regulation of Del-1 by miR-137 or 496 in MDA-MB-231 cells. Plus, we analyzed the expressions of miR-137 or 496 and Del-1 mRNA from 20 patients with triple negative early breast cancer.

Result: miR-137 and -496 levels were low in all breast cancer cell lines. As Del-1 mRNA expression was remarkably higher in MDA-MB-231 compared to the other breast cancer cell lines, further functional analyses were done with MDA-MB-231 representing triple negative breast cancer subtype. Both miR-137 and miR-496 were revealed to directly bind at the 3'-UTR of Del-1. Del-1 by Luciferase reporter assay and Del-1 expression was upregulated by inhibitors and reversed by both mimics of both miR-137 and miR-496. Furthermore, both miR-137 and miR-496 were also demonstrated to inhibit cell proliferation, migration and invasion of MDA-MB-231, suggesting that these miRNAs affect cancer progression via Del-1. MiR-137 and miR-496 were remarkably down-regulated in 7 out of 12 triple negative breast cancer tissues, in particular with high Ki67 and high histologic grade.

Conclusions: Although Del-1 was recently introduced as a new biomarker for triple negative breast cancer, the mechanisms of Del-1 expression were barely identified. The current study firstly demonstrated that microRNA 137 and 496 are involved in Del-1 regulation by binding at Del-1 gene, affecting cancer progression by altering Del-1 expression.

METHYLATION OF THE NT5E GENE IS ASSOCIATED WITH POOR PROGNOSTIC FACTORS IN BREAST CANCER

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Background: CD73 has been known to promote cancer progression and a recent study has reported that the NT5E gene methylation is associated with favorable outcome in breast cancer. The purpose of this study was to investigate epigenetic alterations of the NT5E gene and to evaluate prognostic significance of the NT5E gene methylation in breast cancer.

Methods: By using pyrosequencing of bisulfite treated DNA, we analyzed DNA methylation status of the NT5E gene in fresh frozen primary breast cancer tissues and normal breast tissues. The levels of inflammatory cytokines, intra- or peritumoral lymphocyte infiltration, the levels of T lymphocyte and macrophage infiltration were a assessed. We compared the methylation frequency between tumor and normal tissues and analyzed the correlation between methylation levels of the NT5E gene and clinicopathological characteristics.

Result: The mean methylation level of the NT5E gene in tumor tissues was more higher than that normal breast tissues. The mean methylation frequency of the NT5E gene in postmenopausal women was significantly higher than in premenopausal women. The methylation levels were significantly higher in patients with large tumor size, high histologic grade, negative estrogen receptor expression and negative Bcl-2 expression.

Conclusions: In this study, the NT5E gene methylation was related to breast cancer development, and higher mean methylation levels of the NT5E gene were associated with poor prognostic factors in breast cancer. Our results suggest that methylation of the NT5E gene affect breast carcinogenesis and progression of breast cancer.

B7-H3 AND B7-H4 EXPRESSION IN PHYLLODES TUMOR OF THE BREAST: ASSOCIATIONS WITH CLINICOPATHOLOGIC FEATURES AND T-CELL INFILTRATION

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Background: The aberrant expression of co-inhibitory B7 molecules, B7-H3 and B7-H4, in the tumor microenvironment has been attributed to reduced anti-tumor immunity and immune evasion, prompting the development of immunotherapeutic approaches. This study was undertaken to detect the expression of B7-H3 and B7-H4 in phyllodes tumors (PTs) and its association with the grade and clinical behavior of PTs. In addition, the association of B7-H3 and B7-H4 with the CD3 and CD8+ T lymphocytes was also assessed to investigate their roles in the regulation of tumor immune surveillance.

Methods: Immunohistochemistry was applied to examine the expressions of B7-H3, B7-H4, CD3, and CD8 in 60 benign, 26 borderline, and 15 malignant PTs.

Result: Stromal high B7-H3 and B7-H4 expression was noted in 31 (51.7%) and 0 (0%) of 60 benign PTs, 20 (76.9%) and 2 (7.7%) of 26 borderline PTs, and 13 (86.7%) and 9 (20.0%) of 15 malignant PTs, respectively. Stromal B7-H3 and B7-H4 expression increased continuously as PTs progress from benign through borderline to malignant PTs, respectively ($p = 0.003$ and $p = 0.001$). The recurrence rate was higher in the stromal high B7-H3 or B7-H4 expression group than in the low expression group but this difference was not statistically significant. B7-H3 expression inversely correlated with the intensity of CD3 and CD8+ T cells ($p = 0.001$ and $p = 0.027$, respectively).

Conclusions: These results suggest that B7-H3 and B7-H4 are involved in the progression of PTs and B7-H3 may play a role in immune surveillance mechanisms of PTs.

GENESWELL™ BCT, A NOVEL PROGNOSTIC ASSAY TO PREDICT THE RISK OF DISTANT METASTASIS OF PATIENTS WITH HORMONE RECEPTOR POSITIVE, HER2 NEGATIVE EARLY BREAST CANCER

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Background: GenesWell™ BCT is a novel prognostic assay to predict the risk of distant metastasis of patients who has hormone receptor positive, HER2-negative (HR+/HER2-), and pN0 - 1 breast cancer. Here, we show the development and validation of GenesWell™ BCT in patients with early breast cancer treated with hormone therapy alone.

Methods: GenesWell™ BCT classified the patients into high and low risk group according to BCT Score, a novel prognostic score. The Score was calculated by algorithm that uses relative expression level of six prognostic genes combined with two clinical variables (nodal status and tumor size). One hundred seventy four formalin-fixed, paraffin-embedded (FFPE) breast cancer patient tissues were used for development of algorithm, and 222 FFPE breast cancer patient tissues were used to validate the clinical performance of GenesWell™ BCT.

Result: In the development, rate of distant metastasis within 10 years was significantly higher in high risk group (39.7%) than in low risk group (2.9%) ($p < 0.001$). In addition, a statistically significant difference in 10 years distant metastasis rate was also indicated in the validation cohort (26.3% in high risk group, 3.8% in low risk group) ($p < 0.001$). BCT Score was revealed as an independent predictor of distant metastasis by multivariate analysis adjusted for clinical variables. Moreover, superior prognostic power of BCT Score than other prognostic models based on clinicopathological factors were shown by the C-index estimate.

Conclusions: GenesWell™ BCT predicts the risk of distant metastasis of patients with HR+/HER2- early breast cancer and has superior performance compared with prognostic models based on clinicopathological characteristics.

PREGNANCY-RELATED BREAST CANCER: 10-YEAR EXPERIENCE IN A TERTIARY INSTITUTION IN HONG KONG

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Background: The incidence of pregnancy-associated breast cancer is increasing. Literature suggested that patients with pregnancy-associated breast cancer usually presented at a more advanced stage and thus worse outcomes than non-pregnant patients. The aim of this study is to review our local experience in managing pregnancy-associated breast cancer and to evaluate the prognosis.

Methods: Fifteen patients diagnosed of pregnancy-associated breast cancer and fifteen with early onset breast cancer (≤ 40 years old) were recruited. Background characteristics, tumor features and survival were compared.

Result: Among the fifteen patients with pregnancy-associated breast cancers, nine were diagnosed during pregnancy and six were diagnosed in postpartum period. They present with larger tumor size ($p = 0.01$) than patients with early onset breast cancer. However the overall tumor staging, tumor immunohistochemistry and tumor grade did not differ. Patients diagnosed of pregnancy-associated breast cancer tend to choose mastectomy ($p = 0.058$). The overall survival ($p = 0.58$) and breast cancer event-free survival ($p = 0.74$) were similar between the two groups.

Conclusions: Patients diagnosed of pregnancy-associated breast cancer should be managed with multidisciplinary approach. They present with larger tumors but their prognosis is similar with non-pregnant breast cancer patients.

POST-CHEMOTHERAPY ANTI-MULLERIAN HORMONE AS A PREDICTIVE MARKER FOR RECOVERY OF OVARIAN FUNCTION IN PARTICIPANTS OF ASTRRA TRIAL

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Background: In the era of precision medicine, the prediction of returning of ovarian function by biological markers could be helpful for making a proper treatment strategy in young women treated by chemotherapy. We evaluated the value of post-chemotherapy anti-mullerian hormone (AMH) as a predictive marker for recovery of ovarian function in participants of ASTRRA trial.

Methods: The ASTRRA trial is a randomized phase III trial to evaluate the efficacy of ovarian function suppression in addition to tamoxifen in hormone receptor-positive breast cancer patients who remain or regain premenopausal status after chemotherapy. This analysis included 82 chemotherapy-induced amenorrheic participants of ASTRRA trial. Blood samples were obtained within one month from the enrollment. Post-chemotherapy AMH, estradiol, inhibin B and other clinical factors were analyzed in relation to the regain of ovarian function which was defined by recovery of vaginal bleeding.

Result: The proportion of patients who has regained vaginal bleeding during 5 years was 63.2%. The patients with age <40 years ($p=0.009$), estradiol ≥ 37 pg/mL ($p=0.003$), or AMH $\geq$ 800 pg/mL ($p=0.026$) showed significantly earlier recovery of vaginal bleeding than others. In multivariate analysis, estradiol (hazard ratio 3.171, 95% confidence interval 1.306-7.699, $p=0.011$) and AMH (hazard ratio 2.853, 95% confidence interval 1.011-8.046, $p=0.048$) were remained as independent values for predicting early recovery of vaginal bleeding. The diagnostic accuracy of age, estradiol, and AMH to predicting the recovery of vaginal bleeding for 5 years was 38.3%, 23.3% and 86.7%, respectively.

Conclusions: Post-chemotherapy AMH is a predictor for the recovery of ovarian function presented by vaginal bleeding.

COMPARISON OF SERUM BONE MARKERS IN BREAST CANCER PATIENTS WITH BONE METASTASIS

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Background: Bone is the most common site of metastatic recurrence in breast cancer and bone metastases are a major cause of morbidity for patients with metastatic breast cancer (MBC). The ability to predict breast cancer patients at high risk for bone metastasis development could allow early selection of those most likely to benefit from interventions to prevent or delay bone metastasis. The purpose of this study was to assess the usefulness of these markers as predictors of progression related bone metastasis.

Methods: We prospectively observed bone metastasis and bone marker in 34 with breast cancer patients with bone-only metastasis from January 2014 to December 2015. Serum osteocalcin, carboxyterminaltelopeptide of type I collagen (CTX), serum parathyroid hormone (PTH), 25-hydroxyvitamin, soluble RANKL (sRANKL), osteoprotegerin (OPG) and osteopontin (OPN) were assessed at baseline, after every three month and at the time of progression of bone metastasis. Correlation of serum marker levels with progression of bone metastasis was assessed using receiver operating characteristics (ROC) analysis.

Result: During 24-months, 21 patients (61.7%) with breast cancer revealed the progression of bone metastasis. entered in this study. Serum OPG was significantly elevated in patients with progression of bone metastasis. ROC analyses showed that serum OPG levels were the most reliable predictor of bone metastasis (area under the curve = 0.71).

Conclusions: This study showed an OPG was reliable marker in detecting the progression of bone metastasis in breast cancer. Further studies, which considered biologic subtypes, are needed.

BCL2/P53 IS HIGHLY SIGNIFICANT PROGNOSTIC INDICATORS FOR ER-POSITIVE BREAST CANCER

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Background: B-Cell lymphoma/leukemia 2 (BCL2) and p53 involve in growth control and the apoptosis pathways, which appear to play a key role in tumor progression and prognosis. We analyzed the prognostic and predictive significance of BCL2 and p53 expression in estrogen receptor (ER)-positive breast cancer.

Methods: We retrieved the data of 3,186 patients who were newly diagnosed with malignant breast cancer between August 2006 and December 2013. We analyzed BCL2/p53 index representing the relative expression of each protein and assessed its association with recurrence free survival (RFS), breast cancer-specific survival (BCSS), and overall survival (OS).

Result: A total of 511 (60.2%) cases of ER-positive breast cancer showed BCL2-positive/p53-negative expression. 97 (11.4%) were BCL2-positive/p53-positive expression, 169 (19.9%) were BCL2-negative/p53-negative expression, and 72(8.5%) were BCL2-negative/p53-positive expression. BCL2-positive/p53-negative expression showed an associated with favorable prognostic factors, such as well histological grade ($p < 0.001$), no lymphovascular invasion ($p = 0.004$), lower pathologic stage ($p = 0.033$), progesterone receptor (PR)-positive ($p < 0.001$), HER2 negative ($p < 0.001$), lower Ki-67 level (< 14%; $p < 0.001$), and EGFR negative ($p = 0.001$). BCL2/p53 expression showed a significant association with BCSS and OS in ER-positive breast cancer ($p = 0.002$ and $p = 0.026$, respectively). BCL2-positive/p53-negative and BCL2-positive/p53-positive breast cancer showed similar clinical prognostic course in recurrence and survival. In multivariate analysis, lymph node metastasis and BCL2-positive expression were independent prognostic factors for BCSS and OS. However, there was no correlation between BCL2/p53 expression and RFS.

Conclusions: BCL2/p53 expression could be a predictor of BCSS and OS in ER-positive breast cancer.

FOXA2 PROTEIN EXPRESSION IS ASSOCIATED WITH RECURRENCE IN PATIENTS WITH TRIPLE-NEGATIVE BREAST CANCER

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Background: The lack of available tailored targeted therapy for triple-negative breast cancer (TNBC) results in poor clinical outcome. FOXA2, a transcription factor, plays a pivotal role in the development and functioning of various organs. Recent studies have demonstrated the tumor suppressor function of FOXA2 in various human cancers; however, the role of FOXA2 protein in TNBC is not so well-defined. Therefore, we aimed to investigate the FOXA2 protein expression in TNBC and explore its relationship with clinicopathological variables and prognosis of patients with TNBC.

Methods: We examined FOXA2 expression at protein level immunohistochemically in tissue microarrays consisting of 96 invasive TNBC cases and interpreted using a semiquantitative scoring system. For statistical analysis, immunoreactive scores of < 2 and ≥ 2 were considered low and high FOXA2 expression respectively. FOXA2 expression was correlated with various clinicopathological variables and patients prognosis.

Result: Nuclear FOXA2 protein expression was detected in 43 (44.79%) TNBC tissue samples and 26 of 96 (27.08%) cases demonstrated low FOXA2 expression. The survival analysis revealed that TNBC patients with low FOXA2 expression had significantly shorter disease-free survival ($p = 0.040$, log-rank test) than those with high expression. Multivariate Cox regression analysis showed that lymph node metastasis was an unfavorable prognostic variable for recurrence in both disease-free ($p = 0.024$) and overall ($p = 0.002$) survival. However, no correlation between FOXA2 expression and clinicopathological parameters were observed.

Conclusions: Our results suggest that FOXA2 is significantly associated with relapse in TNBC and may function as a potential prognostic biomarker for patients with TNBC.

CLINICOPATHOLOGIC FACTORS ASSOCIATED WITH PROGNOSIS IN TRIPLE NEGATIVE BREAST CANCER: AN INSTITUTIONAL ANALYSIS

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Background: Triple negative breast cancer (TNBC) is defined by a lack of expression of estrogen and progesterone receptors and human epidermal growth factor receptor2. In this study, we evaluate prognostic factors for survival and recurrence of patients with TNBC with routine clinical treatment in our institution.

Methods: Of 754 female patients who underwent curative surgery followed by standard adjuvant therapies in Hallym Sacred Heart Hospital from 2003 to 2011, 111 patients were confirmed TNBC. We analysis survival using the Kaplan-Meier method. The Cox proportional hazard model was used in the multivariate analysis.

Result: The mean age of patients was 50.14 ± 0.41 (range, 28-76) years and the median follow-up period was 61 months (range 7-137). Five (4.5%) pts had local recurrence only, 11 (95%) pts had distant recurrence and 6 pts died. 5 year disease free survival (DFS) for TNBC group was 92.5% and 5 year overall survival (OS) was 97%. In univariate analysis, recurrence and overall survival were related to lymph node (LN) status, Ki-67, lymphovascular invasion (LVI) and adjuvant immunotherapy using mistletoe. In multivariate analysis, nodal status and Ki-67 were statistically significant factor that was related recurrence, but there were no statistically significant factor that was related to overall survival.

Conclusions: In this study, nodal status and Ki-67 were found be independent prognostic factors for DFS whereas no independent prognostic factors for OS. With many limitation of data, there is no pattern of increasing incidence of early recurrence.

UBE2C IS A POTENTIAL TARGET FOR USE IN COMBINATION THERAPY WITH TAMOXIFEN IN LUMINAL A BREAST CANCER

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Background: Luminal A breast cancer patients generally have a good prognosis after endocrine therapy. However, some patients (approximately 20%) remain at risk for late recurrence and may adjuvant chemotherapy to reduce the risk of recurrence. Therefore, it is important to identify patients at high risk of recurrence. Previously, we validated expression of several candidate prognostic genes by performing quantitative real-time reverse transcription-PCR in 997 FFPE tissue samples, and then assessed association between their expression and risk of overall survival (OS) and recurrence-free survival (RFS) in 819 breast cancer patients. Among these genes, higher UBE2C expression was significantly correlated with shorter OS and RFS. Here, we investigated whether UBE2C might play specific roles in luminal A breast cancer by characterizing functions of UBE2C overexpression in luminal A cell lines.

Methods: UBE2C expression was measured using qRT-PCR, immunoblotting. Cell proliferation was measured by quantifying the metabolic cleavage of the tetrazolium salt in viable cells. Migration was quantified by trans-well assay. The synergism of siRNA and tamoxifen was defined by Chou-Talalay method.

Result: UBE2C expression was relatively high in luminal A cell lines. In these cells, depletion of UBE2C using siRNA led decreased cell proliferation and migration. Interestingly, in MCF-7 cell, combined treatment with UBE2C siRNA and tamoxifen showed a synergistic effect on cell viability (Combination index = 0.745).

Conclusions: Our findings suggest that UBE2C expression was correlated with luminal A breast cancer. In luminal A cells, UBE2C expression enhanced cell proliferation and migration. The combined treatment of UBE2C siRNA and tamoxifen may benefit for treatment of luminal A patients.

IS AJCC STAGE 1B CLINICAL MEANINGFUL? SURVIVAL ANALYSIS FROM A SINGLE INSTITUTION

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Background: Staging refers to the grouping of patients according to the extent of their disease. Staging is useful in determining the choice of treatment, estimating their prognosis and comparing the result of different treatment programs. Distribution of patients' AJCC stage from breast cancer registration data in National Taiwan University Hospital showed low percentage of stage IB patients. The purpose of this study was to verify the staging system in stage IB.

Methods: We analyzed breast cancer patient data base with 4592 patients from 2010 to 2014 at National Taiwan University Hospital. Clinico-pathologic and survival data were recorded. The disease was staged according to the 7th edition AJCC staging system. Survival analysis was performed focused on stage IA, IB and IIA with 2055 patients.

Result: The overall survival analysis of stage IA, IB and IIA breast cancer patients from 2010 to 2014 at National Taiwan University Hospital showed no significance differences between patients with stage IA, IB and IIA. Further survival analysis of patients within stage IB disease showed no survival difference between patients received adjuvant chemotherapy or not in estrogen positive and HER2/neu non-amplified subgroup.

Conclusions: Breast cancer patients in stage IB were rare. There is no overall survival difference between IA, IB and IIA. In patients with nodal micrometastasis, adjuvant chemotherapy for estrogen positive and HER2/neu non-amplified subgroup did not improve overall survival.

CHANGES IN QUALITY OF LIFE, FUNCTIONING, AND SYMPTOMS ACCORDING TO DEPRESSION TRAJECTORY AFTER BREAST CANCER SURGERY

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Background: To investigate the influence of depression trajectory on quality of life, functioning, and symptoms during the year after breast cancer surgery.

Methods: Participants were interviewed 2-5 days and 1 year after surgery. Depression was diagnosed according to the DSM-IV. Quality of life, functioning, and symptoms were evaluated with the EORTC QLQ-C30. Baseline sociodemographic and clinical characteristics were investigated using repeated measures analysis of variance (RMANOVA), and P-values were adjusted with the Bonferroni correction (corrected $p < 0.003$).

Result: Of 335 participants, 247 were evaluated 1 year after surgery. Of the 189 with no depression at baseline, 24 had incident depression at 1 year. Of the 58 patients with depression at baseline, 18 had persistent depression at 1 year. The RMANOVA showed significant differences among groups (no depression, recovered, incident, and persistent) in general health, all functional scales, and some symptom scales (fatigue, nausea and vomiting, dyspnea, insomnia, and appetite loss). Significant time-by-group interactions regarding general health, functional scales (role, emotional, and social), and symptom scales (fatigue, insomnia, and appetite loss) were also observed.

Conclusions: According to the longitudinal follow up, the no-depression and recovered groups showed similar improvements in general health, functioning, and symptoms, but the groups with incident and persistent depression did not. The persistent-depression group showed the worst outcomes, as measured by changes in EORTC QLQ-C30 scores. Research using the EORTC QLQ-C30 to examine the influence of depression should focus on its longitudinal course rather than its status at only one time point.

LONGITUDINAL PATTERNS AND ASSOCIATED FACTORS OF POSTDIAGNOSIS WEIGHT CHANGES IN KOREAN BREAST CANCER SURVIVORS WITH NORMAL BODY MASS INDEX

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Background: This study aimed to describe longitudinal patterns of weight changes from diagnosis to within 5 years after diagnosis and investigate factors associated with short- and long-term weight change among Korean breast cancer survivors with initially normal body weight index (BMI).

Methods: Body weights at diagnosis for 1,546 breast cancer survivors were compared with those at 12, 24, 36, 48, and 60 months after diagnosis. Absolute weight change (kg) and relative weight changes (%) were analyzed. Logistic regression was used to identify factors associated with short-term (1 year) and long-term (5 years) weight change.

Result: A significant decrease in mean weight was predominant at 12 months post-diagnosis. In subgroup analysis, the younger age group showed significant weight gains after 36 months. The older age group and chemotherapy (CT) group showed significant weight losses after 24 months. About 40% of early weight gainers and 60% of early weight losers returned to their initial weight by 60 months post-diagnosis. CT and lower educational levels were associated with short-term weight loss and gain, respectively. For long-term changes, age at diagnosis was the sole associated factor.

Conclusions: Korean breast cancer survivors treated with CT mainly experienced post-diagnosis weight loss rather than weight gain. Short-term weight change was independently associated with chemotherapy and educational level. However, long-term weight change was associated with age at diagnosis.

ESTIMATING PROBABILITY OF DEATH FROM BREAST CANCER AND OTHER CAUSES IN FEMALE BREAST CANCER PATIENTS IN KOREA

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Background: Breast cancer patients are at the risk of dying from diagnosed breast cancer and from other competing causes of death(e.g. CVD). Understanding causes of death and actual mortality patterns experienced by patients are critical in clinical decision-making.

Methods: We conducted competing risks analysis on female breast cancer patients in Korea diagnosed in 1993-2013 (n = 184,721). Five-year probabilities of death from cancer and other causes were estimated by age and stage at cancer diagnosis. Distribution of causes of death is shown to illustrate descriptive patterns of mortality. Data from Korea Central Cancer Registry, linked to the cause of death information was utilized for this analysis.

Result: Most of death is attributed to breast cancer and for non-cancer causes of death, cerebrovascular diseases were the most common. Survival experience from cancer and other causes varied substantially. Younger patients had worse probability of death from breast cancer relative to their competing causes of death. Both cancer and other-cause survival were worse for the elderly; 5-year probability of death increases from 12% (age 65-75) to 27% (over age 75) for breast cancer and 3% to 10% for other causes. For localized cancer patients aged 75-85, 5-year probability of death from cancer (13.6%) and from other causes of death (9.1%) were similar.

Conclusions: Death from breast cancer remains substantial relative to the other competing causes, in particular younger ages and advanced stage. Death from other causes become increasingly important in the elderly diagnosed as early stage cancer. Treatment and heath care decision may benefit by understanding probability of death from cancer and other causes.

CLINICAL OUTCOMES AFTER LETROZOLE TREATMENT ACCORDING TO THE ESTROGEN RECEPTOR EXPRESSION IN POSTMENOPAUSAL WOMEN: LETTER TRIAL

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Background: The LETTER trial investigated adjuvant letrozole for hormone receptor (HR)-positive breast cancer in terms of efficacy and safety.

Methods: In this multi-institutional, open-label, prospective phase 4 LETTER trial, post-menopausal patients with HR-positive breast cancer received adjuvant letrozole (2.5mg/daily) until disease progression, unacceptable toxicity, or withdrawal of consent. The patients were stratified into three groups by ER expression following modified Allred score (AS); low (AS 3-4), intermediate (AS 5-6), and high (AS 7-8). The primary objective was 5-year disease-free survival (DFS) rate. ClinicalTrials.gov, number NCT01069211.

Result: Between Apr 25, 2010, and Feb 5, 2014, 452 patients were enrolled. The proportions of patients categorized as having a low, intermediate, or high ER expression by AS were 12, 23, and 65 percent, respectively. At a median follow up of 56.7 months, the 5-year DFS rate was 94.2 % (95% CI 92.9-95.5%), and the 5-year overall survival (OS) rate was 99.0% (95% CI 98.5-99.5%). The 5 year DFS and OS rates did not differ according to ER expression (5 year DFS, P = 0.418; 90.8% in low, 96.8% in intermediate, and 94.7% in high; 5 year OS, P = 0.242; 98.0% in low, 97.9% in intermediate, and 99.6% in high, respectively). There were 25 drop-out patients due to adverse event (AE) of letrozole. Among the AEs associated with drop-out, the most common were arthralgia (18 [3.9%]), hot flush (1 [0.2%]), skin rash (1 [0.2%]), headache (1 [0.2%]), and others (4 [0.8%]).

Conclusions: Adjuvant letrozole brings a favorable treatment outcome for postmenopausal with HR-positive breast cancer, offering good tolerability.

FIBROADENOMA OF AXILLARY ACCESSORY BREAST TISSUE

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Background: The incidence of ectopic breast tissue is around 2-6% in women. Accessory breast tissue of the axilla is one of the varieties of supernumerary breast tissue. The accessory tissue can undergo the same physiological and pathological processes as the normally located breast. Fibroadenoma in axillary breast tissue is rare.

Methods: We report and discuss a case of fibroadenoma arising in the accessory breast tissue of the right axilla.

Result: A 46-year-old woman presented with a palpable mass in right axilla. Her personal and familial medical history was unremarkable. There was no family history of breast cancer or polymastia. On physical examination, about 2.5 cm sized mass is noted in the right axilla. The mass is firm, nontender, freely mobile, and completely isolated from the right breast. Skin over the swelling is normal, with no nipple or areola made out. Examination of left axilla and neck was normal. Ultrasonography of right axilla revealed a space-occupying lesion with well circumscribed and homogenous, solid mass measuring 2.5 × 1.4 cm in diameter. The patient underwent excisional biopsy under local anesthesia. The histological findings of the resected specimen revealed the typical features of fibroadenoma with accessory breast tissue.

Conclusions: Differential diagnosis of an axillary mass should include fibroadenoma arising from accessory breast tissue.

THE 10-YEAR FOLLOW-UP OF INVASIVE PAPILLARY BREAST CARCINOMA: A CASE REPORT

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Background: A multidisciplinary approach to breast cancer has led to a decrease in the number of patients who refuse treatment. It is difficult to obtain long-term follow-up results, especially of the rare histological subtypes of breast cancer, such as invasive papillary carcinoma. Herein, the authors report a case of invasive papillary breast carcinoma in a patient who refused treatment along with data of the 10-year follow-up.

Methods: A 59-year old woman visited our hospital in May 2016, complaining of a palpable mass on the left breast. The postmenopausal patient denied any underlying disease or family history of breast cancer. Light microscopy revealed that the tumor had a predominantly papillary architecture with the papillae formed by malignant epithelial cells intimately related to fine fibrovascular cores. The patient had been diagnosed with invasive papillary breast carcinoma.

Result: At the first visit of the patient to our hospital in July 2006, the tumor measured 10.4 × 7.2 cm. It was staged as IIIB (T4bN1). In the past 10 years, the tumor had increased up to 12.1 × 4.2 cm. The tumor was staged as IIIC (T4bN3a) in 2016. However, whole body bone scan and 18F-FDG PET/CT showed no evidence of distant metastasis. The tumor was estrogen/progesterone-receptor-positive and C-erbB2 expression was not detected. The measured labeling index of Ki-67 was around 10%. The immunohistochemistry results remained unaltered since 2006.

Conclusions: As demonstrated in the present case, invasive papillary breast carcinoma has a relatively good prognosis. Henceforth, further curative treatments could be considered for patients with this rare histological subtype.

PRIMARY OSTEOSARCOMA OF THE BREAST: A CASE REPORT

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Background: Breast sarcoma is a rare disease and accounts for less than 1% of all primary breast malignancies. Osteosarcoma of the breast is an extremely rare disease and makes up only about 12.5% of the breast sarcomas.

Methods: A 75-year-old female visited our breast clinic for palpable mass on her right breast. After diagnostic work-up and excisional biopsy, she was diagnosed with extraskeletal osteosarcoma and underwent mastectomy. The clinical records, imaging studies, and pathologic reports were reviewed.

Result: The patient presented hard, painless lump which was about 4 cm in diameter on physical examination. The lump was rapidly growing for the past four months. On mammogram, about 2 cm sized dense calcified mass was identified on the right upper breast. On sonogram, about 2.4 cm sized calcified hypoechoic mass with relatively well-defined margin was identified on the right upper inner breast. She underwent excisional biopsy and extraskeletal osteosarcoma was diagnosed. Pathologic report showed 3.5 cm sized tumor with more than 10 mitoses/HPF and positive resection margin. Breast MRI, bone scan, and PET-CT revealed no other lesion. To obtain a negative surgical resection margin, partial mastectomy was performed. Final pathologic report revealed no residual tumor with minimum 2.5 cm resection margin. Immunohistochemistry showed focally positive SMA and negative S-100, CK, and CD31.

Conclusions: Primary osteosarcoma of the breast is a very rare disease and surgical resection obtaining negative resection margin is a treatment of choice. Axillary dissection is not indicated unless enlarged lymph nodes exist clinically. The role of adjuvant therapy is not established.

PROSPECTIVE RANDOMIZED CLINICAL TRIAL TO EVALUATE THE OPTIMAL DOSE OF ICG-RITUXIMAB IN PATIENTS WITH EARLY-AGE BREAST CANCER FOR SENTINEL LYMPH NODE BIOPSY

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Background: To observe the effect and adverse reactions of different-doses of indocyanine green - rituximab on the lymph node imaging of breast cancer patients, and to determine the optimal dose of the new tracer for sentinel lymph node biopsy.

Methods: Consecutive breast cancer patients without clinical axillary lymph node metastases were enllorled in five groups, 10 cases in each group. Different doses of indocyanine green rituximab were injected in the peritumoral intra-parenchyma guided by ultrasound 3-18 hours before the surgery. Radioactive or blue lymph nodes were defined as sentinel lymph node. Meanwhile 2-3 non sentinel lymph nodes were removed. Then all removed lymph nodes were visualized using a MDM-I fluorecenceimaing system (MDM), which is a near infrared imaging system. The GNU Image Manipulation Program (GIMP) was used to assess the fluorescence intensity.

Result: Different doses of indocyanine green rituximab (125-500 μg, 93.75-375 μg, 62.5-250 μg, 25-100 μg, 12.5-50 μg) were injected in fifty patients who were divided into five groups. The positive coincidence rate of lymph nodes increased with the dose of ICG- Rituximab, which in each group were 96%, 82.7%, 69.5%, 36.4%, 8.3%, false-negative rate were 4%,17.3%, 30.5%, 63.6%, 91.7%. And the imaging rate of non-sentinel lymph nodes were 58.6%, 30.2%, 1.56%, 0%, 0%.

Conclusions: The imaging rate and false negative rate are positively correlated with the dose of indocyanine green rituximab. And as a new tracer for sentinel lymph node biopsy in breast cancer, the optimal dose of indocyanine green rituximab is 62.5-250 μg.

INCIDENCE OF CHEMOTHERAPY INDUCED AMENORRHEA IN PATIENTS WITH BREAST CANCER AFTER ADJUVANT CHEMOTHERAPY CONTAINING ANTHRACYCLINE AND TAXANE

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Background: 25% of women with carcinoma of breast are premenopausal and are at risk for chemotherapy-induced menopause. The objective of this study is to determine the rates of chemotherapy-induced amenorrhea in breast cancer patient with Anthracycline and Taxane containing adjuvant regimens. There are inadequate data about the impact of these adjuvant regimens on menstrual function in Vietnamese breast cancer patients.

Methods: 72 premenopausal women with carcinoma of breast who were treated with adjuvant anthracycline and taxane-based chemotherapy at National Cancer Hospital of Viet Nam from January 2015 to June 2016. Menstrual status were obtained prospectively.

Result: 72 patients had sufficient follow-up for evaluation. 67% of patients aged 40 years and younger. All patients had regular menses before chemotherapy. 60 patients (83%) developed amenorrhea after finishing adjuvant chemotherapy, and 67% of these patients (40 patients) resumed menstruation at 12 months after chemo. 51 patients (71%) received Tamoxifen. The rate of long term amenorrhea among these was 22%. There was a statistically significant correlation between age and the development of amenorrhea, patients older than 40 years had higher risk.

Conclusions: Adjuvant anthracycline and taxane-based chemotherapy induces reversible amenorrhea. Age had impact on development of chemotherapy-induced amenorrhea.

THE PROGNOSTIC ROLE OF SPAG5 GENE EXPRESSION IN BREAST CANCER PATIENTS WITH SYSTEMATIC THERAPY

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Background: Despite much effort on the treatment of breast cancer over the decades, a great uncertainty regarding the optimal therapeutic strategy, especially effective precision medicine for breast cancer still existed.

Methods: We used a breast cancer database including 5,667 patients with a mean follow-up of 69 months, measured by Affymetrix microarrays, to analyze the association of SPAG5 gene expression with clinicopathological factors and survival outcomes. Kaplan-Meier survival analyses for relapse free survival (RFS), overall survival (OS), and distant metastasis-free survival (DMFS) were performed.

Result: Mean SPAG5 expression value was higher in ER negative (ER-) than ER positive (ER+) breast cancer patients. Higher expression of SPAG5 could predict worse survival outcomes including RFS, OS, and DMFS. In patients who received chemotherapy alone, SPAG5 had a moderate predictive impact on survival outcomes, but the survival curves did not show a significant difference between low and high SPAG5 transcript expressions. Relatively, in patients receiving hormonal therapy, high SPAG5 expression could strongly predict poor prognosis with detrimental RFS (HR = 1.57, 95% CI 1.2-2.06, $p = 0.001$), OS (HR = 2, 95% CI 1.05-3.8, $p = 0.03$) and DMFS (HR = 2.36, 95% CI 1. 57-3.54, $p < 0.0001$), respectively.

Conclusions: Overall, SPAG5 was significantly higher with some clinicopathological factors that resulted in tumor promotion and progression. SPAG5 could be used as an independent prognostic and predictive biomarker that might have clinical utility, especially in ER+ breast cancer patients who received hormonal therapy.

PREVALENCE AND RELATIONSHIP OF MALNUTRITION AND DISTRESS IN BREAST CANCER PATIENTS USING QUESTIONNAIRES

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Background: Breast cancer is associated with negative feelings and malnutrition, the symptoms of which overlap. However, the relationship between them is still unclear. The objective is to investigate the prevalence of malnutrition and distress in breast cancer patients and examine the relationship between them.

Methods: We did a cross-sectional study in West China Hospital, China, using adapted questionnaires derived from Patient-Generated Subjective Global Assessment (PG-SGA), Nutritional Risk Screening 2002 (NRS2002) and Distress Thermometer (DT). We also focused on the factors associated with distress.

Result: We found that psychological distress in breast cancer patients was common, with 39.5% patients suffering distress. The mean score of PG-SGA was 3.37 (0-6), and 39.1% patients had malnutrition when using ≥ 4 as a cut-off value. Meanwhile, the mean score of NRS2002 was 1.91 (0-11), and 25.8% patients represented malnutrition when using ≥ 3 as the cut-off value. Higher scores of nutritional risk confirmed by PG-SGA ($r = 0.148$, $p < 0.001$) and NRS2002 ($r = 0.142$, $p < 0.001$) were significantly correlated with higher levels of psychological stress.

Conclusions: Malnutrition was correlated with psychological stress. It is meaningful to intervene in the psychological problems early and facilitate food-based interventions to improve the psychological status of breast cancer patients.

A SMART SYSTEM FOR MAMMOGRAPHIC IMAGE CLASSIFICATION

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Background: Breast cancer is a widespread disease in women. Early detection of breast cancer is an important factor in cancer treatment. Mammography is the main screening tool for cancer detection and image classification and retrieval based on masses type and texture can help radiologist for better diagnosis. Accuracy in the feature extraction is an important factor in classification and image retrieval.

Methods: In this paper, a breast tissue density classification model is studied. In the proposed method, a smart system classifies the similar mammographic images into the same classes. The system can help the radiologists to reduce the diagnose errors. In this system, the two-directional two-dimensional principal component analysis has been used for feature extraction and dimension reduction of the mammographic images and a support vector machine has been used for image retrieval.

Result: The proposed model can be used for mammographic images analysis in the large database. The system can separate the breasts with extremely dense from the normal breasts. Thus, image analysis can be simply done in the various classes.

Conclusions: The model is tested on the Mammographic Image Analysis Society (MIAS) database. The average precision rates of the model are about 93%. The proposed model results are compared with the results of other valid literature in a table for better analysis.

EARLY BREAST CANCER DETECTION USING THERMAL INFRARED IMAGES

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Background: Early breast cancer detection is one of the best strategies for cancer damage and death reduction. Breast cancer is one of the most common cancers in the world which spend a lot of costs to treat it. One of the biggest problems in the breast cancer diagnosis is the age of cases which are over 40 years generally.

Methods: We proposed a novel model for the early breast cancer detection. In this practical model, breast cancer is detected by infrared images using image processing and data analysis. This method is a noninvasive, non-contact, risk free, non-radiation and high speed method with high precision for breast cancer detection.

Result: Several methods are proposed which can improve cancer diagnosis and these methods can be used to increase speed and accuracy. The proposed models are thermal pattern of image, fuzzy system and asymmetry breast techniques. The new method of thermographic image analysis for automated detection of high tumor risk areas, based on two-directional two-dimensional principal component analysis technique for feature extraction, and a support vector machine for thermographic image retrieval was tested on 155 random cases.

Conclusions: The sensitivity and specificity of the model are 100% and 90% and false positive, false negative and predictive value of negative test parameters for the proposed model are 9.9%, 0 and 100%, respectively.

ADJUVANT RADIOTHERAPY AFTER SKIN SPARING MASTECTOMY WITH IMMEDIATE AUTOLOGOUS BREAST RECONSTRUCTION

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Background: Skin sparing mastectomy with immediate autologous breast reconstruction has a positive psycho-social and sexual effect, however postoperative radiotherapy could adversely affect its cosmetic results.

Methods: This study included 24 female breast cancer patients underwent skin sparing mastectomy with or without scarifying neo adjuvant chemotherapy (NAC) and immediate reconstruction by autologous transverse rectus abdominis muscle (TRAM) and latissimus Dorsi myocutaneous flap. They received adjuvant chemotherapy followed by 3DCRT, we evaluated them for skin complications and cosmoses.

Result: Faint erythema or dry desquamation detected in 16 patients [66.6%], while 8 patients [29.2%] had moderate to brisk erythema. Two patients (8.3%) had skin edema and one patient (4.2%) had telangiectasia. Two patients complained from moderate pain Fat necrosis within the flap detected only in one patient (4.2%). Twenty-two patients (83.3%) had acceptable cosmoses while 2 patients had un-satisfactory cosmetic results.

Conclusions: Postoperative radiotherapy is safe with acceptable rate of complications after skin sparing mastectomy and immediate autologous breast reconstruction.

PO096

IMPACT OF CHEST WALL MOTION CAUSED BY RESPIRATION IN ADJUVANT RADIOTHERAPY FOR POSTOPERATIVE BREAST CANCER PATIENTS

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Background: According to the anatomy of the breast that lies on the anterior chest wall, intrafraction movement of the clinical target volume can occur due to respiration during treatment delivery. Large treatment margins added to cover the movement may subsequently cause a substantial volume of normal tissue exposed to radiation resulting in increased risk of treatment-related toxicity. So, This study was planned to evaluate the movement distances of breast or chest wall during respiration.

Methods: Consecutive postoperative breast cancer patients, planned for adjuvant radiotherapy in Ramathibodi Hospital from December 2012 to November 2013, were included. CT simulation was performed as free-breathing scan, deep inspiratory breath holding and expiratory breath holding. Using radiotherapy planning system to measure chest wall motion in three axes as antero-posterior (AP), supero-inferior (SI) and medial-lateral (ML).

Result: 38 patients were enrolled, 27 patients underwent mastectomy and 11 had BCS. Median BMI was 23.4 kg/m^2. Median lung volume was 3,160.5 cm^3. Median Haller index was 2.4. The median chest wall movement was 4.2 to 5 .4 mm., 2.5 mm., 0.6-1.1 mm. for AP, SI and ML axis, respectively. There was no significant affecting chest wall motion among factors such as BMI, lung volume, Haller index and type of surgery.

Conclusions: This study show the maximal movement of the chest wall is in Aaxis with is about 5.5 to 7.18 mm to coverage 95% of the patients so additional margin of >7.1 mm especially in anteriorposterior axis is required to ensure the clinical target volume coverage from data of this study.

ALTERED RESTING-STATE HIPPOCAMPUS FUNCTIONAL NETWORKS ASSOCIATED WITH CHEMOTHERAPY-INDUCED PROSPECTIVE MEMORY IMPAIRMENT IN BREAST CANCER SURVIVORS

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Background: Cognitive impairment is a common syndrome following breast cancer chemotherapy due to neurotoxic brain injury. Recent neuroimaging studies suggest hippocampus atrophy contribute to the memory impairment in post-chemotherapy cancer patients. However, it is currently unknown whether breast cancer treatments disrupt the hippocampus functional networks. In this study, we aimed to investigate the intrinsic hippocampus functional connectivity (FC) network and the relationship with prospective memory in chemotherapy-induced cognitive impairment in patients with breast cancer.

Methods: Thirty four breast cancer with adjuvant chemotherapy (CC) and 31 age- and education-matched cognitively normal (CN) women were recruited and administered prospective memory task as well as a resting state functional magnetic resonance imaging scan. Seed-based functional connectivity analysis was used to compare the hippocampus FC networks between two groups. Partial correction analysis was used to detect the association between hippocampus FC network and prospective memory in CC group

Result: Chemotherapy cancer group showed significant poorer in the scores than CN group on mini-mental state examination, verbal fluency test, digit span, and prospective memory. Compared to CN group, the CC group showed increased hippocampus connectivity in frontal and parietal cortex, precuneus, posterior cingulate cortex and cerebellum. In addition, the increasing hippocampus FC networks were negatively correlated with prospective memory performance in CC group.

Conclusions: These findings proposed a hippocampus functional maladaptive mechanism of prospective memory impairment in CICI patients, and the altered hippocampus functional network might serve as a new biomarker for chemotherapy-induced cognitive impairment diagnoses in cancer patients.

CHEMOTHERAPY-INDUCED PROSPECTIVE MEMORY IMPAIRMENT IN BREAST CANCER PATIENTS WITH THE DIFFERENT EXPRESSION OF HORMONE RECEPTOR

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Background: This study aimed to investigate the prospective memory impairment in breast cancer patients with the different expression of hormone receptor, including estrogen receptor (ER) and progesterone receptor (PR).

Methods: A total of 120 breast cancer patients who underwent chemotherapy after operation were divided into two groups, A group included 60 patients with ER-/PR-, and B group included 60 patients with ER+/PR+. After six cycles of postoperative adjuvant chemotherapy, all of patients were administered with neuropsychological tests and prospective memory, such as mini-mental state examination (MMSE), verbal fluency test (VFT) digit span test (DST), event-based prospective memory (EBPM), and time-based prospective memory.

Result: As the neuropsychological background tests results exhibition, the MMSE DST, and TBPM of breast cancer patients with ER-/PR-and ER+/PR+ was slightly increased, and had no a significant difference, and significantly, the VFT and EBPM was significantly increased breast cancer patients with ER+/PR+, and had a significant difference ($p > 0.05$, **: $p < 0.01$), and indicated that patients with ER-/PR- have a significant damage on the EBPM, and however not on the TBPM.

Conclusions: This study indicated that different hormone receptors in breast cancer patients may be associated with the heterogeneity of chemotherapy-induced prospective memory impairment.

EVALUATION OF A SUSCEPTIBILITY LOCI OF BREAST CANCER IN WOMEN OF HENAN POPULATION

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Background: Triple negative breast cancers (TNBC) is an aggressive subtype of breast cancer with poor survival, but there remains little known about the etiological factors which promote its initiation and development. However, the published literature shows a wide variation in the prevalence of germline BRCA mutations in TNBC patients with reported rates varying from 10-42%. Information about gene morphology of TNBC is unknown. With the genome-wide association study (GWAS) development, many studies have confirmed that rs8170 is associated with TNBC in European and Caucasian populations currently, especially in breast cancer with BRCA1/2 mutations. The purpose of this study is to further verify the association between rs8170 (19p13.1) which have been confirmed in European and Caucasian populations and breast cancer susceptibility in sporadic breast cancer among the Han nationality in Henan province, and analyse their genotypes in the internal type of breast cancer.

Methods: In 253 breast cancer case group and 346 healthy control group, rs8170 (19p13.1) is genotyped by SNP im-LDR technique. According to ER, PR, HER2 and Ki67, breast cancer is divided into five types: Luminal A, Luminal B, HER2-enrich, Luminal HER2, TNBC.

Result: Rs8170 (19p13.1) has no significant statistical difference with breast cancer ($p = 0.563$) According to the breast cancer types, the genotypes of rs8170 (19p13.1) have no differences in different types of breast cancer. At the sametime, we found the MAF of rs8170 is very low in Chinese women population (MAF = 0.003).

Conclusions: Rs8170 (19p13.1) from GWAS is not associated with breast cancer risk among the Han nationality in Henan province, and different genotypes of this loci distribute equally in different types of breast cancer.

MEDICATION ADHERENCE IN ADJUVANT ENDOCRINE THERAPY FOR BREAST CANCER PATIENTS

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Background: This descriptive correlation study is aimed to understand the medication adherence to adjuvant endocrine therapy and to identify the factors influencing medication adherence breast cancer patients.

Methods: Data were collected form 101 patients undergoing adjuvant hormonal therapy in general hospital using the self-reporting questionnaires and statistical analysis was performed using SPSS-21.0 program. The level of medication adherence and related factors were measures with ask-12 survey for medication adherence, BMQ-specific for health beliefs, MSPSS for social support, FACT-ES for health-related quality of life. Attitude, knowledge, disability related to medication use were measured of tool developed by Wu.

Result: The average level of medication adherence was 27.1 out of 60. There was statistically significant difference in medication adherence according to the presence of other medications taken together adjuvant endocrine therapy ($p = 0.000$). There was a significant difference according to the type of adjuvant endocrine medication ($t = 5.513$, $p = 0.005$). Family support was statistically significant as a factor influencing medication adherence ($t = 2.488$, $p = 0.015$). The correlation between medication adherence and social support showed negative correlation ($r = -.217$, $p = 0.030$). The correlation between medication adherence and treatment related symptoms showed positive correlation($r = .201$, $p = 0.044$). Family support ($t = -2.368$, $p = 0.020$), type of adjuvant endocrine medication ($t = 3.004$, $p = 0.003$), medications taken together ($t = 2.468$, $p = 0.015$) showed influencing the adherence for adjuvant endocrine medication (explanation power = 15.0%).

Conclusions: In order to increase adherence to adjuvant endocrine medication, family support should be strengthened. Also, it is recommended to develop educational materials.

PROTOCOL AND PRELIMINARY REPORT OF ANALYSIS OF CLINICOPATHOLGIC FEATURES OF PATIENTS WITH BRCA1 C.5339T>C, P.LEU1780PRO, MUTATION IN KOREA

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Background: BRCA1 c.5339T > C, p.Leu1780Pro mutation (L1780P) has been considered to be a variant of unknown significance. However, the recent evidences evaluating the role of L1780P suggested that L1780P is pathogenic or likely pathogenic according to the ACMG guideline. The aim of the study is to evaluate clinicopathologic features of patients with L1780P using retrospective multicenter data in Korea.

Methods: Data collection is retrospectively performed. Thirteen institutions have provided data of patients with L1780P or agreed to participate in the study. Personal identifiers for all patients are removed from this analysis. Clinicopathologic data and information of genetic variants of BRCA1/2 are reviewed and analyzed.

Result: Forty-one patients from 7 institutions were collected. Two institutions reported no data of the patients with L1780P. Data from four institutions are pending.

Conclusions: Detailed protocols and preliminary analyses will be presented at the upcoming GBCC.

COMBINATION OF AGE/BODY MASS INDEX-ADJUSTED SCORES OF PERCENT DENSITY AND DENSE AREA FOR ASSESSING BREAST CANCER RISK

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Background: The aim of this study was to evaluate the usefulness of integrating the scores of percent density (PD) and dense area (DA) from digital mammogram to predict breast cancer risk.

Methods: Mammographic density of 1,441 non-affected healthy women (control group) and 701 breast cancer patients (case group) aged between 40 and 59 were analyzed. Two mammographic density scores from digital mammogram were assessed by CumulusTM. Through adjustment of age and body mass index (BMI) by generalized additive model for location, scale and shape (GAMLSS), each standardized breast density scores (ZPD percentile and ZlnDA percentile) were generated and compared. With the cutoff of 60 percentile, conventional dense breast (group 1: ZPD percentile ≥ 60 and ZlnDA percentile ≥ 60), PD dominant dense breast (group 2: ZPD percentile ≥ 60 and ZlnDA percentile < 60), and DA dominant dense breast (group 3: ZPD percentile < 60 and ZlnDA percentile ≥ 60) could be defined as dense breast.

Result: Compared to non-dense breast (ZPD percentile < 60 and ZlnDA percentile < 60), conventional, PD dominant, and DA dominant dense breast were significantly associated with breast cancer risk: odds ratio (OR) = 7.73 (95% CI = 5.99-9.98), 4.97 (95% CI = 3.59-6.90), and 3.99 (95% CI = 2.84-5.60), respectively. Breast cancers developed in the DA dominant dense breasts were characteristic of older age at diagnosis and hormone receptor negativity.

Conclusions: In addition to conventional dense breast, PD or DA dominant dense breast is also a risk factor for breast cancer. Particularly, DA dominant dense breast may be associated with hormone receptor negative breast cancer.

RANDOMIZED CONTROLLED TRIAL TO REINFORCE PHYSICAL ACTIVITY AMONG BREAST CANCER PATIENTS USING WEARABLE DEVICE

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Background: The purpose of this study is to evaluate the efficacy of smart device for encouraging physical activity during breast cancer treatment.

Methods: In a randomized controlled trial, a total of 152 breast cancer patients scheduled for radiotherapy was allocated: 76 for wearable device group and 76 for counselling group. Patients with wearable device monitored their physical activity whereas counseling group received a telephone counseling once a week during radiotherapy. Primary outcome of the study was moderate to vigorous activity (MVPA) time at the end of radiotherapy, and physical activities was evaluated using Global Physical Activity Questionnaire before radiotherapy, at the end of radiotherapy, 3 and 6 months after completion of radiotherapy patients were follow-up until 6 months after completion of radiotherapy.

Result: The mean age of study participants was 47.04 and all baseline characteristics were not different between the groups. Patients with wearable device had more increased MVPA (102.8 min/wk) than counselling group (57.8 min/wk) at the end of radiotherapy compared to the baseline MVPA and they were also more likely to maintain MVPA for a long-term (6 months post intervention). There was no different with work or transportation related physical activities between the groups.

Conclusions: This study shows feasibility of using wearable device to reinforce breast cancer patients physical activities during anti-cancer treatment. It would be worth to develop personalized intervention using wearable devices which can be applied to patients with other cancer or other chronic diseases who could benefit from regular exercise.

VITAMIN D RECEPTOR GENE POLYMORPHISMS AND BREAST CANCER RISK AMONG POSTMENOPAUSAL WOMEN: META-ANALYSIS

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Background: Protections of vitamin D against various types of cancers has been previously reported in the literature. The mechanism of vitamin D action is mediated by the vitamin D receptor (VDR), which may have anti-stress functions. We perform a meta-analysis from prospective case-control studies on the association of vitamin D receptor (VDR) polymorphism and the risk of breast cancer among postmenopausal women.

Methods: We searched PubMed, EMBASE for papers that describe the association between Fok1, poly-A repeat, Bsm1, Taq1 or Apa1 polymorphisms of the VDR gene and breast cancer risk among postmenopausal women. Summary odds ratios and 95% confidence intervals (CI) were estimated based on a fixed-effect model (FEM) or random-effect model (REM), depending on the absence or presence of significant heterogeneity. Eleven studies were included in the meta-analysis.

Result: There were association between Fok1 gene allele contrast ff vs. Ff +FF (OR: 1.09, 95%CI: 1.02 to 1.16, $p = 0.007$), ApaI aa (OR: 2.2, 95%CI: 1.02-4.5, $p = 0.04$).

Conclusions: No significant associations were observed between the other polymorphisms and breast cancer risk among postmenopausal women.

PROGNOSIS OF BREAST CANCER ADJUSTING FOR OVER-DIAGNOSIS

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Background: Over-diagnosis of cancers has become the core subject whilst population-based cancer screening has gained popularity, especially in the full grown screening program, such as mammography screening in occidental countries. However, the influence for the prognostic factors for breast cancer taken over-diagnosis into account has been scarcely addressed.

Methods: We use data from a retrospective cohort of 1,346 consecutively diagnosed breast cancer at Falun Central Hospital, Sweden, in 1996-1998 and 2006-2010. A zero-inflated Poisson (ZIP) regression model was used to quantify the proportion of over-diagnosis rate and to estimate the effects of tumor attributes and tumor-specific biomarkers on the risk of breast cancer death among the progressive cancers.

Result: The ratio of the deviance to the degree of freedom was 0.49 in the model without considering over-diagnosis, which revealed excess zero event in this dataset. Considering the detection model in the zero part of the ZIP model, the estimated proportion of over-diagnosis was 10% in the mammography screening program in Dalarna. Tumour size, node status, grade, and surgery modality were significant factors related to risk of breast cancer death after considering over-diagnosis. The magnitude of these factors were stronger than their counterparts in the conventional Poisson regression model.

Conclusions: We used a novel method to quantify the degree of over-diagnosis of 10% in a service screening for breast cancer with mammography in Sweden. The effects of prognostic factors after calibration for over-diagnosis were elevated than their counterparts in the conventional Poisson regression model.

CONDITIONAL SURVIVAL OF BREAST CANCER SURVIVORS IN KOREA

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Background: Conditional relative survival (RS) could provide more relevant information than standard 5-year survival, which may be pessimistic because many patients with unfavorable prognosis die shortly after diagnosis. This study aimed to estimate conditional 5-year RS of breast cancer survivors in Korea.

Methods: Breast cancer incidence data from 1999 to 2013 were obtained from the Korea Central Cancer Registry, and mortality data of breast cancer patients were acquired from Statistics Korea. Conditional 5-year RS for each age group was computed for every additional year survived up to 10 years. Period analysis with follow-up period 2009 to 2013 was used.

Result: A total of 184,481 patients were diagnosed as breast cancer and 28,616 patients (15.5%) among them died between 1993 and 2013. Five-year RS at diagnosis was 91.5% and 10-year RS 85.8%. Conditional 5-year RSs were 91.3%, 93.7%, and 95.1% at 1-, 5-, and 10-year after diagnosis, respectively. By age groups, conditional 5-year RS after survival 5 years varied from 91.3% to 95.2% and conditional 5-year RS after 10 years surviving exceeded 93% for all age groups. There was no excess mortality since 5 years after diagnosis for age group 40-49 years, and since 8 years after diagnosis for 50-59 years.

Conclusions: This study showed that the prognosis of breast cancer survivors in Korea has been improved according to time after diagnosis and age. Conditional RS provides clinically relevant information, and it could help breast cancer survivors plan their future and oncologist plan surveillance schedules.

CLINICOPATHOLOGIC CHARACTERISTICS AND SHORT-TERM SURVIVAL OUTCOME OF YOUNG AND OLDER WOMEN WITH BREAST CANCER: EXPERIENCE IN A CANCER CLINIC IN INDONESIA

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Background: Breast cancer generally affects persons older than 40 years and disease outlook in younger patients is frequently unfavorable. Comparison between these two groups has never been analyzed in the local setting. The present study determined the clinicopathologic characteristics in younger patients and evaluated short-term outcome in comparison with older women with breast cancer.

Methods: The records of 731 patients with breast cancer who visited Tulip integrated cancer clinic Dr Sardjito General Hospital Yogyakarta Indonesia between 2007 and 2009 were retrospectively analyzed. Clinical and histopathologic parameters and overall two-year survival rates of patients aged 40 years or less were compared with patients aged more than 40 years. A chi-squared test for noncontinuous variables was used to compare various variables.

Result: Younger patients represented 19% of data observed (139/731). Compared with older cases, younger women had less frequency of later stage (stage III-IV) (young vs older 62.5% vs. 71.3% $p = 0.060$). For tumor size ($p = 0.265$), histologic grading ($p = 0.373$), presence of PR-positive tumors ($p = 0.503$), presence of Her-2 positive tumors ($p = 0.084$), and triple-negative tumors ($p = 0.237$), no significant differences between both groups were observed. ER-positive tumors presented more significantly in older women ($p = 0.030$) than in younger cases. Young and old patients had the same overall short-term survival rates ($p = 0.193$).

Conclusions: Clinicopathologic features and short-term outcome in young breast cancer patients in the local cancer clinic were similar to the older cases. Nevertheless, they showed significantly less frequent of ER-positive tumors compared to the older.

IMPACT OF TUMOR-INFILTRATING LYMPHOCYTES/TUMOR-ASSOCIATED MACROPHAGES IN BREAST CANCER

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Background: Breast cancer is composed of the malignant tumor cells and tumor microenvironment, The inflammatory cells, known as lymphocytes and macrophages, regulate and release inflammatory mediators in breast cancer. Tumor infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs) are regarded to play a key role in progression and metastasis of various tumors. We evaluated their correlation with clinicopathologic parameters and prognositic impact in patients with breast cancer.

Methods: The mRNA expression of immunologic markers (CD68, CD163, CD4, FoxP3) were investigated by quantitative reverse transcription polymerase chain reaction in fresh-frozen breast cancer tissues and adjacent non-cancerous breast tissues. Clinicopathologic parameters were analysed. Also, disease free survival and overall survival were reviewed.

Result: Breast cancer tissues were more likely to have higher mRNA expression than non-cancerous breast tissues ($p < 0.001$). However, CD163 mRNA expression had no significant difference between two groups. Moreover, CD163 and FoxP3 mRNA expression was associated with tumor aggressiveness. The median level of CD163 mRNA expression was significantly higher in T2-T4 tumors than in T1 tumors ($p = 0.001$). A high FoxP3 mRNA expression was significantly associated with a poor overall survival. In multivariate analysis with Cox regression, lymph node metastasis and high FoxP3 mRNA expression were a significant prognostic factors for poor survival.

Conclusions: Our results showed that larger tumor size, advanced stage, lymph node metastasis were associated with high TAMs and TILs infiltration. In addition, high FoxP3 expression was one of the independent prognostic factors for overall survival in stage I to III breast cancer patients.

TARGETING TUMOR METABOLISM IMPROVES LAPATINIB-SENSITIVITY IN BREAST CANCER CELLS

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Background: Metformin, a biguanide, is a widely used pharmaceutical agent in the management of type-2 diabetes. Moreover, Metformin has been shown to have strong anti-cancer effect in many breast cancer cells. Lapatinib is a potent and selective oral dual receptor tyrosine kinase inhibitor of both epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER-2). In the present study, we show that a combination of metformin and lapatinib induces more extensive apoptosis than either drug alone in breast cancer cells.

Methods: Cell viability and cell death were assessed by MTT assay and Annexin V-FITC/PI staining, respectively. Small interfering RNA (siRNA) was used for suppressing gene expression. The protein levels were measured by western blot analysis. Immunofluoresence staining was conducted by fixing cells with 3.7% formaldehyde in PBS and permeabilizing with 0.25% TritonX-100 in PBS. Following permeabilization, a rabbit polyclonal anti-LC3B (Sigma-Aldrich) at 1:1,000 was incubated overnight at 4 C.

Result: Cell viability was reduced by metformin or lapatinib, in a dose-dependent manner. However, Cell death at 5 mM metformin or 10 μM lapatinib was about 15% and 10%, respectively. Combination of metformin and lapatinib synergistically enhances cell death in MCF-7 cells. Metformin/lapatinib treatment induces autophagy, as indicated by LC3B-II accumulation. Metformin/lapatinib sensitized TRAIL-mediated cell death mediated by DR4/DR5 upregulation.

Conclusions: Based on these findings, we propose that combination of metformin and lapatinib may be an effective strategy for sensitizing breast cancer cells.

PO111

THE FUNCTIONAL ROLE OF ITGAV IN STEM CELL-LIKE POPULATIONS INVOLVED IN BREAST CANCER INITIATION AND METASTASIS

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Background: Tumor cells originated from cancer stem cells, initiate extracellular matrix (ECM) degradation during early phase of tumorigenesis and metastasis cascade. Altered expressions of integrins have shown to play important roles in cell proliferation, migration and survival in cancers. This study aimed to identify the role of integrin in breast cancer tumorigenesis and metastasis.

Methods: Expressions of integrins and stem cell markers were examined in MDA-MB-231-induced mammospheres by qPCR. Flow cytometry was used to measure the expression of stem cell markers, CD24 and CD44, on mammospheres. Cell proliferation, cell invasion, stem cell-like properties and clonogenic properties were examined in the alpha-V integrins (ITGAV) siRNA-transfected MDA-MB-231 cells by MTT assay, migration assay, ALDH assay and soft agar assay.

Result: CD44+/CD24- subpopulation was increased in subsequent passages of mammospheres. Expression of ABCG2, COX2, NOTCH2, SNAI2, and ITGAV were upregulated in mammospheres when compared with parental cells. In particular, ITGAV was upregulated by 2.5-fold and 6.5-fold respectively in mammospheres after 3 and 6 weeks of subsequent passages. Silencing of ITGAV by siRNA significantly reduced cell proliferation, invasion and clonogenic properties. Cilengitide, an ITGAV-specific antagonist, also showed reduced cell proliferation. The apoptotic rate was increased in ITGAV-siRNA transfected cells, indicating increased cell survival by ITGAV. Reduction of sphere-forming ability and ALDH activity were also demonstrated in ITGAV-siRNA transfected cells.

Conclusions: Our data demonstrated the tumor initiating role of ITGAV in breast cancer progression. Further investigations are required to examine the downstream pathway of ITGAV leading to breast cancer carcinogenesis and metastasis.

GROWTH INHIBITION BY SODIUM SELENITE IS NOT DEPENDENT ON EXPRESSION OF SELELBP1 IN BREAST CANCER

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Background: Selenium inhibited growth in breast cancer. However, there have not yet been established about mechanism of selenium for growth inhibition in breast cancer cells. We analysed involvement about selenium binding protein (SELELBP1) for growth inhibition by selenium in breast cancer cells.

Methods: Cells selected MCF-7 as positive control, MDA-MB-231 as negative control, Normal human dermis-derived fibroblast (NHDF) as normal control based on expression of SELELBP1. To study involvement about selenium binding protein (SELELBP1) for growth inhibition in breast cancer cell, cells were treated by sodium selenite and chelating agents (EDTA, chromium (II) chloride) and examined to identify their survival cells, cell death, cell cycle.

Result: Survival cells by sodium selenite inhibited dose dependent on manner at the dose of 5 μM/mL, 10 μM/mL in each cell whether expressed SELELBP1 or not. We selected selenite 5 μM/mL dose for analyse of cell death, cell cycle and chelating of sodium selenite on based on results of NHDF. Both of MCF-7 and MDA-MB 231 cells induced S phase arrest in cell cycle analysis by sodium selenite and increased cell death in Anexin V staining whether expressed SELELBP1 or not. These effects by sodium selenite was blocked by chelating agents EDTA plus sodium selenite or chromium (II) chloride plus sodium selenite.

Conclusions: These results showed that growth inhibition by sodium selenite was not dependent on expression of SELELBP1 in breast cancer cells. It is suggested that there might be new mechanism for growth inhibition by sodium selenite in breast cancer cells.

MIR-106B-5P, MIR-17-5P PREDICT RECURRENCE AND PROGRESSION IN BREAST DCIS MODEL BASED ON TGFβ PARADOX

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Background: Ductal carcinoma in situ (DCIS) is a well-known precursor of invasive ductal carcinoma (IDC). Part of patients show disease recurrence as DCIS or IDC after local treatment, but there are no established markers for prediction of recurrence.

Methods: Authors analyzed 30 patients diagnosed as pure DCIS, recurrent DCIS, and IDC progressed in DCIS background. miRNA was extracted from archival tissue, and hierarchical clustering of miRNA microarray was performed. We selected highly expressed miR-17-5p and miR-106b-5p as marker for recurrence of DCIS. Two miRNAs were transfected to MCF-12 and MCF-7 cell line. Cell proliferation assay and Western blot analysis was performed for analyzing the interaction between cell proliferation and TGFβ downstream pathway.

Result: miR-106b-5p single and combined miR-106b-5p and miR-17-5p transfected MCF-12 cell line showed increased proliferation index compared to un-transfected cell line. In MCF-7, miR-106b and miR-17-5p transfected cell line showed inferior proliferation index compared to un-transfected cell line. Western blot analysis showed minimal increased expression of SMAD4, phosphorylated SMAD2 (pSMAD2) in miR-106b-5p and miR-17-5p transfected MCF-12 cell line. However, decreased expression of TGFBR2 and no interval change of SMAD4 and pSMAD2 was detected in miR-106b-5p and miR-17-5p transfected MCF-7 cell line.

Conclusions: MiR-106-5p, miR-17-5p showed increased expression in recurrent DCIS or IDC based on miRNA hierarchical microarray. miRNA transfected MCF-12 cell line showed increased proliferation index and activated TGFβ downstream pathway. miRNA transfection might have made normal cell line to pre-cancerous cell line and TGFβ pathway might have influenced to promote tumor proliferation, based on TGFβ paradox hypothesis.

INHIBITION OF CASEIN KINASE 2 SUPPRESSES PKC-INDUCED CELL INVASION BY TARGETING MMP-9/NF-κB PATHWAY IN MCF-7 CELLS

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Background: Increased expression of matrix metalloproteinase-9 (MMP-9) through nuclear factor-kappa B (NF-κB) activation is known to promote breast cancer cell invasion. Casein kinase 2 (CK2) induces NF-κB activation and has been implicated as an important factor in mammary tumorigenesis. Therefore, we investigated the effect of CK2 on protein kinase C (PKC)-induced cell invasion, and the underlying molecular mechanisms in MCF-7 breast cancer cells.

Methods: To investigate the effect of inhibition of CK2 on TPA-induced MMP-9, western blot analysis, zymography, and real-time PCR were performed. In addition, Western blot analysis were performed to verify the activities of MAPK,P65 and P50, in TPA-induced MCF-7 cells. Matrigelinvastion assay was used to investigate the inhibitory effects of CK2 on MCF-7 cells.

Result: We found that inhibition of CK2 suppressed PKC-induced transcriptional activation of NF-κB, and inhibited TPA-induced MMP-9 secretion/expression and cell invasion. In addition, inhibition of CK2 blocked PKC-induced phosphorylation of p38 and c-jun N-terminal kinase (JNK).

Conclusions: Our study indicates that CK2α regulates PKC-induced cell invasion through regulation of NF-κB-mediated MMP-9 expression.

ABSCOPAL EFFECT ON 4T1 MOUSE CANCER CELL BY HYPOFRACTIONATED IRRADIATION SCHEDULES

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Background: Radiation therapy is generally considered as local treatment, however it has been reported that it is possible to act outside irradiated field by the immune response (abscopal effect). The aim of this study was to evaluate the abscopal effect and immunologic changes in 4T1 mouse breast cancer cells and to determine the most effective radiation therapy schedule.

Methods: After transplantation of 4T1 mouse breast cancer cells into both flank of 16 balb/c mice, the mice were irradiated on one side with various irradiation schedules (6 Gy × 3 (group 1), 8 Gy × 2 (group 2), or 13 Gy × 1 (group 3) fractions). Tumor sizes on the untreated side were compared with control group. Spleen and bone marrow cells were obtained, and analyzed for T cell immunity related dendritic cell maturation factors.

Result: The mean mass sizes of unirradiated side were 110.0, 84.3, 73.5, and 90.0 mm^2 in control, group 1, group 2, and group 3, respectively. The mean size between control and irradiated group was showed a tendency ($p = 0.067$). Although expression of MHC class I and II was increased in splenocyte of irradiated group, there was no difference between the experimental groups. Expression of TNF-α and IFN-γ was increased in the irradiated mice, which was more dominant in group 1.

Conclusions: It was showed a tendency that the abscopal effect occurred in 4T1 mouse breast cancer cells. And, the expression of T cell immunity factors was increased by irradiation. However, there was no statistically significant difference according to each irradiation schedules.

BERBERINE SUPPRESSES THE CELL MOTILITY THROUGH THE DOWN-REGULATION OF TGF-β1 IN TRIPLE NEGATIVE BREAST CANCER CELLS

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Background: Transforming growth factor-βs (TGF-βs) are multifunctional growth factors and powerful modulators of the EMT in a variety of cancer cells including breast and lung cancer.

Methods: MMP-2 and MMP-9 expression was analyzed by Zymography. The levels of smad3 phosphorylation were analyzed by Western blotting. In addition, TGF-β1 expression was dectected by Confocal microscopy. All of mRNA expression was analyzed by Real-time PCR. The rates of cell migration were detected by Wound healing assay.

Result: In clinical data set, we found that aberrant TGF-β1 expression is associated with poor prognosis in breast cancer patients. Our results also showed that the levels of MMP-2 and -9 expressions as well as the capacity of cell migration are increased by TGF-β1 treatment. On contrary, basal levels of MMP-2 and MMP-9 are suppressed by a specific TGF-β receptor I inhibitor, SB431542. In addition, TGF-β1-induced MMP-2, MMP-9, and cell migration also decreased by SB431542. Interestingly, we found for the first time that BBR decreases the level of TGF-β1 but not TGF-β2 in triple negative breast cancer (TNBC) cells. Furthermore, Berberine (BBR) significantly decreased the levels of MMP-2 and -9 expressions as well as the capacity of cell migration in TNBC cells.

Conclusions: BBR decreases the levels of MMP-2 and MMP-9 expression through the down-regulation of TGF-β1 and then suppresses cell migration in TNBC cells. Therefore, we demonstrated that BBR may be a promising drug for treatment of TNBC.

UP-REGULATION OF FIBRONECTIN BY PI-3K/AKT ACTIVATION IS ASSOCIATED WITH POOR PROGNOSIS IN LUMINAL A TYPE BREAST CANCER MODELS

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Background: Fibronectin (FN) plays an important role on cell adhesion, invasion, and epithelial to mesenchymal transition (EMT) process in a variety of cancer cells including breast cancer.

Methods: All of mRNA expression was analyzed by Real-time PCR. The levels of protein expression were analyzed by Western blotting. Anchorage-independent growth was analyzed by soft agar assay. Cell proliferation was detected by MTT assay. Clinical data were analyzed by KM plotter (Breast). Constitutively active Akt was transfected by adenoviral system.

Result: Here, we found that high FN expression is associated with poor prognosis in luminal type A breast cancer patients. In addition, the levels of FN mRNA and protein expression significantly increased in tamoxifen resistant MCF7 (TamR) cells when compared with tamoxifen sensitive MCF7 (TamS) cells. To verify the regulatory mechanism of FN expression in TamR cells, we investigated the phosphorylation levels of signaling molecules such as Akt, JNK, and STAT3. Our results showed that the level of Akt phosphorylation augmented in TamR cells but not JNK. Induction of FN mRNA and protein expression was decreased by a Akt inhibitor, LY294002 and AktIV, in TamR cells. Furthermore, our results showed that the level of FN expression was significantly increased by constitutively active (CA)-Akt overexpression in TamS cells. Finally, we found that colony formation of TamR cells was completely blocked by AKT IV treatment.

Conclusions: We demonstrate that aberrant FN expression is directly associated with poor prognosis and FN expression is up-regulated through PI3K/Akt pathway in tamoxifen resistant breast cancer cells.

EFFECTS OF ADAM10 AND ADAM17 INHIBITORS ON NATURAL KILLER CELL EXPANSION AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC) AGAINST BREAST CANCER IN VITRO

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Background: The aim of this study was to investigate the influence of ADAM10 and ADAM17 inhibitors on expanded NK cell to enhance antibody-dependent cellular cytotoxicity (ADCC) in breast cancer cell lines.

Methods: NK cells were expanded in medium supplemented with an ADAM10 or ADAM17 inhibitor to prevent the shedding of soluble CD16/FcγRIII. The expression level of CD16 and production of Interferon-gamma (IFN-γ) was detected by flow cytometry with each specific antibody. The ADCC activity of expanded NK cell was estimated by mediating of trastuzumab with a specific cell line for each subtypes of breast cancer such as MCF-7, MDA-MB-231, SKBR3, and BT-474 cells.

Result: The ADAM17 inhibitor increased the purity of expanded NK cells to 90% after 14 days at 5 and 10 uM in-vitro ($p = 0.015$, 0.034, respectively). Inhibition of ADAM10 suppressed the expansion of NK cells, although the NK purity was increased by 1 μM of the inhibitor. The expression of CD16 was significantly increased by 1 and 5 μM of the ADAM17 inhibitor ($p = 0.046$, 0.028, respectively). ADAM17 inhibitor treated NK cells significantly increased the lysis of MCF-7 ($p = 0.006$), SKBR-3 ($p = 0.003$), and BT-474 ($p = 0.003$) cells. The augmentation of ADCC activity of NK cells was inversely proportional to the shedding of soluble CD16. Inhibition of ADAM17 increased the production of IFN-γ in expanded NK cells.

Conclusions: The inhibition of ADAM17 enhanced the purity of expanded NK cells and the cytotoxic activity of these cells against trastuzumab treated breast cancer through ADCC activity.

ROLE OF PPARγ ACTIVATION IN THE DYNAMICS OF MACROPHAGE POLARIZATION IN BREAST CANCER

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Background: Macrophages in the complex architecture of tumor microenvironment exhibit cellular plasticity and have various subtypes with distinct phenotypic properties. Peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand-activated transcription factor expressed in macrophages and has been shown to promote macrophages to alternatively activated M2 phenotype in metabolic diseases. Its role in macrophage polarization in breast cancer is not fully understood.

Methods: CD206 and CD163 (M2 markers) expression was evaluated in the breast cancer patient's data extracted from Gene Expression Omnibus (GEO) and Array Express. Percentage of CD206+ macrophages was evaluated using flow cytometry in the breast tumors from MMTV mice and the mammary fat pad of the control mice along with the gene expression of PPARγ. Macrophage education by murine breast cancer cells was assessed by ex vivo differentiation of bone-marrow derived macrophages (BMDMs) in the presence or absence of breast cancer cell conditioned media and also PPARγ agonist. Obtained macrophages were analyzed by flow cytometry,ELISA and mRNA expression.

Result: Clinically we found that CD163+ and CD206+ M2-macrophages were strongly associated with invasive-Claudin-low subtype. In the MMTV mouse model,CD206+ macrophages were higher in the breast tumors as compared to control mammary tissues. Interestingly, data from patients also revealed a strong positive correlation between expression of CD206, CD163 and PPARγ. Furthermore, the most metastatic cell line 4T1 and PPARγ agonists, skew macrophages toward the more immunosuppressive M2 subtype.

Conclusions: This study demonstrates that breast cancer cells influence macrophage differentiation and that Tumor Associated Macrophage (TAM) differentiation status correlates positively with PPARγ expression. Further studies need to be done in order to explore the signaling mechanism involved in governing this dynamic process.

MOLECULAR CLASSIFICATION WITH NANOSTRING NCOUNTER SYSTEM IN TRIPLE-NEGATIVE BREAST CANCER

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Background: Previous studies have shown that several distinct subtypes identified by gene expression profiling (GEP) consisted of triple-negative breast cancer (TNBC). Compared with the subtypes defined by GEP, we developed molecular classification with NanoString nCounter system in TNBC.

Methods: GEP was conducted on 196 formalin-fixed paraffin embedded containing TNBC tumors collected at Gangnam Severance Hospital. To select core genes for classification, 120 samples from public GEP database were used. Correlation between nCounter system and GEP using identical RNA was done in 188 samples. Drug response assay with adenosine triphosphate was done in a part of the patients.

Result: To classify TNBC into 4 major subtypes (Basal-like: BL, Luminal androgen receptor: LAR, Mesenchymal: M, and Immune-modulatory: IM) according to the Vanderbilt classification, we selected 110 genes in 220 samples with GEP (100 from Gangnam Severance Hospital and 120 from public database). In other 96 samples, the classification with the 110 genes were validated. In 150 tumors except unspecified subtype by the Vanderbilt, correlation between 110 genes classification and the Vanderbilt system was 74.5%. Correlation between nCounter system and GEP was 90.0% (135 of 150). In patients with in vitro drug response assay with cisplatin (n = 36), patients with BL had a significant higher responsiveness than patients with other subtypes ($p = 0.028$).

Conclusions: Our work shows the feasibility of molecular classification with nCounter system in TNBC. Future study warrants the clinical utility of this classification to guide subtype-tailored therapy in patients with TNBC.

PO121

DOWNREGULATION OF MICRORNA-204-5P PROMOTES TUMOR PROGRESSION AND METASTASIS IN BREAST CANCER

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Background: MicroRNAs play important roles in tumorigenesis and tumor metastasis. Several studies suggested that that downregulation of miR-204-5p is associated with poor prognosis and metastasis of breast cancer by regulating proliferation, apoptosis, migration, invasion of breast cancer cells in vitro. However, the underlying mechanisms of in vivo anti-tumor or anti-metastatic activity of miR-204-5p remains to be elucidated.

Methods: To detect mature miR-204-5p expression in breast cancer patients and breast cancer cells, we used TaqMan microRNA assay (assay ID # 000508). To generate miR-204-5p overexpressing cells, cell were transfected with control or miR-204-5p expression vector (Genolution pharmaceuticals, Seoul, Korea) using Lipofectamine 3000.

Result: We found that miR-204-5p was highly down-regulated in breast tumors. To investigate the potential molecular mechanisms of miR-204-5p mediated anti-tumor or anti-metastatic effects in breast cancer cells, we generate stable breast cell lines overexpressing miR-204-5p. miR-204-5p suppress tumor growth and metastasis in both syngeneic 4T1 murine allograft breast cancer model and MDA-MB-231 Xenograft model via inhibiting proliferation, migration and invasion of breast cancer cells. With RNA-seq and in silico analysis of miR-204-5p target genes, we found PIK3CB was highly down-regulated in miR-204-5p overexpressing cells, and experimentally validated that PIK3CB was a direct target of miR-204-5p. Now, were studying the underlying molecular mechanisms related to PI3K signaling, especially the regulation of PIK3CB by miR-204-5p.

Conclusions: In conclusion, miR-204-5p inhibits the initial progression of breast cancer and metastasis by blocking proliferation, migration as well as invasion. These findings indicate that miR-204-5p may be a novel therapeutic strategy against breast cancer progression and metastasis.

CLINICOPATHOLOGIC FACTORS CONTRIBUTING TO SUCCESSFUL ENGRAFTMENT IN PATIENT-DERIVED XENOGRAFT MODELS OF BREAST CANCER

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Background: Patient-derived xenograft (PDX) is an in vivo mouse model that can provides the similar tumor biology and genomic profiles of patients with cancer. Successful establishment of PDX model depends on several factors. The aim of the study is to figure out the influencing factors for successful engraftment of PDX models of breast cancer.

Methods: NOD/SCID or NOG female mouse between 6 and 12 weeks was used in the study. We harvested xenograft tumor of F3 mouse and performed histologic examination to confirm that xenograft tumor is a human breast cancer origin. To evaluate factors affecting successful engraftment, patients clinical data and engraftment conditions were reviewed.

Result: We implemented total 62 cases of breast cancer for establishment of PDX models Majority of cases were triple-negative breast cancer (TNBC) (54/62, 87.1%), followed by HER2 positive and hormone-positive breast cancer (each subtype, 4/62, 6.5%). Overall successful engraftment rate was 24.2% (15/62), and successful engraftment rate in TNBC was 27.8% (15/54). In univariate analyses, large tumor and poor histologic grade were significantly associated with successful engraftment of PDX model ($p < 0.05$). In PDX models from patients with neoadjuvant chemotherapy, disease progression during neoadjuvant chemotherapy and poor histologic grade were significantly associated with successful engraftment of PDX model ($p < 0.05$). In multivariate analysis, poor histologic grade was independently associated with successful engraftment of PDX model ($p = 0.01$). Higher T stage was marginally related to successful engraftment of PDX model ($p = 0.07$).

Conclusions: Breast cancer from patients who showed disease progression to neoadjuvant chemotherapy may be the best candidates for PDX establishment.

IS IMMEDIATE BREAST RECONSTRUCTION IS FEASIBLE OPTION FOR LOCALLY ADVANCED STAGE BREAST CANCER?: SINGLE INSTITUTION EXPERIENCE

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Background: Immediate reconstruction is one of options to improve cosmesis in breast cancer. This study compared clinical outcomes after mastectomy with versus without immediate reconstruction in advanced stage breast cancer.

Methods: From 2009 to 2014, total 41 patients finished the planned adjuvant therapies including chemotherapy and radiotherapy after mastectomy. According to clinical stage, IIb and III were regarded as intermediate and high risk groups, respectively. Immediate reconstruction had been decided after patients and physician thoroughly discussed the clinical status and feasibility. Kaplan-Meier survival analyses and Log-rank tests were conducted to compare survival differences of surgical methods.

Result: Median age was 49 years. Neoadjuavnt chemotherapy and immediate reconstruction were done in 13 and 12 patients, respectively. Among 24 patients in high risk groups, 7 patients received immediate reconstruction. 10 patients died during follow-up periods. 14 and 6 patients experienced disease progression and loco-regional failure, respectively. In terms of risk group, overall survival, disease free survival and loco-regional control were favored in intermediate groups ($p = 0.021$, 0.009 and 0.004, respectively). Of 7 patients, 3 loco-regional failure were developed in high risk group with immediate reconstruction. In high risk group, there were no differences between modified radical mastectomy and immediate reconstruction for overall survival (5-year 47.1% vs. 34.3%, $p = 0.649$), disease free survival (5-year 45.3% vs. 42.9%, $p = 0.849$) and loco-regional control (5-year 76.0% vs. 57.1%, $p = 0.378$).

Conclusions: Skin sparing mastectomy with immediate reconstruction was not inferior to modified radical mastectomy. However, immediate reconstruction would be cautious because clinical outcomes in high risk group were poor.

SURVIVAL BENEFIT OF SURGICAL REMOVAL FOR THE PRIMARY TUMOR IN STAGE IV BREAST CANCER PATIENTS

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Background: Several studies have suggested that primary tumor removal improved overall survival in stage IV breast cancer. However, survival benefit of local treatment still remains controversial. The purpose of this study is to determine whether surgical removal of the primary tumor provides survival benefits for stage IV breast cancer.

Methods: We retrospectively reviewed the records of 157 patients who were diagnosed with stage IV breast cancer initially at Seoul National University Bundang Hospital between 2003 and 2014. The Kaplan Meier analysis was used for estimation of median survival. The log-rank test was used to compare differences according to patient and tumor characteristics. Multivariate cox regression analysis for survival was used for controlling potential confounding variables.

Result: Of 157 stage IV breast cancer patients, 97 patents (62%) underwent surgical removal for primary tumor. The median survival was longer for patients who had better response of chemotherapy (70 vs. 47 months, $p = 0.023$) and surgery (118 vs. 28 months, $p < 0.001$) than who did not. The median survival in patients who received radiotherapy was better than that in patients who did not (65 vs. 39 months, $p = 0.002$). Patients with luminal A had a median survival of 118 months which was the longest compared to other subtypes ($p = 0.002$). Multivariate Cox regression showed that surgery of the primary tumor, better response of chemotherapy and luminal A subtype were significantly independent predictors of survival ($p < 0.001$ and $p = 0.042$).

Conclusions: Our results showed that the primary tumor removal, better chemo-response and luminal A subtype were associated with improvement in better survival. Therefore, surgical management for the primary tumor should be more actively considered in stage IV breast cancer patients.

RISK OF CARDIAC MORTALITY AFTER ADJUVANT RADIOTHERAPY FOR BREAST-CONSERVED PATIENTS IN KOREA

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Background: The cardiac toxicity after breast radiotherapy (RT) is not well-studied in Asia.

Methods: We identified patients with lumpectomy and adjuvant radiotherapy from three cohorts-2,577 women in Yonsei Cancer Center Registry (YCCR), 24,235 women in Korean Breast Cancer Registry (KBCR), and 495 in National Health Insurance Service-National Sample Cohort (NHIS). Radiation-related risk was studied by comparing left-sided versus right-sided tumors.

Result: Internal mammary node was included in radiation field in 17.5% of cases and the mean dose to heart was 6.2 Gy for left-sided tumors and 1.5 Gy for right-sided tumors in YCCR cohort. During follow-up, 1 cardiac death was observed in YCCR cohort (median follow-up, 6.1 years), 9 cardiac deaths in KBCR cohort (median follow-up, 7.2 years), and 1 cardiac death and 4 coronary revascularizations in NHIS cohort (median follow-up, 4.6 years). Left-sided tumors were not associated with significantly higher risk than right-sided tumors, with adjusted hazard ratios of 1.95 for cardiac death (95% CI 0.49-7.81) in KBCR cohort, and 1.77 for coronary revascularization (0.16-20.0) in NHIS cohort. Breast cancer-related deaths represented the greatest single cause-of-death. Across all three cohorts, cause-of-death patterns, overall survival, cancer-specific survival, disease-free survival were similar in the left-sided and right-sided tumors.

Conclusions: Across three cohorts on institutional and population levels in Korea, adjuvant radiotherapy for left-sided tumor was not associated with increased risk of cardiac mortality and morbidity. Since the absolute risk increase with radiotherapy might be negligibly smaller for women at lower or no baseline risk, proper use of formula predicting risk which has been validated in their population is warranted for a decision tool to weigh up risk at the individual level.

NO MORE NO MANS LAND OF THE BREAST; ONCOPLASTIC SURGERY FOR UPPER INNER QUARDRANT LESION

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Background: The surgical management of breast cancer has evolved significantly over the years, from radical mastectomy to breast conserving surgery. Oncoplastic surgery (OPS) was introduced as a new surgical approach for achieving breast conserving surgery and minimizing breast deformity. However, the tumor in upper inner quadrant (UIQ) of breast is always a big challenge to a breast surgeon. We introduced new OPS incision for lesion in the UIQ of the breast.

Methods: We performed breast conserving surgery by snail incision. Snail incision named after the shape of incision. The incision of tumor area seems like snails body and peri-areolar incision seems like snails shell. Skin incised toward areolar and wide excision was conducted typical way. The skin of peri-areolar area was de-epithelized to make symmetry with contra-lateral breast. After resection, breast parenchyma was approximated by absorbable string.

Result: Post-operative pictured showed good aesthetic appearance. Nipple-areolar complex was made with counter-lateral breast and the deformity was minimal. This feature was maintained after radiotherapy. The snail incision could minimize nipple necrosis or edema because it maintains blood supply and lymphatic distribute optimally.

Conclusions: Snail incision could be an alternative technique for lesion in the UIQ of the breast in OPS. Although, it could be applied to all lesions in breast. It is especially effective method for the surgery of the no-man's land; UIQ of breast.

PERIAREOLAR ZIGZAG INCISION IN THE CONSERVATIVE SURGICAL TREATMENT OF BREAST CANCER

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Background: Breast conserving surgery followed by radiation therapy is today standard therapy for early breast cancer. There are a number of different types of incisions. Numerous minimal approaches have evolved due to this concern. Periareolar incision is often used when the small tumor relatively close to the nipple. But it has a disadvantages include limited exposure of the surgical field. In plastic surgery, various methods such as zigzag incisions have been recommended to achieve satisfactory esthetic results.

Methods: Between January 2016 and September 2016, 148 women with breast cancer underwent BCS or mastectomy in ASAN medical center. Periareolar zigzag incision was performed and excision margins of the specimen were identified frozen sections and paraffin-embedded or permanent sections in all patients in this study. We retrospectively analyzed tumor characteristics, the operative time, size of specimen, the distance from the tumor to nipple.

Result: A total of 148 patients were reviewed, 72 included in the final analysis. The mean age of the patients was 52.6, median tumor size was 1.6 cm, median tumor distance from the nipple was 4.0 cm, median excised specimen sized was 5.1 cm, median operation time was 70.0 minute. Free resection margin was confirmed by frozen biopsy and permanent biopsy. There were no patients underwent reoperation.

Conclusions: We suggest that periareolar zigzag incision can provide a good surgical field to remove a relatively large tumor and may provide cosmetically good outcomes.

PO128

LATE COMPLICATIONS OF RADIOTHERAPY SECONDARY TO PAAG INJECTIBLES TO BREAST AFTER BREAST CONSERVATION SURGERY

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Background: While seroma formation is a reported complication following injection of Polyacrylamide hydrogel (PAAG) into the breast, we were unable to find any reports of this complication associated with radiotherapy in breast cancer treatment. As this may become more of a problem in the future, this report will assist further surgeons with counseling for the patients regarding complications from breast conservation treatment.

Methods: PAAG is a common breast augmentation technique used mainly in China. We often see patients after this particular augmentation technique during our daily practice and it often makes screening difficult. We present a case of a lady with invasive ductal carcinoma who underwent breast conservation surgery and radiotherapy and developed late complications of seroma formation with subsequent infection requiring debridement.

Result: The case presented is a 45 year old lady with PAAG injectibles and presented with a T2N2M0 breast cancer that underwent successful breast conservation surgery and axillary clearance with radiotherapy. However 10 months post surgery and radiotherapy she presented an extensive seroma in an area of the breast other than the surgical site. This seroma was complicated by a chronic wound post aspiration and had to undergo debridement and vacuum assisted dressing (VAC) dressing with subsequent successful closure of the wound.

Conclusions: We present this case as a documentation of successful treatment of a post radiotherapy associated seroma. This information would be helpful to surgeons and patients to understand this potential complication when deciding on surgical treatment for breast cancer in patients with this history.

EFFECTS OF HORMONE RECEPTOR STATUS ON THE DURABLE RESPONSE OF TRASTUZUMAB BASED THERAPY IN HER2 (+) METASTATIC BREAST CANCER

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Background: Although the majority of HER2 (+) metastatic breast cancer (MBC) patients treated with trastuzumab-based therapy experience disease progression within two years, long-term durable response was observed in about 10% of HER2-positive MBC. The aim of this study is to find the clinico-pathologic factor for durable response of trastuzumab based therapy.

Methods: We found 1,218 MBC patients diagnosed from 2006 to 2015 in Yonsei MBC database. Of these patients, 294 patients showed HER2 positive status, and 153 patients received trastuzumab plus taxane chemotherapy as first-line setting. Clinico-pathologic factors were reviewed. For the evaluation of durable response, landmark analysis was performed.

Result: The median follow up time was 28 months (95% CI, 4.4-83.0 months). Of 153 HER2 (+) patients, HR (-) patients were 73 (47.7%) and bone is the most common metastatic site (84, 54.9%). The median PFS and overall survival (OS) was 12 and 39 months, respectively. HR (-) patients showed a tendency toward longer PFS (median, 13 vs. 11 months, $p = 0.160$) compared to HR (+) patients. Patients with non-visceral metastasis had longer median PFS and OS than those with visceral metastasis. (median PFS, 15 vs. 11 months, $p = 0.012$; median OS, 75 vs. 34 months, $p = 0.03$). Landmark analysis at 9 months including 84 patients suggested that PFS of HR (-) patients was significantly longer than HR (+) patients (median, 19 vs. 9 months, $p = 0.008$).

Conclusions: Among patients with HER2 (+) MBC, HR status is a possible predictive biomarker for durable response of trastuzumab based therapy.

THE USE OF ACELLULAR DERMAL MATRIX COMBINED WITH FIBRILLAR FOR PARTIAL DEFECT OF BREAST IN SMALL- TO MEDIUM-SIZED BREASTS CONSERVING SURGERY

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Background: Currently, with the progress of surgical technique, the breast-conserving surgery (BCS) has become popular. Some patients will have local defects with breast conserving surgery without appropriate oncoplasticsurgery. Therefore, more and more attention has been paid to the oncoplastic surgery. At present, there are so many approach of oncoplastic surgery, but each has its advantages and disadvantages. We introduce a surgical technique using acellular dermal matrix (ADM) with fibrillar for a remnant defect of breast.

Methods: Between September 2016 and November 2016, 2 women underwent BCS with ADM and fibrillar for auxiliary repair after oncoplastic volume displacement techniques.

Result: The mean age of the patients 51.5 years and their mean body mass index were 21.5 kg/m^2. Cosmetic outcomes were evaluated to be excellent by the patients and the breast and the plastic surgeons.

Conclusions: The use of ADM combined with fibrillar repairs partial defect in patients with small- to moderate-sized breasts with the advantages of small trauma, short operation time, easy to grasp. This surgical technique can be performed in all the quadrants and worth promoting.

EFFICACY OF COMBINED AROMATASE INHIBITOR AND GOSERELIN IN PREMENOPAUSAL HORMONE RECEPTOR-POSITIVE METASTATIC BREAST CANCER

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Background: Premenopausal women with hormone receptor-positive metastatic breast cancer (MBC) have few endocrine based treatment options. We compared the efficacy of aromatase inhibitor (AI) plus goserelin with that of tamoxifen plus gorserelin in those patients.

Methods: Between January 2010 and December 2016, we retrospectively reviewed the medical records of 31 premenopausal MBC patients treated with AI+goserelin group and 26 patient treated with tamoxifen+goserelin group.

Result: The median follow up period was 28.6 months. The median progression free survival was 39.2 months in AI+goserelin group and 32.6 months in tamoxifen+goserelin group. Progression free survival outcome was not significantly different between AI+goserelin group and tamoxifen+goserelin group ($p = 0.200$). In AI+goserelin group, the ratio of patients who achieved complete response (CR), partial response (PR), stable disease (SD) lasting more than 6 months, and clinical benefit were 6.5%, 6.5%, 80.6%, and 93.5%, respectively. In tamoxifen+goserelin group, the ratio of patients who achieved CR, PR, SD lasting more than 6 months, and clinical benefit were 6.5%, 6.5%, 53.8%, and 73.1%, respectively. There was no patient experienced grade 3 or 4 toxicity.

Conclusions: Our study demonstrated that AI+goserelin group might not be inferior to tamoxifen+goserelin group in the treatment of premenopausal hormone receptor-positive MBC, suggesting that it could be another promising treatment option in those patients who have failed conventional endocrine therapy.

SURVEY OF KOREAN SURGEONS FOR PRACTICE PATTERN AND PERCEPTIONS REGARDING MARGIN STATUS AFTER BREAST-CONSERVING SURGERY

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Background: The purpose of this study is to survey how surgeons in Korea define surgical margins and decide re-excision after breast-conserving surgery.

Methods: We sent an e-mail survey to the members of the Korean Breast Cancer Society in April 2014 and November 2016. The questionnaire comprised of 17 questions regarding intraoperative margin evaluation and surgeon's personal indication for re-excision of margin. The definition of negative margin was also investigated in 2016 only.

Result: A total of 127 responses were obtained in 2014 and 72 responses in 2016. In 2016, 54 (75%) respondents defined negative margin for invasive cancer as no ink on tumor. 35 (48.6%) respondents defined negative margin for ductal carcinoma in situ (DCIS) as no ink on tumor, followed by 17 (23.6%) and 11 (15.3%) surgeons defining it as >2 mm and >1 mm from margin, respectively. 89 (84%) and 63 (87.5%) surgeons routinely performed intraoperative resection margin assessment in 2014 and 2016, respectively. Margin assessment methods were all done by frozen section biopsy. There was no significant difference of re-excision indication in invasive cancer at resection margin between the two surveys. However, the indication for re-excision in DCIS at resection margin differed by time. In 2014, 19 (17.9%) surgeons would not re-excise when margin is positive or close to DCIS, whereas in 2016, only 1 (1.4%) surgeon would never re-excise.

Conclusions: This study revealed difference among surgeons in definition of negative margin and indication for re-excision. This difference was more prominent in DCIS and also differed across time.

THE FIRST CASE REPORT OF ROBOT-ASSISTED NIPPLE SPARING MASTECTOMY AND IMMEDIATE RECONSTRUCTION IN KOREA

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Background: Robotic surgery system enhances surgical procedures by applying advanced technologies such as artificial arm joints with high degrees of freedom in addition to high-quality 3D images. However, the application of robotic surgery system to breast surgery has not been much attempted.

Methods: In brief, 49 years old female patient who was diagnosed with ductal carcinoma in situ of her right breast in preoperative biopsy agreed to undergo robot-assisted nipple sparing mastectomy and immediate reconstruction using tissue-expander. Under general anesthesia, through a 6 cm axillary incision, sentinel lymph node biopsy using blue dye and radioisotope was performed. After sentinel lymph node biopsy, a subcutaneous skin flap was made from axilla to just beneath nipple-areolar complex. Superficial subcutaneous tissue was dissected using the robotic arms below the nipple areolar complex to the breast borders including the outer, inner, upper, and lower margins. The deep layer was then dissected from the lateral margin of the pectoral muscle fascia to entire deep layer of the retromammary tissues. Fully mobilizing of the breast parenchyme was completed, and then the specimen was removed through the axillary incision. The tissue-expander was inserted into the pocket under the pectoralis major that was elevated using the robotic arms by plastic surgeons.

Result: The total operation time was 409 minute. The console time was 132 minute for mastectomy and 25 minute for reconstruction. The patient was discharged without immediate postoperative complications at postoperative day 9.

Conclusions: We report the first case of robot-assisted nipple sparing mastectomy and immediate reconstruction in Korea.

A REAL-WORLD RETROSPECTIVE STUDY OF APATINIB PLUS CHEMOTHERAPY IN METASTATIC BREAST CANCER

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Background: Antiangiogenic therapy in combination with chemotherapy has shown improved clinical outcome in advanced breast cancer (ABC). Apatinib is an orally administered tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGFR-2), which exhibited objective efficacy in metastatic breast cancer (MBC). We performed a retrospective observational analysis to evaluate the efficacy and safety of apatinib plus chemotherapy in the real-world practice of patients with MBC.

Methods: Patients who have failed at least one prior chemotherapy regimen for metastatic disease were included in this study. The primary endpoint was progression free survival (PFS). Secondary end points included objective response rate (ORR), clinical benefit rate (CBR), overall survival (OS) and safety. Data analysis included association between clinicopathological characteristics or treatment choice and PFS.

Result: Of the 23 patients analyzed, 14 (60.9%) received plant-derived anticancer agents combined therapy and 9 (39.1%) combined with non-plant-derived agents. Objective response rate (ORR) was 34.7% and clinical benefit rate (CBR) reached 52.2% on last tumor assessment. With a median follow-up of 9.0 months, the estimated median PFS and OS were 5.4 months (95% CI 3.5-7.3) and 8.2 months (95% CI 4.7-11.7), respectively. Toxicities were tolerable or could be clinically managed. The most frequently observed adverse events (AEs) of all grade were hypertension, myelosuppression, hand-foot syndrome, proteinuria, fatigue and gastrointestinal reaction. The most common grade 3/4 treatment-related AEs were myelosuppression (39.1%) and gastrointestinal reaction (17.4%).

Conclusions: In this retrospective observational study, combination of apatinib with chemotherapy demonstrated clinically relevant efficacy and tolerability in metastatic breast cancer.

ACHIEVING NATURAL LOOKING PTOSIS THROUGH RECREATING INFRA-MAMMARY FOLD IN IMPLANT-BASED RECONSTRUCTION

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Background: In breast reconstructive surgery, the infra-mammary fold (IMF) plays a significant role in creating natural-looking ptosis of reconstructed breast. We present our experience of recreating the IMF in patients with implant-based reconstruction.

Methods: We marked an IMF about 1cm below the IMF level of contra-lateral breast IMF. In the subpectoral procedure, the inferior origin of the pectoralis major is released with or without an acelluar dermal matrix. In recreating IMF, we first attached the dermis of skin flap to the fascia or to periosteum along the IMF by interrupted suture with 1-0 Vicryl. After that, we fixed the initial stitch beneath the medial IMF, followed by penetration of dermis by barbed suture (1-0 V-loc) along the entire IMF. This procedure ends with drawing out the suture thread from the lateral end of IMF, adjusting the level and depth of the IMF.

Result: From 2014 to 2016, this method was performed in 35 patients who previously underwent implant-based reconstruction. In immediate reconstruction (n = 28) regardless of breast size and degree of original ptosis, all the patients achieved an optimal outcome in terms of inferior quadrant shape and ptosis. However, in case of delayed reconstruction (n = 7), patients achieved only a moderately ptotic-looking breast without natural ptosis, while still maintaining a clean-cut IMF. After a minimum period of 4 months of follow up, no patients experienced IMF slack or scalloped appearance.

Conclusions: The technique proposed here enables the achievement of smooth curvature of IMF and more natural-looking ptosis of breast easily and reliably.

A MULTICENTER, REAL-WORLD RESEARCH OF THE ADHERENCE TO ENDOCRINE THERAPY WITH SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS) IN PREMENOPAUSAL WOMEN IN CHINA

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Background: Although international clinical trials have clearly demonstrated the benefit of selective estrogen receptor modulators (SERMs) in premenopausal women with primary breast cancer, little is known about how these drugs are actually used in the general population. At present, there is no data concerning the adherence and reasons of non-adherence in premenopausal women starting tamoxifen or toremifene as adjuvant breast cancer therapy in China. This real-world research was conducted to provide the current prevalence of adherence and to evaluate the impact of non-persistence to adjuvant hormone therapy (HT) with SERMs on disease-free survival (DFS) in China.

Methods: Total 975 subjects from 10 medical centers of China were initiating tamoxifen or toremifene for primary breast cancer from January 2009 to June 2010. Of these, 787 patients were analyzed for persistence/non-adherence in the study. With longer than 5-year follow-up data, we examined the rate of completing the planned hormone therapy and factors related to discontinuation.

Result: Overall persistence decreased to 66.07% (520/787) by year 5 of therapy. Treatment non-persistence was mainly associated with side effects (36.33%), switching from SERMs to other hormonal therapies (25.09%) and stop after 5 years (11.98%). Factors associated with treatment persistence were age, side effects, doctors and switching therapies. For survival analysis, we found a trend for better outcome in patients continuing therapy more than 2 years and completing 5-year treatment.

Conclusions: Adherence to SERMs among premenopausal breast cancer survivors in China is suboptimal. Side effects were the leading cause of discontinuation. Early discontinuation may related to worse outcome. Further investigation is critical to identify interventions to improve continuation.

CLINICAL SIGNIFICANCE OF LYMPH NODE RATIO IN DETERMINING SUPRACLAVICULAR LYMPH NODE RADIOTHERAPY IN N1 BREAST CANCER PATIENTS (KROG 1418): A MULTICENTER STUDY

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Background: To evaluate the clinical significance of lymph node ratio (LNR) and its usefulness as an indicator of supraclavicular lymph node radiation therapy (SCNRT) in patients with pN1 breast cancer.

Methods: We retrospectively analyzed the clinical data of pN1 breast cancer patients who underwent partial mastectomy and sequential adjuvant chemotherapy and postoperative radiation therapy in 12 hospitals (N = 1,121). According to SCNRT status, 579 patients were selected through propensity score matching. The cut-off value of LNR was adopted as 0.09 based on the ROC curve according to recurrence.

Result: Median follow-up durations were 63 months (range, 11-111). The treatment failed in 37 patients (6.3%) and there was no significant difference in disease free survival rate (DFS) between with SCNRT groups and without SCNRT groups. High LNR showed significantly worse DFS in both univariate and multivariate analysis (0.010 and 0.019, respectively). In subgroup analysis, the effect of SCNRT on DFS was significantly different in patients who had LNR greater than 0.1 ($p = 0.006$).

Conclusions: High LNR can be used as an independent prognostic factor in N1 breast cancer patients. It may also be used as one of the factors that will help decide whether or not to perform SCNRT to improve DFS.

LYMPH NODE RATIO CAN BE USED AS A GOOD PROGNOSTIC FACTOR FOR PATHOLOGIC N3A BREAST CANCER PATIENTS

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Background: Pathologic N3a breast cancer refers to ten or more metastatic axillary lymph nodes. The aim of this study was to evaluate clinicopathological factors and importance of lymph node ratio (LNR) in N3a breast cancer patients treated with surgery without neoadjuvant chemotherapy.

Methods: We retrospectively analyzed medical records of 129 patients who underwent surgery. They were diagnosed pathologically as N3a breast cancer from May 2004 to December 2012. LNR was defined as the number of metastatic lymph nodes divided by the total number of resected lymph nodes. It was calculated by Receiver operating characteristics (ROC) curve. The median follow up period was 72.3 months (range, 10-143 months).

Result: Of the 129 patients with N3a breast cancer, 56 (43.4%) had recurrence and 33 (25.6%) had died during the follow up. Disease free survival (DFS) rates and overall survival (OS) rates at 5 years after surgery in all patients were 62.4% and 83.7%, respectively. LNR > 0.8 (hazard ratio [HR]: 1.878; 95% confidence interval [CI]: 1.092-3.232; $p = 0.023$) and histologic grade 3 (HR: 1.965; 95% CI: 1.150-3.358: $p = 0.013$) were prognostic factors associated with DFS. LNR > 0.68 (HR: 2.393; 95% CI: 1.073-5.337; $p = 0.033$) and advance T stage (T3-4) (HR: 2.220; 95% CI: 1.079-4.568: $p = 0.03$) were significantly associated with OS.

Conclusions: Although the values of LNR associated with DFS and OS are slightly different, LNR can be used as a good prognostic factor for N3a breast cancer patients.

BREAST VOLUME MEASUREMENT AND RECONSTRUCTION

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Background: Recently, reconstructive surgery after mastectomy is increasing. If the volume of the breast can be predicted in the case of nipple-areola complex sparing mastectomy (NSM), a patient and doctor can decide the reconstruct method whether to use flap or implant.

Methods: From March of 2012 to June of 2015, retrospective review of 110 patients who underwent mastectomy was performed. The volume of breast measured by preoperative mammography and the weight of breast removed by surgery was compared.

Result: There was no significant difference between the volume of breast measured by mammography and the weight of breast removed by surgery.

Conclusions: Before the operation, the mammography is performed routinely. Therefore, it is possible to determine the reconstruction method such as insertion of the implant or latssimus dorsi musculocutaneous flap (LDMCF) based on the volume of the breast obtained by the mammography.

SINGLE PORT LAPAROSCOPIC HARVESTED OMENTAL FLAP FOR IMMEDIATE BREAST RECONSTRUCTION: EXPERIENCE IN SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

Sumin Chae, Yerang Jang, Hyejin Kim, Eunyoung Kang, Eun-Kyu Kim

Seoul National University Bundang Hospital, Korea

Background: Recent advances in laparoscopic surgery have allowed laparoscopic harvesting of omental flap with reduced breast deformity and donor-site morbidity. We report our experience of single port laparoscopic harvested omental flap (SLHOF) for immediate breast reconstruction. We evaluated the safety and cosmetic outcome of this technique.

Methods: Between February 2015 and December 2016, 73 patients with malignant neoplasm of breast underwent SLHOF in Seoul National University Bundang Hospital by single surgeon and single gastrointestinal surgeon. A medical chart was reviewed to obtain the information about patients characteristics, operation method, operation time, length of hospital stay, complications and cosmetic results. Cosmetic outcomes were evaluated by three professionals and classified into excellent, good, fair, or poor.

Result: The patients were in the age range of 29-59 years with a median follow-up periods of 6 (0-22) months. Fifty-eight (79.5%) patients underwent nipple-sparing mastectomy (NSM), and the others (20.5%) underwent breast conserving surgery (BCS). Mean operation time was 203.5 minutes, and SLHOF reconstruction was performed without conversion to laparotomy or failure of harvesting. There were 6 (8.2%) complications, including pedicle injury, partial skin ischemia, wound complication, bleeding, and umbilical hernia. Success rate of graft survival was 98.6% and the mean length of hospital stay was 6.9 days. The cosmetic results were mostly satisfactory in 91.8% of patients classified as excellent or good.

Conclusions: Based on our experience, SLHOF is a feasible and safe option for immediate breast reconstruction after NSM or wide BCS with minimal donor-site morbidity and great cosmetic outcomes.

CLOSE RESECTION MARGIN AFTER BREAST-CONSERVING THERAPY: RE-EXCISION OR NOT?

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Background: The purpose of this study is to investigate the prognosis of invasive breast cancer patients underwent breast conserving surgery (BCS) with close resection margin followed by re-excision compared to those without additional surgery.

Methods: Seven hundred and sixty-six patients with invasive breast cancer pT1-3 treated by BCS during 2003-2013 were included in this study. We identified 94 patients that had clear but close resection margin (≤ 2 mm) after BCS. Patients were divided into two groups: Further re-excision group and no additional surgery group. We analyzed the relationship between further re-excision for close resection margin and patients outcomes.

Result: Thirty-two (34%) patients had additional surgery to obtain wider resection margin and the others did not have any additional surgery. The median follow-up period was 56 months. The 5-year RFS for re-excision group and no additional surgery group were 87.5% and 89.8%, respectively ($p = 0.489$). The IBTR for each groups are observed in 2 (6.3%) and 0 (0%), respectively ($p = 0.113$). The 5-year OS of re-excision group did not significantly differ from those of no additional surgery group (96.7% vs. 93.5%, $p = 0.490$). After adjusting age, histology, T stage, N stage, histologic grade, estrogen receptor, progesterone receptor, HER2/neu, Ki-67 expression, lymphovascular invasion, multifocality, and systemic therapy, there were no differences in IBTR, RFS, and OS between two groups.

Conclusions: In case with clear but close resection margin, re-excision seems to be unnecessary in the era of multidisciplinary therapy. No re-excision for close margin might improve cosmetic outcome and patient's satisfaction without affecting the prognosis.

METFORMIN REVERSES DRUG-RESISTANCE OF 4T1 BREAST CANCER TUMORSPHERES TO DOXORUBICIN BY DOWNREGULATING AKT AND STAT3 SIGNALING PATHWAYS

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Background: Recent studies reported that metformin, the firs-line medication for the treatment of type2 diabetes, exhibited anticancer and chemoprotective effects in diverse cancer cells. In this study, we investigated the effects of metformin on drug-resistance of 4T1 murine breast cancer tumorspheres and its underlying mechanism to overcome drug-resistance.

Methods: 4T1 murine mammary cancer cells were cultured as tumorspheres and their proliferation rate and chemosensitivity were measured using WST-8. Flow cytometry was applied for cell cycle analysis and western blot analysis and RT-PCR were performed to assess changes of protein and mRNA expression. The in vivo anti-tumor effect of metformin was measured in BALB/c female mice implanted with 4T1 cells into mammary fat pad.

Result: 4T1 tumorspheres exhibited accumulation of cells at the G0/G1 phase as compared to cells in monolayer culture, suggesting that the majority of cells in tumorsphere are quiescent. We found that activated AKT and STAT3 signaling pathways in 4T1 tumorspheres conferred drug-resistance to doxorubicin. However, metformin selectively targeted tumorspheres rather than cells in monolayer culture and increased cytotoxicity of doxorubicin to tumorspheres by inhibiting the activated AKT and STAT3 signaling pathways. Furthermore, metformin exhibited synergistic antitumor effects with doxorubicin on 4T1 tumor-bearing BALB/c mice.

Conclusions: These results demonstrate that metformin sensitizes quiescent 4T1 breast cancer cells to doxorubicin by inhibiting AKT and STAT3 signaling pathways. Thus, this study suggests that combinations of metformin and cytotoxic anticancer drugs may offer an advantage for treating the drug-resistant cancers.

EFFICACY OF VACUUM ASSISTED BIOPSY DEVICE FOR THE REMOVAL OF BENIGN BREAST LESION MORE THAN 2CM

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Background: The excision of breast lesion using with Vacuum assisted biopsy device is popular. It is useful method for treatment of benign breast lesion and diagnosis of confuse breast lesions. The purpose of this study was to evaluate the efficacy of Vacuum assisted biopsy device for the removal of benign breast lesion more than 2 cm.

Methods: From July 2014 to June 2016, removals of benign breast lesion more than 2cm with using Vacuum assisted biopsy device were performed for 61 women. Preoperative biopsies were done. In preoperative Core needle biopsy, 48 lesion was fibroepithelial lesion and 3 lesion was fibrocystic disease and 3 lesion was sclerosing adenosis and 3 lesion was IDP, 1 lesion was radial scar and 1 lesion was lesion is intraductal hyperplasia. All lesions were removed using an 8-gauge probe without sonographic residual lesions. The mean follow-up period was 20.25 months (max, 28 months; min, 6 months).

Result: The mean tumor diameter was 2.79 cm (max, 6 cm; min, 2.03 cm). The mean age is 31 years old (max, 49; min, 17). Postoperative histopathologic cofirmation was done. 36 lesion was confimred fibroadenoma and 11 lesion was confirmed phyllodes tumor. 7 lesion was confirmed intraductal papilloma. All patient did not developed local recurrence.

Conclusions: Vacuum assisted biopsy device is useful for the removal of benign breast lesion more than 2 cm.

APPLICATION OF THREE-DIMENSIONAL PRINTED SURGICAL GUIDE BASED ON PRETREATMENT SUPINE MAGNETIC RESONANCE IMAGING FOR BREAST CONSERVATION SURGERY

Beom Seok Ko, Sang Wook Lee, Hee Jeong Kim, Jong Won Lee, Il Yong Chung, Gui Yun Son, Ji Sun Kim, Saebyul Lee, Byung Ho Son, Nam Kug Kim, Hak Hee Kim, Gyungyub Gong, Sei Hyun Ahn

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Background: Many studies have shown that magnetic resonance imaging (MRI) is the most accurate technique for evaluating residual disease after neoadjuvant chemotherapy. The objective of this study was to evaluate the use of three-dimensional (3D) printed surgical guides in breast cancer patients undergoing breast conservation therapy after receiving neoadjuvant chemotherapy.

Methods: This study included breast cancer patients who underwent partial breast resection after receiving neoadjuvant chemotherapy. Breasts and tumors were modelled in three dimensions using pre-treatment supine magnetic resonance images. Surgical guides were created using a 3D printer to mark the primary tumor. After surgery, the distances to the margins of the tumor were measured.

Result: From October 2016 to January 2017, twenty patients underwent surgery. Their median age was 46.0 years (range: 34-61 years). Complete pathological remission occurred in five patients. The median time to surgery was 78 minutes (52-90 minutes) in patients without axillary dissection, and 98 minutes (range: 42-121 minutes) in patients with axillary dissection. The median value of residual tumor bed size was 1.6 cm (range: 0.9-6.8 cm) and the median value of the removed tissue size was 6.5 cm (range: 4.5-12.0 cm). All patients had clear resection margins. The median distance from the tumor to the margins was 1.2 cm (range: 0-5.9 cm).

Conclusions: Breast surgical guides created by a 3D printer may help conserve the extent of surgery needed in patients who received neoadjuvant chemotherapy by accurately marking the extent of the primary tumor based on pre-treatment magnetic resonance images.

THE RELATIONSHIP BETWEEN TIMING OF RADIOTHERAPY AND SURVIVAL OUTCOMES IN NODE-POSITIVE BREAST CANCER PATIENTS

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Background: For patients with node-positive breast cancer, four cycles of doxorubicin and cyclophosphamide (AC) followed by four cycles of taxane had been a standard adjuvant chemotherapy regimen. Usually radiotherapy is added after completion of chemotherapy. However, timing of radiotherapy depends on patients' situation. Radiotherapy between AC and taxane can be an option in some cases. Authors tried to evaluate the effect of treatment sequence on loco-regional recurrence and distant metastasis.

Methods: We collected data of individual patient who diagnosed as node-positive breast cancer without distant metastasis and underwent breast conserving surgery or mastectomy at Ewha Womans University Medical Center from September 2009 to January 2012. Oncologic outcomes and surgery-radiotherapy interval (SRI) were retrospectively analyzed using a Cox proportional hazards model according timing of radiotherapy.

Result: Seventy-one patients received radiotherapy after AC followed by taxane chemotherapy and 74 patients did radiotherapy between AC and taxane regimen. Mean SRI was 5.6 months in radiation after chemotherapy group and 3.1 months in radiation between chemotherapy group ($p = 0.000$). Loco-regional recurrence rate was not different in both groups (1.3% vs. 3.9%, $p = 0.904$) Loco-regional recurrence rate was not different in both groups (1.3% vs. 3.9%, $p = 0.904$) Also 6-year overall survival (OS) and distant metastasis free survival (DMFS) were not significantly different (OS, 90.5% vs. 89.1%, $p = 0.854$, DMFS, 95.0% vs. 81.8%, $p = 0.161$).

Conclusions: Radiotherapy between AC and taxane chemotherapy did not affect loco-regional recurrence and survivals. Sequence of radiotherapy may be changed within reasonable SRI limits in some clinical situations.

THE FACTORS INFLUENCING ON ADHERENCE AND PERSISTENCE OF ENDOCRINE THERAPY IN KOREAN BREAST CANCER PATIENTS USING NATIONWIDE POPULATION-BASED COHORT STUDY

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Background: This study investigated factors influencing on adherence and persistence of endocrine therapy (ET) in Korean breast cancer (BC) patients.

Methods: The patients newly diagnosed with BC between 2004 and 2012 were analyzed using cohort data from the National Health Information Database collected by the National Health Insurance Service in Korea. We identified patients received ET during the study period and the prescribing information was collected. We defined nonadherence to less than 80% in medication possession ratio, and that of non-persistence to more than 180 days in gap between previous dispensing date and later dispending date.

Result: The first in the year of starting medication, adherence and persistence rate were 80.1% (1,153/1,440) and 88.0% (1,267/1,440), which decreased steadily by 70.9% (891/1,256) and 73.0% (917/1,256) in the 2nd year, 64.5% (664/1,030) and 63.5% (654/1,030) in the 3rd year, 53.5% (439/820) and 50.0% (410/820) in the 4th year, and 43.3% (270/623) and 38.0% (238/623) in the 5th year, respectively. In the analysis with 623 patients who diagnosed with BC between 2004 and 2009, age, socioeconomic status, primary operation, and chemotherapy were statistically important factors influencing on adherence (Chi-square test, $p < 0.001$, $p = 0.002$, $p = 0.001$, and $p < 0.001$, respectively). Persistent showed similar results that women with older than 50 years, lower income, primary operation, and chemotherapy showed poorer persistence (Chi-square test, $p = 0.007$, $p = 0.008$, $p = 0.001$, and $p = 0.001$, respectively).

Conclusions: The adherence and persistence rate decreased steadily to less than 50% in the 5th year of ET. The patients with older than 50 years, lower income, primary operation, and chemotherapy were more likely not to take medicine well or to discontinue ET.

BETTER PREDICTION MODEL OF AXILLARY RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH CLINICALLY NODE-POSITIVE BREAST CANCER

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Background: Neoadjuvant chemotherapy (NAC) is the standard of care for patients with clinically node-positive breast cancer. The aim of this study was to assess the factors that predicted axillary pCR and established a model predicting of axillary pathologic complete response in our patient population.

Methods: We retrospectively identified 201 patients with clinically node-positive breast cancer who were treated with NAC and underwent Axillary lymph node dissection (ALND) between 2010 and 2015 at Seoul St. Marys Hospital, Catholic University of Korea. We analyzed the Baseline patient and tumor characteristics, clinical tumor response rate and pathologic tumor and nodal responses. The overall prediction of the model including tumor response rate was assessed by receiver operating characteristic (ROC) curve analysis.

Result: Axillary pCR was achieved for 68 patients (33.8%) who underwent ALND after NAC in our study. In multivariate analyses using axillary lymph node (LN) pCR after NAC as dependent variable factors, showed that higher histologic grade ($p = 0.03$, OR = 2.54 [95% CI: 1.09–5.93]), and higher tumor response rate ($\geq 47.1\%$) ($p = 0.001$, OR = 3.212 [95% CI: 1.584–6.515]) were significantly associated with an increased probability of achieving axillary pCR. Compared the model that included tumor response rate with excluding tumor response rate, the model that included tumor response rate was significantly improved the AUC from 0.649 to 0,732 ($p = 0.022$) to estimate axillary pCR.

Conclusions: We demonstrates the including of tumor response rate in the model have statistically significant improvement in the model performance to estimate axillary pCR. Therefore, we can predict axillary LN status accurately and avoid unnecessary axillary LN dissection.

RETROSPECTIVE ASSESSMENT OF CONCORDANCE BETWEEN IBM ARTIFICIAL INTELLIGENCE PLATFORM, WATSON FOR ONCOLOGY DECISION AND REAL PRACTICE FOR ADJUVANT TREATMENT OF BREAST CANCER AT A SINGLE CENTER IN KOREA

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Background: IBM Watson for Oncology (WFO) is a cognitive computing system provides treatment options for several cancers including breast cancer. We investigated concordance of WFO recommendations for adjuvant treatment of breast cancer compared with real practice in a single center in Korea.

Methods: We retrospectively reviewed medical records of 217 consecutive female patients who received curative surgery for breast cancer without neoadjuvant treatment between January and October 2016. Fifteen patients were excluded as they had histology that WFO does not support. WFO treatment recommendation came into three categories recommended (REC), for consideration (FC), non-recommended (NREC).

Result: Regarding adjuvant chemotherapy regimen, site regimen was among REC in 11% (n = 23), FC in 48% (n = 97), and NREC 41% (n = 83). Two were not included in WFO's list. Among NRECs, WFO recommended adjuvant chemotherapy in 52 patients who did not receive adjuvant chemotherapy (hormone-positive/HER2-negative node-negative disease, n = 46; node-positive breast cancer with age more than 68, n = 5; T1bN0M0 HER2-positive, n = 1) and WFO recommended adjuvant chemotherapy not covered by Korean National insurance system in 3 patients with stage I breast cancer. In 146 of all 202 patients (72.3%), dose-dense AC followed by T +/- Trastuzumab or paclitaxel+trastuzumab was WFO's single REC (the most recommended) regimen, which was not covered by Korean National insurance system.

Conclusions: WFO's REC and FC adjuvant chemotherapy regimen were in 60% of concordant with real practice in Korean patients with breast cancer. Further improvement from WFO is needed regarding hormone-pos/HER2-neg node-negative disease, elderly, and local insurance system.

PRETREATMENT OF METFORMIN ENHANCES THE CHEMOSENSITIVITY OF T-DM1 THROUGH CAVEOLIN-1 IN HER-2 POSITIVE BREAST CANCER

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Background: Trastuzumab Ematansine (T-DM1) has been approved to treat HER-2 (+) breast metastatic cancer. Phase III trial of MARIANNE showed the effect in prolongation of progression free survival in the treatment of T-DM1 was not superior to Trastuzumab plus taxane in the first line therapy of HER-2 (+) metastatic cancer. Enhancement of the chemoresponse is a strategy to shift T-DM1 into the first line treatment.

Methods: Caveolin-1 in breast cancer cells cell line SKBR-3 and BT-474 was manipulated with molecular strategy to detect the chemosensitivity of T-DM1. Subsequently, breast cancer cells were pretreated with Metformin to demonstrate the expression of caveolin-1. Then, the cytotoxicity studies were performed by proliferative assay and apoptotic evaluation.

Result: Pretreatment with Metformin in breast cancer cells could induce the overexpression of caveolin-1 and promote the chemosensitivity of T-DM1. Correlated apoptotic change could be detected during cytotoxic effect.

Conclusions: Combined treatment with Metformin with T-DM1 maybe a new strategy to shift T-DM1 into the first line treatment of HER-2 (+) metastatic breast cancer.

THE PREDICTIVE FACTORS OF DETECTING CIRCULATING TUMOR CELLS USING THE TAPERED-SLIT MEMBRANE FILTERS IN OPERABLE BREAST CANCER

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Background: The standard for Circulating Tumor Cells (CTC) detection remains the CellSearch system, which is still the only system that has been approved by the FDA for in vitro diagnosis purposes. But, the antibody-based CTC isolation method have trouble in maintaining the viability of CTCs due to irreversible antibody binding. So, we developed the tapered-slit membrane (TSM) filters for CTC isolation and detection, and analysed the change of CTC after treatment for breast cancer using this method.

Methods: In this prospective and single center study, we conducted the CTC isolation using the TSM filters in 127 patients with primary breast cancer before their operation, after operation and after 6 months. We assessed the positive rate of CTC at their initial diagnosis and analyzed the clinicopathological factors associated with the change of CTC after appropriate adjuvant treatments.

Result: In 127 patients, 56 (44.1%) were showed positive CTC and the mean CTC was 0.85 preoperatively. We found that the HER2 molecular subtype (78.6% vs. 39.8%, $p = 0.012$) and p53 negative expression (55.4% vs. 35.2%, $p = 0.023$) were predictive factors of positive CTC. There was no correlation between preoperative CTC and TNM stage. The CTC change after operation was not associated with any clinicopathological characteristics. Similar results was shown in the CTC change after adjuvant treatments.

Conclusions: CTC is found more frequently in HER2 subtype breast cancer and p53 negative breast cancer. To assess CTC as the prognostic factor, additional survival data will be required.

PO151

LETS HAVE AN INTEREST OF EXTRAMAMMARY FINDINGS ON PRE OPERATIVE BREAST MRI

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Background: Breast ultrasonography is the primary important modality in making a diagnosis of breast cancer. Today, breast Magnetic Resonance Imaging (MRI) is increasingly being used in work up of breast cancer patients. Breast MRI has high sensitivity, so it is useful in detection of malignancy and determine extent of breast cancer.

Methods: In addition, other parts are also included on breast MRI; lungs, mediastinum, bone and the upper abdomen. Because the abnormalities detected on the above structures may influence the staging and provide a clue to systemic metastasis, which results in the change of treatment strategy. So we must pay attention not only breast and axilla, but also other structures included on breast MRI.

Result: Contents Malignant 1. Lung - Pulmonary metastasis from breast, Primay lung cancer, Pleural seeding 2. Hepatic metastasis from breast 3. Bone metastasis from breast Benign 1. Lung - RML collapse mimicking pleural metastasis, Pleural effusion 2. Mediastinum - Thymic cyst 3. Liver - Hepatic cyst, Liver cirrhosis, Hemangioma 4. Bone - Rib fracture, Pectus excavatum, Sternostomy d/t ventricular septal defect (VSD) 5. Others - Ascites, Chest wall lipoma.

Conclusions: The purpose of this presentation is to review the unexpected extramammary findings seen on the preoperative breast MRI.

ADDITIONAL NON-SENTINEL LYMPH NODE METASTASIS OF CLINICALLY NODE NEGATIVE BREAST CANCER PATIENTS WITH POSITIVE SENTINEL LYMPH NODE AND ITS PREDICTING FACTORS IN THE POST-Z0011 TRIAL ERA

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Background: The aim of this study is to identify patients with additional non-sentinel lymph node (SLN) metastasis and factors that are most helpful in predicting additional non-SLN metastasis in clinically node negative breast cancer patients with a positive sentinel lymph node biopsy.

Methods: The data from 114 consecutive patients with 1-2 SLN positive breast cancer and clinical/ultrasound negative axilla who had undergone ALND from January 2003 to December 2015 were studied. The univariate and multivariate associations of clinicopathologic factors for non-sentinel lymph nodes metastases were analyzed.

Result: Of the 114 patients, 39 (34.2%) had additional metastases in non-SLN and 11 (9.6%) had more than 4 lymph nodes metastases. Median tumor size was 1.8 (range, 0.3-6.5). Mean number of retrieval SLN was 1.82 (range, 1-6) and mean number of metastatic axillary lymph nodes was 2.11 (range, 1-18). There were no significant association between additional non-sentinel lymph node metastases and clinicopathologic factors, such as Tumor size, tumor grade, lymphovascular invasion, estrogen receptor, progesterone receptor and HER2. There were also no significant correlation between these clinicopathologic factors and more than 4 lymph nodes metastases suggesting pN2-3.

Conclusions: Our results showed that around 10% of clinically node negative breast cancer patients with 1-2 metastatic sentinel lymph nodes had more than 4 metastatic lymph nodes and these additional nodal metastases had no correlation with clinicopathologic factors. In the post-Z0011 era, special tools to predict additional extensive nodal metastases of patients satisfying the Z0011 criteria are needed to identify more precise staging.

TIMING AND DILUTION OF PATENT BLUE DYE IN SENTINEL NODE BIOPSY OF INVASIVE BREAST CANCER; DOES IT MAKE A DIFFERENCE IN DETECTION?

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Background: Sentinel lymph node biopsy the current standard for staging of invasive breast cancers in assessing axillary metastasis. Despite this, there is a lack of standardised protocol which govern the methodology of sentinel node biopsies. The optimal timing of lymphoscintigraphy with radiocolloid injection and the use of dilute or concentrated patent V blue dye (Aspen Pharmacare Australia) for optimal detection of sentinel node intra-operatively are some of the variable which exist between different surgical practices.

Methods: A retrospective multicenter study was performed of patients with biopsy proven invasive breast cancers requiring sentinel node biopsy from July 2015 to June 2016 (n = 178). Whole cohort received Patent Blue V peri-tumoural subdermal injections as dilute (1 mL saline with 2 mL Patent blue, n = 120) or concentrated (2 mL Patent blue only, n = 58). The cohort was divided into protocol A group who received lymphoscintigraphy radio-colloid injection < 12 hours pre-operatively (n = 131) and protocol B group who received the injection > 12 hours (n = 47).

Result: Of a total of 499 sentinel lymph nodes harvested, 5 were detected using blue lymphatic tracking only (0.01%), 180 using lymphoscintigraphy only (36.1%) and 191 using dual methods (38.3%). There were no statistically significant relationship between dilution status of Patent blue dye in detection of blue-only nodes ($p = 0.756$) nor hot-and-blue nodes ($p = 0.278$). There was also no significant evidence for greater detection of blue-only ($p = 0.568$), hot-only ($p = 0.678$) and hot-and-blue ($p = 0.235$) nodes between protocol A and protocol B candidates.

Conclusions: Dilution status of Patent Blue V dye and timing of lymphoscintigraphy radiocolloid injection shows no statistically significant difference in detection of sentinel lymph nodes.

HISTOPATHOLOGIC CORRELATION OF RESIDUAL TUMOR IN BREAST WITH RESIDUAL MAMMOGRAPHIC MICROCALCIFICATION AND MRI AFTER NEOADJUVANT SYSTEMIC TREATMENT

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Background: The objective of this study was to estimate the accuracy of residual mammographic (MMG) microcalcification and enhancing lesion in magnetic resonance imaging (MRI) in predicting residual tumor after neoadjuvant systemic treatment (NST).

Methods: This is a single-center, retrospective study. We included patients with breast cancer who underwent NST and have microcalcifications in the post NST mammogram and had the surgery from January 2, 2013 to December 30, 2014. All the patients had post NST imaging exams of MMG and MRI. Final pathologic tumor size with histopathology and biomarker status was obtained after surgery. Analysis of correlation between image findings and pathology was evaluated.

Result: Of 151 patients that were included in this study, 125 patients (82.8%) had residual invasive tumor and 26 patients (17.2%) had pathologic complete response. In overall, MRI correlated better than MMG in predicting tumor size (intraclass correlation coefficient [ICC] = 0.769 vs. 0.651), but for HR+/HER2- subtype, MMG had higher correlation than MRI (ICC = 0.747 vs. 0.575). Specially in HR- subtype, MRI had strong correlation with pathology (ICC for HR-/HER2+ = 0.939 and TN = 0.75), while MMG tend to overestimate the tumor size (ICC for HR-/HER2+ = 0.543 and TN = 0.479).

Conclusions: Overall post-NST residual microcalcifications on MMG have lower correlation with residual tumor size than MRI. In other than HR+/HER2- subtype, the extent of calcifications on pre-OP evaluation may not be accurate in evaluating the residual extent of the tumor after NST.

RADIOGRAPHIC FEATURES OF MUCINOUS BREAST CARCINOMA

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Background: Mucinous breast carcinoma is often misdiagnosed as a benign lesion on breast imaging. We aim to describe features of mucinous breast cancer from our institution.

Methods: Consecutive patients in our institution diagnosed with invasive mucinous breast cancer were identified retrospectively.

Result: We identified 197 patients who were diagnosed with invasive mucinous breast cancer from March 2000 to July 2014. The median age at diagnosis was 48 years old. 85.2% of our patients presented with a palpable breast lump, 4.1% reported having breast pain while 2.0 % had nipple discharge. 8.6% were detected incidentally on screening exercises. 45 out of 197 (22.8%) were called BIRADS 3 and below on initial radiological investigation, while 152 patients (77.2%) were called BIRADS 4/5. On mammography, 66.5% (131 out of 197) patients had reported masses with 63.4% (83 out of 131) with reported irregularities. It is noted that only 8.6% (17 out of 197) of the patients had reported architectural distortion and microcalcifications were seen in 31.0% (61/197) patients. On ultrasound studies, 81.4% (160 out of 197) patients had masses reported, of which only 95 (59.4%) were described as having at least one malignant characteristic.

Conclusions: In our series, 45 out of 197 patients (22.8%) presented with benign radiological features showing that mucinous breast cancer remains an imaging challenge. Therefore other factors such as patients history need to be taken into consideration before conservative management can be taken.

A PREDICTION MODEL FOR AXILLARY LYMPH NODE METASTASIS IN EARLY BREAST CANCER

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Background: The aim of this study was to develop and validate a prediction model for axillary lymph node (ALN) metastasis in early breast cancer.

Methods: Using a nationwide database, we recognized breast cancer patients who underwent surgery between June 1980 and August 2016. A total of 41,895 patients were included for analysis. The total cohort was randomly divided, in a ratio of 7:3, for development and validation of a prediction model for ALN metastasis in early breast cancer, respectively. Multivariable logistic regression was performed to identify independent predictors of ALN metastasis. Multiple imputation was done 10 times to resolve missing data and only factors that were significant in more than half of the datasets were included in the prediction model.

Result: Palpability at diagnosis, multifocality, tumor location, tumor size, histologic subtype, histologic grade, lymphatic invasion, vascular invasion, estrogen receptor and progesterone receptor status and Ki-67 expression level were independent predictors of ALN metastasis. A prediction model was developed using these 11 factors and scores were appointed according to the beta coffecient of multivariable logistic regression analysis. Area under the receiver-operating characteristic (ROC) curve (AUC) was 0.753 and 0.754 in the training set and validation set, respectively. Using a cutoff value of 4, the sensitivity of the scoring system was 97.9% and 97.7%, respectively.

Conclusions: This prediction model can provide more accurate information preoperatively, especially when considering sentinel lymph node biopsy in ductal carcinoma in situ cases.

ASSOCIATION BETWEEN TUMOR UPTAKES OF BREAST-SPECIFIC GAMMA IMAGING AND FDG PET/CT, AND CORRELATION WITH PROGNOSTIC FACTORS AND MOLECULAR SUBTYPES IN BREAST CANCER

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Background: Breast-specific gamma imaging (BSGI) and F-18 FDG PET/CT are molecular imaging modalities with a different mechanism of tumor uptake. The purpose of this study was to investigate the association between the tumor uptakes of two modalities in breast cancer and to find the correlation of these with the prognostic factors and molecular subtypes.

Methods: A total of ninety-six patients with invasive ductal carcinoma who underwent preoperative BSGI and FDG PET/CT were enrolled, retrospectively. The semi-quantitative indexes of breast tumor uptake were measured on both modalities, expressed as tumor to background ratio (TBR) and SUVmax. These indexes were compared with the prognostic factors and molecular subtype.

Result: The overall correlation between TBR and SUVmax was positively moderate ($r = 0.504$). On subgroup analysis according to molecular subtypes, it had the significant correlations with luminal A, luminal B and HER2 groups (each for $r = 0.361$, $r = 0.641$ and $r = 0.630$). No correlation was found with triple-negative cancer (TNBC) which implies biological heterogeneity in TNBC. Both TBR and SUVmax were the significant correlation with tumor size ≥ 2 cm, the incidence of axillary lymph node metastasis, histologic grade, PR status, Ki-67 $\geq 14\%$ and luminal types.

Conclusions: Both TBR of BSGI and SUVmax of PET/CT in the breast cancer were correlated with prognostic factors. Biological heterogeneity of TNBC could result in no correlation of tumor uptake between two modalities. Further studies are needed to elucidate the potential role of tumor uptake of two modalities in TNBC.

THE ACCUCARY OF CORE NEEDLE BIOPSY OF AXILLARY LYMPH NODE IN BREAST CANCER

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Background: Preoperative axillary staging by ultrasound (US) guided core needle biopsy is important for determining the preoperative or surgical management. This study examined the accuracy of preoperative core needle biopsy (CNB) of axillary lymph node (ALN) and the associated factors with axillary lymph node metastasis among patients with negative findings preoperatively.

Methods: A retrospective review of 1,772 patients who received US guided core needle biopsy between January 2009 and September 2016 was performed. Records of 552 breast cancer patients who had not received neoadjuvant chemotherapy were included. Total patients were categorized to 4 subgroups by comparing CNB with postoperative pathology of ALN. Accuracy rate of US guided CNB and subgroup analysis was done by t-test and chi-square test among negative CNB result.

Result: Of 552 cases 489 showed concordant pathologic results (accuracy 87.8%). Sixty percent (n = 332/552) did not show ALN metastasis, among them 272 had concordance postoperative result (sensitivity 78%). Among 220 patients with positive CNB findings 213 had concordant results (specificity 97.5%). In subgroup analysis among 332 patients, true negative subgroup (n = 272) showed higher rates of calcification in cancer lesion (42.4% vs. 21.5%, $p = 0.013$) and mucinous type (4.8% vs. 0%, $p = 0.009$). False negative group had more nodules (2.26 vs. 1.5, $p = 0.002$).

Conclusions: Preoperative US guided CNB of ALN shows relatively high accuracy rates. In proportion of 10% false negative results might be observed. Further evaluation is needed for detecting associated factors about false negative result.

EARLY PREDICTION OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER: COMPARISON OF DYNAMIC CONTRAST-ENHANCED MRI AND CONTRAST ENHANCED ULTRASOUND

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Background: The purpose of this study was to determine the diagnostic performance of dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) and dynamic contrast-enhanced ultrasound (CEUS) parameters to assess response to neoadjuvant chemotherapy (NAC) in patients with breast cancer.

Methods: The institutional review board approved the study, and written informed consent was obtained from each patients. DCE-MRI and CEUS were performed before and after NAC in 39 patients with breast cancer. DCE-MRI parameters (transfer constant [Ktrans], rate constant [kep], and relative extravascular extracellular space [ve], and initial area under the concentration curve [AUC]) were derived from whole-tumor volumes using histogram analysis. Various CEUS perfusion parameters were obtained from single-section region of interest. After surgery, all DCE-MRI and CEUS parameters and their changes obtained before and after NAC were compared with histopathologic response using the Miller-Payne Grading system.

Result: Twelve (30.8%) patients showed a good response (Miller-Payne grade 4 or 5) and 27 (69.2%) showed a minor response (Miller-Payne grade 1, 2, or 3). Many post-NAC DCE-MRI histogram metrics were significantly different between good responders and minor responders. Mean, 25th, 50th, and 75th percentiles of Ktrans, Kep, and AUC of post-NAC DCE-MRI had good diagnostic performance (AUC, 0.76 0.81) for the prediction of good responders to NAC. However, few differences were found in CEUS parameters between two groups.

Conclusions: Histogram analysis of DCE-MRI is helpful for early prediction of the pathologic response to NAC.

CIRCULATING PLASMACYTOID AND MYELOID DENDRITIC CELLS IN BREAST CANCER PATIENTS

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Background: Dendritic cells (DCs) are the most efficient antigen presenting cells and are comprised of plasmacytoid-(pDC) and myeloid-(mDC) derived DC subsets. DCs play an indispensable link between innate and adaptive immunity; importantly, several cancers exhibit dysfunction of DCs. This study aimed to correlate the levels of circulating DCs with clinical outcome in breast cancer patients.

Methods: From January 2013 to November 2013, the peripheral blood of 53 breast cancer patients were used. We phenotyped circulating plasmacytoid dendritic cells (pDCs) and myeloid dendritic cells (mDCs) using flowcytometry. Then we correlate peripheral blood DC immunophenotypes with prognostic factor of these cancer patients.

Result: ER positive breast cancer patients had higher levels of circulating mDCs ($p = 0.025$) and HER-2 positive patients had higher levels of circulating pDCs ($p = 0.04$) in univariate analysis. There was no relations in the levels of circulating DCs with T stage, N stage, Ki67 index, histologic grade, nuclear grade and lymphovascular invasion. Patients with HER-2 positive cancer had higher levels of circulating pDCs with odds ratio 1.35 in multivariate analysis ($p = 0.042$).

Conclusions: Our new results suggest that circulating pDCs and mDCs could be a prognostic indicator in breast cancer patients. These prognostic indicators were independent and emphasize the important role of immunity in ensuring breast cancer patient survival.

PO161

BREAST MASS ASSESSMENT BETWEEN BY SURGEON AND S-DETECT (SMART-DETECT SAMSUNG MEDISON CO., LTD)

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Background: Ultrasonography has been widely used in the preoperative examination of breast mass. With US assessment of breast lesions, we described the feature by the Breast Imaging-Reporting and Data System (BI-RADS). Among various ultrasound techniques, we employs S-Detect (TM) for categorization of breast masses again. And we evaluated the categories of the doctor's BIRADS and the S-Detect.

Methods: Between April 2016 and December 2016, the doctors (from local clinics and our clinic) evaluated breast masses with ultrasonography, categorized by BI-RADS and did gun biopsy. From the biopsy, a total of 62 patients got the benign results for a total of 83 masses and were recommended the excision and underwent the mammotome breast biopsy in our instititute. We categorized a total 83 breast masses with smart-detect (S-detect) again and we did mammotome breast biopsy.

Result: All breast masses were diagnosed as benign from gun biopsy and confirmed the final pathology as benign after mammotome breast biopsy. Among a total of 83 masses, doctors categorized them as BIRAD 3-17 (20%), IVa-56 (67%), IVb-9 (10%), IVc -1 (1.2%) and the accuracy is 20%. Before excision, S-Detect categorized them as probably benign 62 (75%), probably malignancy 21 (25%) and its accuracy is 75%.

Conclusions: When we compared the doctor's and S-Detect's categories, the prediction accuracy was higher for S-Detect, but the sensitivity was not obtained because it was not performed on malignant tumors. Although this study was performed only for benign masses, we confirmed the possibility of applying S-detect for the evaluation and diagnosis of breast mass. Furthermore It is needed to evaluate a breast malignant lesion.

EFFICACY OF INTRAOPERATIVE CIRCUMFERENTIAL FROZEN BIOPSY ANALYSIS OF LUMPECTOMY MARGIN DURING BREAST CONSERVING SURGERY

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Background: This study is to investigate the value of intraoperative circumferential frozen biopsy of lumpectomy margin during breast conserving surgery (BCS) for breast cancer.

Methods: Total 509 breast cancer patients from 2007 to 2011 were tried with intraoperative entire-circumferential frozen biopsy (IOFB) during BCS. We analyzed the accuracy of IOFB and the clinical characteristics of patients.

Result: Among 509 patients, 437 patients (85.9%) was performed by partial mastectomy (PM), 72 patients (14.1%) by total mastectomy (TM), finally. Mean turnaround time of IOFB in the first lumpectomy margin was 42 minutes (10-85 minutes) per case. Median tissue blocks was 13. 123 patients (24.2%) had positive margins in the first lumpectomy margin. 55 patients in those underwent additional excisions, only and 63 patients were converted into total mastectomy. False positive tumor-margin was just one case. 362 (71.1%) patients had tumor-negative margin in 1st margin. 24 cases (4.9%) had false negative tumor margin and 5 patients were converted into TM. Atypical ductal hyperplasia (ADH) versus ductal carcinoma *in situ* (DCIS) diagnosed cases in IOFB were 24 (4.7%) patients. DCIS cases among those were 8 cases in permanent section and 4 patients were converted into TM. There was no difference of age, stage, biologic factors like estrogen receptor, progesterone receptor, c-erb B2, tumor grade between PM cases and TM cases. Factors as invasive lobular carcinoma, multiple tumors, high size of tumor, multiple excisions increased the conversion into TM.

Conclusions: Intraoperative circumferential frozen biopsy during breast conserving surgery is useful for evaluating lumpectomy margin and for preventing reoperation.

RANDOMIZED PHASE 3 STUDY OF A NOVEL, LONG-ACTING G-CSF, EFLAPEGRASTIM (SPI-2012, ROLONTISTM) VERSUS PEGFILGRASTIM IN THE MANAGEMENT OF CHEMOTHERAPY-INDUCED NEUTROPENIA IN EARLY-STAGE BREAST CANCER

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Background: Eflapegrastim is a novel investigational biologic that uses innovative proprietary long-acting protein/peptide discovery (LAPSCOVERY™) technology with potentially unique distribution to areas rich in FcRn receptors. A successful dose-finding Phase 2 trial including a pegfilgrastim control arm established the dose for a Phase 3 non-inferiority trial.

Methods: This is an open-label, active-controlled, global, multicenter, Phase 3 study eflapegrastim (3.6 mg equ of G-CSF) to pegfilgrastim (6 mg equ of G-CSF) in a 1:1 randomization with once per cycle treatment for 4 cycles in patients with early-stage breast cancer (ESBC) receiving TC. Histologically confirmed ESBC patients are enrolled if they are: eligible to receive adjuvant or neoadjuvant TC chemotherapy; ≥ 18 years old, with adequate hematologic, renal and hepatic function. Excluded if they have: a known sensitivity or previous reaction to *E. coli* derived products; concurrent adjuvant cancer therapy; locally recurrent/metastatic or contralateral breast cancer; previous exposure to filgrastim, pegfilgrastim, or other G-CSF therapy; bone marrow or hematopoietic stem cell transplant or radiation therapy prior to enrollment, or are pregnant or breast-feeding.

Result: The primary endpoint is non-inferiority in DSN of a single dose of eflapegrastim to pegfilgrastim in Cycle 1. A 2-sided 95% confidence interval (CI) of the difference will be calculated using bootstrap resampling with treatment as the only stratification factor. Secondary endpoints include Time to Absolute Neutrophil Count (ANC) Recovery; Depth of ANC Nadir; incidence of Febrile Neutropenia. Safety and pharmacokinetics will also be assessed.

Conclusions: Target Accrual: Approximately 580 patients (USA, South Korea). Enrollment began January 2016.

SCREENING FOR PSYCHOLOGICAL DISTRESS IN BREAST CANCER PATIENTS AND PSYCHIATRIC REFERRAL ACCEPTANCE AMONG SCREEN-POSITIVE PATIENTS

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Background: This study aimed to identify the clinical characteristics of breast cancer patients with high levels of distress and the screen-positive patients who accepted the offered referrals for psychiatric consultations.

Methods: From November 2011 to October 2013, 1,681 breast cancer patients at Asan Medical Center were screened for distress using the Center for Epidemiologic Studies Depression Scale (CES-D). High-risk patients who scored 19 on the CES-D were offered referrals to a stress clinic at Asan Cancer Center. The clinical characteristics of screen-positive patients and the accepted referrals were analyzed.

Result: Using 19 as a cutoff score, 771 out of 1,681 patients were screened as positive and offered referrals to the stress clinic. The screen-positive patients tended to be smokers ($p = 0.033$) with a previous history of psychotropic medication ($p = 0.045$), mastectomy ($p < 0.0001$), and recurrence ($p = 0.041$). Among these 771 patients, 182 accepted referrals and visited the stress clinic. The CES-D score was significantly higher in the referral-accepters group (28.708.27, mean SD) than in the nonaccepters group (26.906.79, $p = 0.006$). However, there were no intergroup differences in age, primary or recurrent disease, family history of breast cancer, operation type, or stage.

Conclusions: Applying the CES-D questionnaire resulted in 45.8% of patients being screened as positive for psychological distress, and indicated that smoking, a family history of breast cancer, previous history of psychotropic medication, planned mastectomy, and advanced stage might be clinical predictors for a high level of distress. However, only 23.6% of the patients accepted referrals, and the only significant clinical predictor for referral acceptance was a high CES-D score.

APPLYING THE RECENT CLASSIFICATION ALGORITHMS TO DEPRESSION SCREENING AND ATTEMPTING PATTERN EXTRACTION OF PATIENT REPORTED OUTCOMES THAT NEGATIVELY AFFECT CLASSIFICATION ACCURACY

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Background: Psychological distress in cancer patients has been associated with poor adherence to the treatment process and poor quality of life. However, patients often do not have a depression screening test due to lack of time for clinicians and patients during office visits. Thus, clinicians have used smartphones, based on expectations for smartphone applications as a breakthrough technology for monitoring the mental health status of cancer patients. However, using electronic patient reported outcomes (ePROs) on mental health through smartphones raises new concerns, which are the question of the accuracy of depression screening. Therefore, we conducted a study to improve the accuracy of the depression screening in cancer outpatient settings.

Methods: We have employed deep learning algorithm, one of recent classifier algorithms to develop depression-screening models, and compared the results of the deep learning-based model with the traditional statistical model. Furthermore, we extracted ePRO patterns that negatively affect depression screening accuracy.

Result: Deep learning based model has an AUC of 0.8856 and has the lowest error rate of 11.61% with the cutoff probability of 0.5, with a sensitivity of 58% and a specificity of 96.12% at the cutoff probability. In addition, traces of mental fluctuations in ePROs statistically reduce the accuracy of the depression-screening model.

Conclusions: Our results suggest that active attempts to apply the recent classification technology to the medical environment are essential. In addition, if there is evidence of mood swings in the ePRO, clinicians should adjust the cutoff score of the depression screening depending on whether the specificity or sensitivity is important.

THE ANALYSIS OF HER2 POSITIVITY AND ITS CLINICAL IMPLICATION ACCORDING TO DIFFERENT DETECTION METHODS OF IMMUNOHISTOCHEMISTRY AND FLUORESCENCE IN SITU HYBRIDIZATION IN HER2 POSITIVE BREAST CANCER

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Background: According to ASCO/CAP guideline, when breast cancer patients have 3+ of the score in immunohistochemistry (IHC 3+) or gene amplification(nucleus than 6 per copy) in fluorescence in situ hybridization (FISH+), we can diagnose HER2 positive. In this study, we compared the outcomes based on difference of the methods in the expression of HER2 protein in patients with HER2 positive breast cancer.

Methods: This study was performed retrospective analysis of HER2 positive breast cancer in 26,020 patients, out of these, 22,336 patients IHC 3+ and 3,684 patients with FISH+ from the Korean Breast Cancer Society Registry. The measurements of outcomes were compared to breast cancer specific survival and overall survival between each IHC 3+ and FISH+ whether with or without trastuzumab.

Result: In Kaplan-Meier method, breast cancer specific survival showed significant difference between IHC 3+ group and FISH+ group, 5-year cumulative survival rates of IHC 3+ and FISH+ were each 95.4% and 99.1% ($p < 0.0001$) in patients without trastuzumab, and each 98.9% and 100.0% ($p = 0.0187$) in patients with trastuzumab. There was no significant difference in overall survival between IHC 3+ group and FISH+ group with or without trastuzumab. In Cox proportional hazards model, FISH+ group was better breast cancer specific survival than IHC 3+ group in without trastuzumab, but there was no significant difference in breast cancer specific survival between IHC 3+ group and FISH+ group with trastuzumab.

Conclusions: IHC 3+ group was worse breast cancer specific survival than FISH+ group in without trastuzumab. It is considered to be a need for further research in the future.

BODY MASS INDEX IS NOT ASSOCIATED WITH WORSE CLINICOPATHOLOGICAL CHARACTERISTICS IN PREMENOPAUSAL BREAST CANCER PATIENTS

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Background: High body mass index (BMI) is associated not only with a higher incidence of breast cancers but also with poorer prognosis. It is speculated that both enhanced production of estrogens and other factors associated with obesity are involved in these associations, but the biological characteristics associated with high BMI have yet to be thoroughly identified. This study aims to determine the association between BMI and the distribution of breast cancer subtypes defined by estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2/neu) expression in premenopausal breast cancers.

Methods: A total of 160 female breast cancer patients were involved. The histological type of the tumor, ER and PR expression, HER2/neu with immunohistochemistry and HER2/neu gene evaluation with interphase fluorescence in situ hybridization (if necessary), age, body weight, height and menopausal status at diagnosis were investigated retrospectively. The patients were stratified as quartile points of BMI categories, respectively: < 21.2, ≥ 21.2 to < 23.3 (reference), ≥ 23.3 to < 25.8 and ≥ 25.8 kg/m^2.

Result: Median BMI was 23.4 kg/m^2 in the premenopausal and 24.0 kg/m^2 in the postmenopausal group ($p = 0.03$). BMI at diagnosis did not differ significantly between the molecular subtypes ($p = 0.39$). Distribution of BMI strata was similar between the molecular subtypes both in pre- and postmenopausal breast cancer ($p = 0.26$ and $p = 0.18$, respectively). Tumor size and lymph node metastasis status was not significantly different according to BMI categories in premenopausal breast cancer.

Conclusions: BMI was not associated with worse clinicopathological characteristics in premenopausal breast patients.

AQUAPORIN3 OVEREXPRESSION IN EARLY BREAST CANCER AND ITS PARADOXICAL RELATIONSHIP WITH CLINICOPATHOLOGIC FACTORS AND PROGNOSIS

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Background: The aim of this study is to evaluate relationship of Aquaporin3 (AQP3) with clinicopathologic factors and prognosis.

Methods: AQP3 expression was investigated on the basis of the immunohistochemistry of tissue microarray specimens from 357 stage I-II breast cancer patients who underwent surgery between 2003 and 2008. We scored the staining intensity (0 through 3) and percentage of positive tumor cells (0 through 4), and the staining score was defined as sum of these scores used to categorize the AQP3 expression as negative (0 through 2), weak (3 through 5), or strong (6 or more).

Result: A total of 231 (64.7%) patients were identified as AQP3-positive (staining score > 2), including 97 (27.2%) cases of strong expression (stating score > 5). AQP3 strong expression has a borderline significant correlation with stage II (versus I, $p = 0.074$), but AQP3 had a significant correlation with positive hormone receptor status ($p = 0.007$) and histologic grade I-II (versus III, $p = 0.069$) suggesting favorable prognosis. In a univariate analysis, AQP3 strong expression had significance association with disease free survival (DFS, $p = 0.012$) and borderline significant association with overall survival (OS, $p = 0.059$). Mutivariate Coxs regression revealed that AQP3 strong expression was an independent prognostic factor of DFS (HR 1.707, 95% CI 0.988 to 2.950) and OS (HR 1.906, 95% CI 1.161 to 3.127).

Conclusions: Our study showed that AQP3 strong expression in tumor tissue had a negative correlation with prognosis in patients with early breast cancer. However, AQP3 strong expression had, paradoxically, a correlation with positive hormone receptor status and lower histologic grade classifying as favorable prognostic factor.

IMPACT OF HYPERCHOLESTEROLEMIA ON CLINICAL OUTCOME IN OPERABLE BREAST CANCER PATIENTS

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Background: Hypercholesterolemia is associated with carcinogenesis and prognosis of breast cancer (BC). In this study, we evaluated the impact of serum cholesterol after surgery on recurrence and survival in operable BC patients.

Methods: We analyzed 920 women with invasive BC who underwent surgical resection from 2003 to 2011 at a single institution. We retrospectively obtained clinical information including serum cholesterol level (at the time of surgery and 6 months after surgery). BC subtypes were classified according to estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), and Ki-67. Univariate, multivariate Cox-regression and Kaplan-Meier curve analysis were used to analyze the correlation between serum cholesterol and relapse-free survival (RFS).

Result: Median age was 49.0 years old (range 20-89). The majority of patients had stage I (stage I: 448, stage II: 337, stage III: 135) and Luminal subtype (Luminal A: 44.0%, B: 21.2%, HER2: 19.3%, TNBC: 15.4%). Adjuvant (or Neo-) chemotherapy was administered in 658 (71.5%) patients. During median follow up time of 58.1 months, there were 102 recurrence cases. Mean change of cholesterol was -2.17 mg/dL (SD: 41.3). The presence of hypercholesterolemia (> 250 mg/dL) during follow up showed a negative influence on RFS (HR 2.07, 95%CI 1.18-3.65; $p = 0.012$). In multivariate analysis, hypercholesterolemia after 6 months of surgery was confirmed as independent prognostic factor for RFS (HR = 2.04, 95%CI 1.12-3.73; $p = 0.020$), after adjustment of other significant clinical factors (age, BMI, subtype, stage, Ki67, chemotherapy, endocrine therapy, trastuzumab use, diabetes, and statin use).

Conclusions: Hypercholesterolemia after surgery is an independent poor prognostic factor in stage I-III breast cancer.

PREDICTORS OF NONSENTINEL LYMPH NODE METASTASIS FOR EARLY BREAST CANCER PATIENTS WITH ONE OR TWO POSITIVE SENTINEL LYMPH NODES

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Background: The purpose of this study was to assess the predictors for avoiding axillary node dissection, particularly in patients with having T1-T2 tumor and detecting one or two positive sentinel lymph node (SLN) metastasis.

Methods: SLN biopsy with axillary node dissection was performed in 134 patients with one or two positive SLNs in breast cancer between January 2013 and December 2015. Data were collected retrospectively and analyzed using chi-square, logistic regression analyses and receiver operating characteristic (ROC) analysis.

Result: Of 134 patients, forty-one (30.6%) had metastasis in the non-SLN. Univariate analysis showed that estrogen receptor (ER), progesterone receptor (PR), Ki-67 index, and the number of positive SLN were associated with non-SLN involvement. In Multivariate analysis, only ER and Ki-67 index were predictors for non-SLN status (odds ratio [OR] = 7.65, 95% confidence interval [CI] = 1.04 56.09, $p = 0.045$; OR = 1.08, 95% CI = 1.04 1.12, $p = 0.001$). And ROC analysis indicated that 20% was a cutoff point for predicting non-SLN metastasis (sensitivity 97.6%; specificity 45.2%; negative predictive value 97.7%). On closer re-examination of data based on these results, non-SLN metastasis was not found at the patients with four or more collected lymph nodes including SLN, positive ER state, and Ki-67 index less 20%.

Conclusions: We suggest carefully that if patients have particular result of pre-operative immunohistochemistry (positive ER and Ki-67 < 20%), axillary node dissection is unnecessary despite one or two metastasis of four or more collected lymph nodes including SLN.

MIR-222 EXPRESSION LEVEL AS A PREDICTIVE MARKER FOR TUMOR PROGRESSION IN HORMONE RECEPTOR-POSITIVE BREAST CANCER

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Background: MiR-221/222 gene cluster has been reported to be associated with promotion of epithelial-mesenchymal transition (EMT), down-regulation of estrogen receptor-alpha, and tamoxifen resistance in breast cancer. We studied the expression level of miR-222 in human breast cancer samples to analyze its relationship with clinicopathologic features of the tumor including estrogen receptor status, expression of EMT markers, and clinical outcome of patients.

Methods: Quantitative RT-PCR was performed to detect the expression level of the miR-222 in 197 cases of invasive breast cancer. EMT marker expression (expression of vimentin, smooth muscle actin, osteonectin and N-cadherin; loss of E-cadherin) was evaluated by immunohistochemistry.

Result: High level of miR-222 expression was associated with high T stage, high histologic grade, high Ki-67 proliferation index, and HER2 amplification. Its expression was significantly higher in luminal B and HER2+ subtypes than in luminal A and triple-negative subtypes. In hormone receptor-positive subgroup, there was a significant negative correlation between miR-222 and estrogen receptor expression levels, and miR-222 expression was associated with EMT marker expression. In total, high level of miR-222 expression was not associated with clinical outcome of the patients. However, subgroup analyses by hormone receptor status revealed that high level of miR-222 expression was a poor prognostic factor in hormone receptor-positive subgroup, but not in hormone receptor-negative subgroup.

Conclusions: This study showed that miR-222 is related to down-regulation of estrogen receptor, EMT, and tumor progression in hormone receptor-positive breast cancer, indicating that miR-222 may be associated with endocrine therapy resistance and poor clinical outcome in hormone receptor-positive breast cancer.

THE ROLE OF 18F-FDG/PET IN PREDICTION OF AXILLARY NODE METASTASIS AND RECURRENCE IN T1, T2 BREAST CANCER

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Background: The treatments of early stage breast cancer have shifted to a minimum effective treatment such as axillary node (ALN) conservation or omission of adjuvant chemotherapy. There is a growing need for better prognostic factors to support clinical decision-making. The purpose of this study is to assess the utility of positron emission tomography (PET) for predicting recurrence and ALN metastasis in T1 and T2 breast cancer.

Methods: From 2008 to 2011, a total of 180 medical records of T1 and T2 breast cancer patients who underwent preoperative PET were retrospectively reviewed. For survival analysis, the cutoff value of SUVmax was determined to be 5.3 using ROC curve.

Result: In T1 tumors (n = 97), the mean level of SUVmax in patients with ALN metastasis was significantly higher than patients without ALN metastasis (5.27 ± 3.22 vs. 3.80 ± 2.37, $p = 0.021$). It remained independent predictive factor for ALN metastasis in multivariate analysis (Hazard ratio = 1.084; 95% confidence interval = 1.044-1.502; $p = 0.016$). However, in T2 tumors (n = 83), there was no difference in SUVmax according to nodal status (7.56 ± 4.03 vs. 7.48 ± 4.24). In total, the recurrence free survival of patients with higher SUVmax (≥ 5.3) was significantly worse than those with lower SUVmax ($p = 0.015$). The association was valid only in the HR+/HER2- subtype (n = 96, n = 0.025).

Conclusions: Our study demonstrated that Tumor SUVmax might be an independent predictive factor for ALN metastasis in T1 breast cancer, and higher SUVmax (≥ 5.3) could predict tumor relapse for T1, T2 breast cancer. Identifying SUVmax can help approach for more tailored treatments in patients with T1, T2 breast cancer.

DIFFERENCES IN CLINICAL OUTCOMES BETWEEN CHRONIC KIDNEY DISEASE (CKD) AND NON-CKD BREAST CANCER PATIENTS

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Background: Breast cancer is one of the health-threatening diseases of women. In addition, there is increasing in the number of chronic diseases including CKD as it enters an aging society. Among them, we evaluated the relationship between breast cancer and CKD with various pathologic factors and medical characteristics.

Methods: From 2007 to 2015, we included 21 patients with CKD and 84 patients with non-CKD among 1,445 breast cancer patients. Non-CKD control patients (n = 84) were selected after matching following the year at first diagnosis, age, stage, and hormone receptor status. Primary end points were disease-free survival (DFS) and overall survival (OS).

Result: Diabetes was more common in the CKD patients, although the difference was but not significant ($p = 0.076$). Factors associated with breast cancer treatment did not show significant results. Among the related factors, only GFRs and hypertension showed significant results. Breast cancer related death of three cases was confirmed only occurred in the CKD group ($p = 0.007$). The 5-year DFS for patients with CKD was 84% and 96.5% for non-CKD patients ($p = 0.003$). The 5-year OS was 82.5% and 100% for non-CKD patients ($p < 0.01$).

Conclusions: CKD does appear to have a significant effect on OS and DFS of breast cancer patients. However, few patients factor had significant effect on OS and DFS except hypertension and GFRs. There is a need to study molecular biologic factors associated with CKD and further investigate how this has affected breast cancer patients.

A NOVEL PROGNOSTIC MODEL IN HORMONE RECEPTOR-NEGATIVE, HER2-POSITIVE BREAST CANCER

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Background: Breast cancer is generally classified into four general subtypes according to the status of hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2). Because treatment strategies for breast cancer are dependent on molecular subtype and prognosis, it is important to identify specific prognostic biomarkers for each subtype to determine appropriate treatments. In this study, we identified molecular subtype-specific novel prognostic variables in breast cancer.

Methods: We performed Cox proportional hazard analysis to evaluate relationship between 16 candidate prognostic genes selected from public microarray data and clinical outcome in each breast cancer subtype.

Result: The prognostic significance of gene variables varied according to the subtype. Univariate analysis indicated that most of proliferation related genes (p-genes) were significantly associated with risk of distant metastasis in HR+/HER2- subtype, and immune response related genes (i-genes) were correlated with in patients with HR-/HER2+ breast cancer, but not other subtypes. On the contrary, none of clinical variables were significantly associated with risk of distant metastasis in HR-/HER2+ subtype. In multivariate analysis adjusted for clinical and gene variables, MMP11 and CD2 are independent prognostic factors in HR-/HER2+ breast cancer. We further developed a novel prognostic model to predict the risk of distant metastasis in HR-/HER2+ breast cancer based on these genes. As a result, risk prediction model for HR-/HER2+ breast cancer could discriminate high-risk from low-risk patients.

Conclusions: Our novel prognostic model can provide accurate information on the risk of distant metastasis and help to guide treatment for patients with HR-/Her2+ breast cancer.

TRIPLE POSITIVE BREAST CANCER: STRATEGY OF SYSTEMIC THERAPY

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Background: Triple positive breast cancer is one of sub-type of breast cancer that is defined namely, ER/PgR/Her-2 positive tumors. It has multiple strategies for systemic therapy according to the characteristics of hormonal responsiveness and Her-2 responsiveness. Each targeted treatment strategy plays cross-talks between HER-2 and estrogen receptor signaling pathway resulting in endocrine resistance and Anti Her-2 resistance. Selecting the patient who favors anti estrogen therapy or anti Her-2 therapy is important for triple positive breast cancer patients to maximize the therapeutic efficacy and minimize cross talks which promotes resistance and to reduce overtreatment.

Methods: We analyzed total of 2201 breast cancer patients who newly diagnosed in Seoul St. Mary's hospital from October 2009 to March 2016. Among the patients, 158 patients were classified as triple positive breast cancer.

Result: During the follow up of 35.9 months, 9 patients recurred in triple positive breast cancer. We compared triple positive group with Luminal A subgroup (722 cases) which favors hormonal therapy and with HER-2 subgroup (205 cases) which favors Anti-Her2 therapy. And analyzed the characteristics and patterns of recurrence. The results shows the pattern of recurrence in triple positive group is similar to that of Luminal A subgroup, interpreted as similar recurrence rate (Luminal A: 4.0%, Triple positive: 5.7%, HER-2: 10.7%) and similar pattern of late recurrence {Time to recurrence (months): Luminal A: 29.2, Triple positive: 31.2, HER-2: 18.73} pattern.

Conclusions: In conclusion Triple positive breast cancer follows pattern of disease recurrence in Luminal A subtype especially in patient with small tumor volume with high allered score.

CLINICAL OUTCOMES AND PROGNOSTIC DIFFERENCE IN STAGE IIIC BREAST CANCER

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Background: The purpose of this study was to evaluate clinical outcomes and prognostic difference in stage IIIc breast cancer patients.

Methods: We retrospectively identified 135 stage IIIc breast cancer patients who underwent breast cancer surgery from January 1996 to December 2013. Internal mammary lymph node (IMN) and supraclavicular lymph node (SCN) metastasis were identified with image studies. We evaluate overall survival (OS) and disease free survival (DFS) by N stage in stage IIIc breast cancer.

Result: In 135 patients, 71 patients were N3a stage, 40 patients were N3b stage, 24 patients were N3c stage patients. At mean follow up of 61.2 months, 54 patients had developed disease recurrence and 41 patients had died. The OS and DFS of total patients were 69.6% and 60%, respectively. The OS for stage IIIc patients who corresponded N3a, N3b, N3c were 63.4%, 82.5%, and 66.7%, respectively. The DFS for stage IIIc patients who corresponded N3a, N3b, N3c were 56.3%, 72.5%, and 50.0%, respectively. However, no statistical difference was identified in OS and DFS by N stage ($p = 0.197$ and 0.107). In multivariate analysis, endocrine treatment (HR 0.337, 0.131-0.868, $p < 0.024$) and radiotherapy (HR 0.420, 0.180-0.981, $p < 0.045$) were significantly associated with overall survival.

Conclusions: Our findings suggest that patients with N3b stage tended to have a relatively good prognosis among the patients with stage IIIc disease. Further studies warrant the clinical significance of IMN involvement in patients with stage IIIc breast cancer.

FACTORS ASSOCIATED WITH UPGRADING IN PATIENTS WITH PAPILLARY BREAST LESION ON CORE-NEEDLE BIOPSY

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Background: Breast papillary lesions have variable clinical presentation and pathologic spectrum. A precise diagnosis of breast papillary lesions obtained from core-needle biopsy is sometimes not possible. Traditionally, surgical excision is recommended for benign papillary lesion on core-needle biopsy because of their malignant potency. The aim of this study was to identify factors associated with upgrading to malignancy in patient with benign papillary lesion on core-needle biopsy.

Methods: We retrospectively reviewed 100 female patients who were diagnosed as benign papillary lesion on core-needle biopsy and underwent subsequent surgical excision between January 2006 and January 2017. Ultrasound-guided core-needle biopsy was performed using a 14-gauge needle gun method.

Result: The upgrade rate to malignancy was 7% (0% in intraducal pappiloma (IDP) without atypia, 23.1% in IDP with atypia, and 12.9% in papillary neoplasm; $p < 0.05$). The univariate analysis showed that, the age at diagnosis, size of lesion on ultrasonography, and IDP without atypia on core-needle biopsy were associated with upgrading. The multivariate analysis showed that lesion size ≥ 2 cm was significantly associated with upgrading to malignancy (Odds ratio = 6.894, $p = 0.045$).

Conclusions: Upgrading to malignancy in patients with benign papillary lesion on core needle biopsy was associated with size of lesion ($\geq$ 2 cm).

Poster Exhibition

HIGH EXPRESSION OF KI67 LABELING INDEX IS A PROGNOSTIC MARKER OF EARLY RECURRENCE IN PATIENTS WITH HORMONE RECEPTOR-NEGATIVE BREAST CANCER

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Background: The aim of this study was to identify the prognostic impact of ki67 labeling index predicting early recurrence in hormone receptor (HR)-negative breast cancer (BC).

Methods: The BC patients surgically treated between 1998 and 2015 were retrospectively identified. Only those with HR-negative BC were included and the patients with Ductal carcinoma in situ (DCIS) or de novo stage IV BC were excluded in the analysis. We defined early recurrence as to recur within 2 years after surgery.

Result: Of a total of 587 patients, 316 (53.8%) had triple-negative BC and 236 (42.8%) had HER2-positive BC. During 54months (12-159 months) of median follow-up period, 77 patients had systemic or loco-regional recurrence, and among them, 51 patients had early recurrence. After categorization of ki67 index with a cutoff value of 70%, age, T stage, N stage, and ki67 were significant prognostic factors of early recurrence (hazard ratio of ki67: 4.80, 95%CI: 2.46-9.37) in the univariate analysis. Cox regression analysis showed that T stage, N stage, and ki67 index 70% or more were statistically significant prognostic factors of early recurrence-free survival (hazard ratio of ki67: 3.86, 95%CI: 1.69-8.82). Among 77 patients with recurrence in 587 patients, mean time to recurrence was 11.3months (4-27 months) in twelve patients with ki67 index 80% or more, compared to 25.6months (4-93 months) in 65 patients with low expression of ki67.

Conclusions: Ki67 labeling index was a significant prognostic factor of early recurrence-free survival, and HR-negative BC patients with ki67 70% or more were tend to have early recurrence more frequently than those with low expression of Ki67.

CHRONOLOGICAL CHANGING PATTERNS IN THE SURVIVAL OF KOREAN PATIENTS WITH BREAST CANCER AND CLINICAL FACTORS RELATED TO THE SURVIVAL CHANGES

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Background: Advances in the treatment of breast cancer have contributed to marked improvements in patient outcomes over the past two to three decades. The aim of this study was to evaluate survival of patients with breast cancer chronologically and to investigate whether the observed changes over time.

Methods: Statistics from the Korean National Cancer Registry based on all 60,571 cases of invasive breast cancer during the 21-year period 1988-2008 were analysed. We divided the study period into 4 periods (P1: 1988-1992, P2: 1993-1997, P3: 1998-2002, P4: 2003-2008).

Result: The patients treated in P4 showed significantly better 5-year overall survival (OS) compared with those in the P1 when adjusted for follow-up duration. In the multivariate analyses, younger age, mastectomy in operation methods, high stage, high histologic grade, lymphovascular invasion, progesterone receptor negativity, amplification of human epidermal growth factor receptor 2 and adjuvant chemotherapy were poor prognostic factors. The multivariate analysis demonstrated that periods at diagnosis were significantly and independently associated with overall survival in the overall group of patients. In analysis using age-period-interaction models, Hazard ratio for overall survival of the age under 35 years compared to the older age tended to diminish todays than it was in the past.

Conclusions: The clinical factors related to the survival change of breast cancer have changed in ways that resulted in high overall survival over the past 10 years in Korea, and the surgical management of the disease has changed accordingly. Analysis of nationwide registry data will contribute to a better understanding of the outcome of breast cancer.

EVALUATION OF THE EFFICACY OF PROPHYLACTIC ANTIEMETIC AGENTS ON POSTOPERATIVE NAUSEA, VOMITING AND PAIN IN BREAST CANCER PATIENTS UNDER GENERAL ANESTHESIA

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Background: Postoperative nausea and vomiting (PONV) is one of the uncomfortable symptoms that patients experience after surgery under general anesthesia. The purpose of this study was to evaluate the efficacy of prophylactic antiemetic drugs on PONV and pain in patients with breast cancer surgery.

Methods: We compared the proportion of additional medication of antiemetics and analgesics on the day of the surgery between the control group without the use of prophylactic antiemetics from August 31 to October 5, 2016 and the experimental group with the use of prophylactic palonosetron 0.075 mg from October 31 to November 5, 2016.

Result: A total of 287 patients were enrolled for the study (154 control and 133 experimental groups) excluding 60 patients with plastic or other combined surgery, and 12 patients with benign excision. Demographic characteristics including sex, age, height, weight, BMI and past history were homogeneous between the two groups. The proportion of additionally administered antiemetic drugs in the operating room or the recovery room after surgery was significantly lower in the experimental group ($p = 0.016$). After returning to the ward, there were no significant differences in the administration rate of additional antiemetics ($p = 0.143$) and analgesics ($p = 0.406$) between the two groups.

Conclusions: The use of prophylactic antiemetics undergoing breast cancer surgery under general anesthesia significantly reduced PONV in the early postoperative period. We suggest further study to evaluate efficacy of the administration of prophylactic antiemetics immediately after returning to the ward to alleviate late PONV of the patients.

DEVELOPMENT AND EVALUATION OF RETURN-TO-WORK PROGRAM FOR YOUNG BREAST CANCER SURVIVORS: A PILOT STUDY

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Background: Research has identified barriers and facilitators affecting breast cancer survivors' return to work (RTW) following the end of active treatment. However, there was limited intervention for helping young breast cancer survivors return to work after treatment. This study aims to develop and evaluate mind and body based return to work program among young breast cancer survivors.

Methods: After systematic review, in-depth interview, and network analysis of online community of breast cancer survivors, we developed a 4-weeks group-based education program to help young breast cancer survivors' return to work after cancer treatment. The intervention program was based on mind and body medicine teaching mind-control, balanced diet, physical activities, self-management for altered appearance. The program was provided to 26 young breast cancer patients who worked before cancer diagnosis at an university-based cancer center in Seoul, Korea. Posttraumatic growth, rumination, distress, anxiety, depression and fatigue were assessed before, right after the intervention and 1 month after the intervention.

Result: The mean age of the participants was 41.6 years old and the mean survivor length was 14.1 months. On average, participants had 10.8 years of working experience. There was a statistically significant improvement of posttraumatic growth after the intervention ($p = 0.01$). A significant improvement was shown in terms of relationship with others, personal strength, spiritual change and appreciation of life.

Conclusions: Mind and body based return to work intervention would be effective for young breast cancer survivors and further study is necessary with larger sample for longer follow-up.

EMPLOYMENT STATUS AND WORKING ADJUSTMENT IN BREAST CANCER SURVIVORS

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Background: Breast cancer is one of common cancers in Taiwan and many patients were diagnosed before retirement. As the improvement of cancer treatment, there is growing numbers of survivors and the return-to-work issue becomes more important. Studies have documented that the cancer survivors need assistant for returning to work. Thus, the study aimed to assess the employment status and working adjustment after the completion of primary breast cancer treatment.

Methods: This was a cross-sectional study via mailed survey. A convenience sample of 75 breast cancer survivors was those who were working and have been diagnosed for 2-to-5 years. Working adjustment was measured via Working Ability Index.

Result: The sample had a mean age of 47.1. The majority of them was married, had college or higher education, were working in private sectors and held professional or administrative positions. Most of them had stage 0 to II breast cancer and were not receiving cancer treatment other than adjuvant hormonal therapy. The women reported moderate working difficulty and working adjustment. Half of them has had modified their work time or job assignments after cancer diagnosis. Multivariate analysis revealed that poor working adjustment was predicted by advanced stage, worried about death, cancer care, and less support on work role demand.

Conclusions: Returning to usual work might be difficult for breast cancer survivors. Providing supportive care may help them to adjust for the impact of cancer and to enhance their working adjustment after cancer.

LONG-TERM SURVIVAL PREDICTION FROM HEALTH-RELATED QUALITY OF LIFE IN BREAST CANCER PATIENTS: A PROSPECTIVE COHORT STUDY

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Background: Interest in health-related quality of life (HRQOL) has been increasing recently in breast cancer patients. The purpose of this study is to investigate the relationship between HRQOL and long-term survival in prospective breast cancer cohort.

Methods: Between May 2004 and September 2006, 284 patients who were diagnosed invasive breast cancer, age over 18-years old and absence of other cancers were enrolled in the cohort. Patients were asked to complete the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Quality of Life Questionnaire BR23 (QLQ-BR23) immediately, 3 months and 12 months after breast cancer diagnosis.

Result: Of the 284 patients, 180 (63.4%) responded at the 3 month after diagnosis, and 208 (73.2%) responded at 12 month after diagnosis. Median follow-up periods was 100 months (range: 1.1-152), 5-year overall survival was 92% and 10 year overall survival was 86%. In multivariate analysis, patients who had financial difficulties and breast symptoms (aHR, per 20-point increase in score 1.30 (95% CI 1.07-1.58) and aHR 1.82 (95% CI 1.38-2.40) respectively) showed worse survival at diagnosis. Financial difficulties were significant predictive factors of worse survival in 3 month follow-up analysis (aHR 1.55 [95% CI 1.13-2.12]). In 12 month follow-up analysis, nausea/vomiting (aHR 1.58 [95% CI 0.99-2.54]) and constipation (aHR 1.40 [95% CI 1.07-1.85]) were statistically associated with worse survival.

Conclusions: HRQOL has independent prognostic value for long-term survival in breast cancer patients. Longitudinal assessment of HRQOL is useful to predict long-term survival.

RESULTS OF VICRYL MESH IMPLANTATION AND PATIENT SATISFACTION IN BREAST CONSERVING SURGERY

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Background: Breast conserving surgery (BCS) is standard therapy in breast cancer. To resolve unsatisfaction of breast deformity, using Vicryl mesh into the defect of breast was introduced in 2003, But, the safety and efficacy of this method has not confirmed yet. This study was designed to assess the safety and efficacy of using a Vicryl mesh when performing BCS

Methods: From 11, 2013 to 12, 2015, We performed retrospective analysis between BCS with Vicryl mesh and BCS only groups at out hospital. Age, BMI, underlying disease, mass location, specimen size, tumor size, operation time, malignancy or benign, additional excision, operation method, postoperative wound infection, perioperative treatment, and recurrence were analysed. We also performed oral interviews with these patients regarding overall satisfaction, satisfaction with breast shape, postoperative pain, postoperative motion limitation. Of the total 66 patients, 63 patients were included and 3 patients who refused interview were excluded (BCS with Vicryl mesh = 31, BCS only = 32).

Result: There were no statistically significant differences between two groups. Postoperative wound infection was more frequently occurred in Vicryl mesh group, but this difference was not statistically significant ($p = 0.053$). Univariate & multivariate logistic regression were performed to find factors related to infection, but there was no factor related to infection statistically significant.

Conclusions: BCS with Vicryl mesh showed no significant difference in patients satisfaction compared to BCS only. Although not statistically significant in this study, using Vicryl mesh appears to increase the incidence of postoperative wound infection, so Vicryl mesh insertion should be performed carefully.

EFFECTIVENESS OF PSYCHOEDUCATIONAL INTERVENTION AMONG CANCER SURVIVORS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Psychoeducational intervention (PEI) has been highlighted as a promising education intervention, but the effect of PEI in the management of quality of life and psychological symptoms remains unknown. This study was a systematic review and meta-analysis designed to investigate the effects of psychoeducational intervention among cancer survivors.

Methods: Ten databases were searched. Two reviewers independently performed the selection of the studies, data extraction and assessment. The risk of bias was assessed using Cochrane Collaborations tool. For estimating the effect size, meta-analysis of the studies was performed using Comprehensive Meta-Analysis program.

Result: Of 18,780 publications identified, 35 met inclusion criteria, and 25 studies were used to estimate effect size of psychoeducational interventions. Effect sizes (standardized mean difference [SMD]) were heterogeneous and random effects models were used in the analyses. psychoeducational interventions were effective for quality of life (ES = 0.23; 95% CI = 0.08, 0.38), coping and self-efficacy (ES = 0.68; 95% CI = 0.26, 1.11), anxiety (ES = -0.27; 95% CI = -0.38, -0.14), depression (ES = -0.29; 95% CI = -0.40, -0.17), and psychological distress (ES = -0.29; 95% CI = -0.40, -0.17). Publication bias was not detected except psychological distress.

Conclusions: Psychoeducational intervention appears to be effective in improving quality of life and coping and self-efficacy, and they are effective in reducing psychological symptoms in cancer survivors. However, findings of this study should be interpreted with caution as there is a relative lack of data in this field, and more well-designed studies are needed.

EFFICACY OF THERAPEUTIC AGENT FOR WOUND HEALING, NEO DERMAL ACTIVATOR, ON BREAST SURGERY IN PATIENTS WITH BREAST CANCER

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Background: The purpose of this study is to evaluate the efficacy of dressing material containing plant extracts which is rich in procyanidins, Neo dermal activator (NDA), on surgical wound of breast cancer patients.

Methods: This prospective randomized, controlled study assessed 54 patients who underwent breast cancer surgery. Patients were randomly divided into two groups before definitive surgery in the operating room: 27 patients using NDA and 27 patients using conventional wound care. We applied conventional wound dressing immediately after surgery to the control group and added Neo dermal activator to NDA group. Surgical site infection (SSI) rates within POD 7 were evaluated. After 6 months from surgery, we evaluated wound condition and patient satisfaction using visual analogue scale score.

Result: The mean of age was 54 ± 11.32 years. Patients who received neoadjuvant chemotherapy and those with adjuvant radiotherapy were 18.5% and 68.5%, respectively. SSI rates within POD 7 between two groups were not significantly different. One case of SSI was reported during 1 month after surgery in both groups, respectively. Satisfaction for sense was not different between two groups. Meanwhile, satisfaction for appearance ($p = 0.011$), scar ($p = 0.046$), and self-confidence for wearing exposed clothes ($p = 0.019$) showed higher scores in NDA group. Total score of patient satisfaction was higher in NDA group ($p = 0.019$).

Conclusions: NDA did not influence on SSI rates in patients who underwent breast cancer surgery. NDA may be safe and increase patient satisfaction for postoperative wound care on breast surgery.

INCIDENCE OF PERMANENT CHEMOTHERAPY-INDUCED ALOPECIA AMONG BREAST CANCER PATIENTS: A FIVE-YEAR PROSPECTIVE COHORT STUDY

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Background: While chemotherapy-induced alopecia is considered temporary and usually reversible within 1-6 months after chemotherapy, some patients report persistent alopecia several years after chemotherapy. The frequency of long-term permanent chemotherapy-induced alopecia (PCIA) and hair related changes is unknown. This study aimed to assess the incidence of PCIA among breast cancer patients by quantifying changes in hair density and thickness before chemotherapy, after two cycles of chemotherapy, and one, three, six, and 36 months after completion of chemotherapy

Methods: This was a prospective cohort study of 61 patients 18 years of age or older with a postoperative diagnosis of stage I to III breast cancer who received adjuvant chemotherapy between February and September 2012 at an outpatient breast cancer clinic in Korea. Objective hair density and thickness were measured using a noninvasive bioengineering device.

Result: At 6 months after completion of chemotherapy, 11.5% and 30.8% of patients experienced PCIA in terms of hair density and thickness, which did not recovered until after 36 months after completion of chemotherapy. Patients who received a combination of doxorubicin and cyclophosphamide followed by four additional cycles of paclitaxel were more likely to experience PCIA compared to patients with other type of chemotherapy.

Conclusions: Permanent and severe alopecia is a common side effect of breast cancer adjuvant chemotherapy. Additional research is necessary to translate these findings into interventions for improving distress due to permanent alopecia in breast cancer patients after completion of chemotherapy.

COMPARING MENOPAUSAL SYMPTOMS IN WOMEN RECEIVING ADJUVANT CHEMOTHERAPY AND HORMONE THERAPY FOR BREAST CANCER: 5 YEAR LONGITUDINAL COHORT STUDY

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Background: Multiple randomized trials have shown that adjuvant chemotherapy improves long-term survival for most women with breast cancer. In addition, women with estrogen receptor–positive (ER+) tumors are offered tamoxifen for 5 years after completion of adjuvant chemotherapy. One of the most subtle and chronic adverse effects of adjuvant chemotherapy and hormone therapy is symptoms associated with an accelerated menopause. This study aims to comparing effect of adjuvant chemotherapy, hormone therapy on menopausal symptoms in long-term breast cancer survivors.

Methods: A total of 422 patients with non-metastatic breast cancer who were expected to received adjuvant breast cancer treatments were recruited from July 2010 to July 2011 at two cancer hospitals in Seoul, Korea. Study participants were asked to complete Menopause Rating Scale (MRS) at diagnosis and 12-, 24-, 36-, and 60 months after surgery. To examine changes overtime, mixed effect analysis was performed using STATA 12.

Result: After excluding 35 patients who did not received adjuvant chemotherapy, the final sample was consisted with 385 patients. Among them, 135 received chemotherapy only, 96 received hormone therapy only, and 156 patients received both adjuvant chemotherapy and hormone therapy. Patients with chemotherapy plus hormone therapy were diagnosed with breast cancer at younger age (44.9) compared to patients chemotherapy and patients (48.4) with hormone therapy (45.9). At baseline, patients had more psychological symptoms than somatic or urological symptoms, and patients in different treatment group had similar level of menopausal symptoms. At 12 months after diagnosis, patients were experiencing about 2 times severe somatic and urological symptoms compared to those at baseline and it lasted even after 5 years after diagnosis. While patients with chemo plus hormone therapy experienced more menopausal symptoms than other patients groups, but it was not statistically significant adjusted for baseline age, stage, and menstruation.

Conclusions: Both patients with chemotherapy and patients with hormone therapy experience increased somatic and urological symptoms and it last even 5 years after treatment. Healthcare provider should keep in mind that any anticancer treatment could induce menopausal symptoms which require long-term management.

IMPACT OF MIND AND BEAUTY EDUCATION ON BODY IMAGE AND SEXUALITY AMONG YOUNG BREAST CANCER PATIENTS: A RANDOMIZED CONTROLLED TRIAL

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Background: The proportion of breast cancer patients under 40 years old in Korean is higher than Western countries. Young women with breast cancer are more likely to suffer from altered appearance due to cancer treatment, which leads to lower body image and sexuality. This randomized controlled trial aims to evaluate the effects of mind and beauty education on body image and sexuality among breast cancer patients under 40 years old.

Methods: Breast cancer patients under 40 years old were recruited from August 2014 to April 2015 at hospital in Seoul and randomly assigned to intervention and control. Participants in intervention received structured 8 hours education for 4 weeks (4 hours for mind control and 4 hours for appearance management), while control did not until end of the follow-up. Body image and sexuality were evaluated before the intervention (T1), right after intervention (T2), and 6 months after intervention (T3) using EORTC QLQ-BR23. Linear mixed model and intention-to-treat analysis were performed.

Result: A total of 54 and 55 participants were assigned to intervention and control, respectively. While there was no difference with the mean of body image between two groups at baseline, intervention reported significantly improved body image than control at T2 (mean difference, 16.60; 95% CI, 6.72 to 26.47) and T3 (10.09; 0.05 to 20.13). In addition, patients in the intervention group had better sexual functioning and enjoyment compared to control.

Conclusions: This study suggests potential positive effects of mind and beauty education to improve body image and sexuality in young breast cancer patients who faced unique problems.

THE CLINICAL CHARACTERISTICS OF ASYMMETRIC GYNECOMASTIA: A SINGLE-CENTER EXPERIENCE

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Background: The purpose of this study is to report the clinical characteristics of the asymmetric gynecomastia patients who underwent surgery in our institution.

Methods: From January 2014 to May 2016, 43 out of 1,175 patients who underwent surgery in our hospital had asymmetric gynecomastia. We compare the clinical characteristics (age, body mass index (BMI), classification according to the glandular amount, Simon classification and asymmetry ratio) of patients with and without the asymmetry. According to Simons classification, results of aforementioned variables were also compared in asymmetric cases.

Result: 3.7% of gynecomastia patients show asymmetry. In these cases, larger left breast cases were more common (73.5% vs. 26.3%). There were no significant differences in the age and breast size according to the Simons classification. BMI was significantly higher in patients without asymmetry (25.5 ± 3.37 vs. 24.1 ± 2.63). Patients with asymmetry had more true-type (entirely glandular) gynecomastia based on the amount of glandular amount (73.5% vs. 43.4%). Asymmetry ratio was also significantly higher in the group with asymmetry (3.74 ± 8.91 vs. 0.26 ± 0.51). According to the Simon classification in asymmetric cases, age, classification according to the amount of glandular tissue and asymmetry ratio showed no significant differences. Statistics revealed that BMI was directly proportional to the breast size according to Simons classification.

Conclusions: Asymmetry of gynecomastia is commonly observed yet the diagnostic criteria according to the breast size or tissue amount hasn't been reported. Further studies are planned to provide more accurate diagnostic standard.

FIBROADENOMAS ARISING FROM ACCESSORY BREAST TISSUE

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Background: Accessory breast has received little attention in its screening, although it is common occurring in 2–6% women. It develops the same pathological changes as the normally located breast tissue such as inflammation, fibroadenoma, phyllodes tumor, and carcinoma.

Methods: Of 1452 patients who have been treated with an excision of accessory breast tissue from September 2012 to November 2016 at the Damsoyu Hospital, patients with fibroadenoma proven by pathological report were analyzed for clinical factors retrospectively.

Result: Fifteen patients had accessory breast tissues with fibroadenoma (1.03%). Unmarried patients were 11 (73.3%), and married patients were 4 (26.6%). The age of the patients ranges from 24 to 48 years. The major clinical manifestations were cyclic pain with palpable mass and cosmetic problem. The size of tumor ranges from 2 mm to 36 mm. 11 patients were diagnosed to fibroadenoma arising from accessory breast tissue on preoperative breast ultrasound examination. 4 patients were diagnosed to fibroadenoma arising from accessory breast tissue only by pathological reports after operation.

Conclusions: In conclusion, breast surgeons should keep in mind that accessory breast tissues can develop any tumorous conditions as normally located breast tissue and when tumors or nodules are found along the mammary line, the presence of accessory breast tissue should be considered during the investigation.

INVASIVE MUCINOUS CARCINOMA OF THE BREAST COEXISTING WITH DUCTAL CARCINOMA IN SITU: A CASE REPORT

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Background: There are a multifarious of breast tumor with mucin production. Mucinous carcinoma of the breast is the most common type among them.

Methods: A 56-year-old female patient presented to a palpable mass in the right breast (a firm, painless tumor). There was no palpable lymph node in the axillary or supraclavicular region. Mammography showed a high density lobulated shaped mass in the upper inner portion of the right breast. Ultrasonography evidenced a 1.0 cm × 0.8 cm lobulated hypoechoic solid mass without any calcification. Surgical excision was formed in other hospital and pathologic examination showed invasive mucinous carcinoma. MR image showed persistent enhancement exist in peripheral portion of the previous excision site. Surgical re-excision was performed the specimen include ductal carcinoma in situ.

Result: Pathologic specimen showed the tumor was biphasic; Tumor consists of well differentiated tumor cells floating in a sea of lightly staining amorphous mucin. Considerable amounts of carcinoma in situ components are noted in the periphery of the tumor (Hematoxylin and Eosin stain, × 100).

Conclusions: We report a rare case of invasive mucinous carcinoma of the breast tumor coexisting with ductal carcinoma in situ in a 56-year-old female patient.

UNUSUAL PRESENTATION OF PACHYMENINGITIS IN COEXISTING OF VULVAR PAGETS DISEASE AND BREAST CANCER: A CASE REPORT

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Background: Pachymeningitis is an uncommon clinical finding of metastatic breast cancer; however, complete investigation would strongly recommended in patient with focal meningeal enhancements. Few studies have been reported coexisting Pagets disease of the vulva and breast cancer, but little is well-known about the incident of concurrent tumors with multiple visceral and leptomeningeal involvements. Here, we reported the unique case of breast cancer with coexisting primary extramammary Pagets disease of the vulva that metastasized to brain, liver and bone which is even extremely uncommon.

Methods: A 49-year-old Thai woman presented with progressive headache and diplopia for 1 month with preceding pruritic rashes at vulva for 5 months. Physical examination showed multiple cranial nerve palsies without breast mass or lymphadenopathy, but presented with a large scaly erythematous patch at vulva.

Result: Neuroimaging revealed pachymeningitis at right frontoparietal convexity and thickening of cavernous sinus. Biopsy at right middle turbinate reported carcinoma with positive AE1/AE3, CK7, ER, and GCDFP 15 staining, while biopsy at the lesion at vulva showed Pagets cells within epidermal layer of the vulvar with positive CK7, CEA and GCDFP-15 and negative CK20 staining. Biopsy at right breast mass similarly showed invasive ductal carcinoma. Metastatic work up revealed multiple liver and bone metastases. The patient was treated with hormonal treatment and radiation. Other additional results were to be evaluated.

Conclusions: Metastatic cancer to dura, liver and bone with the coexisting of Pagets disease of vulva and breast cancer was extremely rare and very challenging in diagnosis.

SOLITARY LIVER METASTASIS AFTER FIVE YEAR OF DUCTAL CARCINOMA IN SITU WITH BILATERAL MASTECTOMY AND BREAST RECONSTRUCTION: A CASE REPORT

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Background: Ductal carcinoma in situ (DCIS) developed with distant metastasis (DM) is extremely uncommon. Solitary metastasis is even extremely rare. Most patients with DM have a preceding invasive locoregional recurrence. The median time from diagnosis of DCIS to diagnosis of DM is varying from 1.44-7.88 years. Hereby we reported the single liver metastasis in patient after 5 years of DCIS treatment.

Methods: A 51-year-old Thai woman presented abnormal calcification in right breast from screening mammogram. She underwent needle-localized wide excision both breasts. Pathology reported a 1.9 cm DCIS and scattered DCIS on left and right breast, respectively. Immunohistochemistry showed ER 80%, PR 30% and HER-2 2+. Then bilateral subcutaneous mastectomy, axillary lymph node dissection and breast reconstruction were performed. She received postoperative radiation and tamoxifen for prevention.

Result: Five year after first diagnosis, her CA15-3 was rising to 112 IU/mL. But, neither breast local recurrence nor other distant metastases except single 8.9 cm liver nodule at segment VI were identified by imaging. Metastatectomy revealed pathological result of metastatic invasive ductal carcinoma with ER 90%, PR 70%, HER-2 negative. She had 4 cycles of adjuvant docetaxel and cyclophosphamide. Until now, she still be on treatment with letrozole.

Conclusions: Distant metastasis from DCIS is unusual, mostly presented with multiple metastatic sites. If the solitary metastasis is suspicious, the biopsy proven prior to surgery is necessary.

SUCCESSFUL MANAGEMENT OF SYNCHRONOUS MALE BREAST CANCER WITH RECURRENT MESENTERIC SARCOMA PREVIOUS TREATMENT TO ACUTE MYELOID LEUKEMIA: A CASE REPORT

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Background: The incidence of synchronous multiple primary cancers is rise due to improvements and increasing use of diagnostic modalities such as computed tomography scanning and positron emission tomography scanning. One of the important factors that affect survival rate to cancer is early detection and appropriate treatment to disease.

Methods: Twenty two years ago, he was diagnosed and treated for acute myeloid leukemia at another hospital. In 2011, He was diagnosed with liposarcoma on mesentery and underwent surgery. Follow up computed tomography (CT) scan showed a small enhancing nodular lesion in left breast and 5 cm sized heterogeneous enhancing mass at left inner quadrant mesentery. Ultrasonography (US)-guided core needle biopsy was performed on the breast and mesenteric lesion and the histopathological examination of the biopsy specimen revealed invasive breast carcinoma, no special type and sarcoma.

Result: A 46-year-old man who presented diagnosed with breast cancer and mesenteric liposarcoma and underwent left subcutaneous mastectomy and mesentery and small bowel resection in 2014. He received four cycles of an adjuvant chemotherapy regimen and hormonal therapy by tamoxifen. He has now 33 months of follow-up, still treatment by tamoxifen.

Conclusions: We report a case of a man who was successfully managed for synchronous male breast carcinoma and recurrent mesenteric sarcoma previous treatment to acute myeloid leukemia treatment.

DESMOID TYPE FIBROMATOSIS OF THE BREAST AFTER AUGMENTATION MAMMOPLASTY WITH IMPLANT

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Background: Desmoid-type fibromatosis of the breast is exceedingly rare fibroblastic tumor. Desmoid-type fibromatosisis is frequently locally aggressive. The breast and axilla is an unusual location for the development of this tumor.

Methods: We report a case of desmoid-type fibromatosis in the breast in a 50-year-old female who presented with painful and fixed hard masses in breast and axilla. One year previously, she had undergone bilateral breast augmentation with implant.

Result: The result of core needle biopsy was benign mesenchymal lesion. She underwent mass excision and revision of augmentation. Masses were located along the capsule of implant. Final pathology showed a desmoids-type fibromatosis with focally positive margin, without muscle or fascial involvement. Because she had large implant and she didn't want to remove the implant, no further intervention was performed. After 2 years, she had recurrence, and wide excision was performed. Pathology result was desmoids type fibromatosis and lobular carcinoma in situ. She started to take tamoxifen without radiation therapy.

Conclusions: There were few cases which desmoids type fibromatosis after augmentation with implant.

VALIDITY, UTILITY AND TECHNICAL CONSIDERATIONS IN EXPANDED PANEL TESTS FOR HEREDITARY BREAST CANCER

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Background: Gene panel tests for hereditary breast cancer are rapidly emerging, although important questions remain: First, can cost-effective test methods deliver equal or superior performance as traditional methods on the full spectrum of disease causing variants? Second, do these tests provide medical benefits which outweigh the increased uncertainty that naturally follows from testing more genes in more patients?

Methods: We examined records for over 50,000 patients tested for 80 cancer risk genes, including comparable results for 20,000 patients from public databases. A prospectively accrued cohort of over 1,000 patients was used to evaluate management implications of panel versus traditional tests.

Result: Approximately 50% of positive findings from expanded panel tests would warrant consideration of changes in management (under NCCN guidelines) compared to traditional genetic tests. The majority of panel findings are consistent with the personal (70%) and family (90%) history of each patient, although most of these genes would not have been indicated for testing under traditional guidelines. Classifications (pathogenic vs. not-pathogenic) of genetic variants produced using public literature and rigorously following a system based on ACMG guidelines were highly (99.8%) consistent with those produced by incumbent laboratories with large proprietary databases. However, many (13%) of these variants would not be detected using off the shelf NGS laboratory technologies and require specialized methodologies to report.

Conclusions: Modern genetic tests offer substantial advantages compared to prior clinical standards. Global laboratories can and must implement sophisticated variant detection and classification procedures to realize these important advantages for their patients.

THE ANALYSIS OF BREAST CANCER CASE IN THE CENTRAL POLICLINIC OF KHABAROVSK, RUSSIA

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Background: The breast cancer takes leading positions among the female population with oncological diseases, and in the Far East region indicators of disease make 41,0 cases, mortality 16,4 cases on 100 thousand population. Unfortunately, that Breast cancer (BC) is diagnosed in the III-IV stages in 60% causes. Also a share of active identification of mamma pathology is very low.

Methods: Thus, the purpose of our work was studying of data on cases of breast cancer in the central policlinic of Khabarovsk, chosen casually. 464 cards of the account which correspond to number of observed patients with BC diagnosis that makes 9% from the attached population of policlinic were analyzed.

Result: The tumor was actively revealed only at 3,88% people. Nontheless, social status of the majority observed was presented as women with a higher education, Authors would like to notice, that 19 ladies from 464 (4,1%) were medicine workers, 12 from them (2,3%) were doctors. The majority of tumors were found out on 3-4 stages, there was a big percent of inoperable tumors and breast cancer in young women group.

Conclusions: Thus, despite on information of mammas self- checkup, calling of plural specialists to sight of mammas, the obligatory mammagraphia above 39 years the activity revelations of breast cancer are not just taken place. So, it will need the greatest work on BC preventive measures, especially the risk factors of breast cancer by help of the active questionnaire, a information systems creation of analyses of risk factors, the taking of women with risk factors into account and more activity observation this cohort

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[Indication] 1 Breast Cancer • Metastatic and locally advanced breast cancer 1) 1st line treatment of patients with locally advanced or metastatic breast cancer in combination with doxorubicin. 2) In combination with trastuzumab, treatment of patients with HER2 overexpressed (IHC 3+ or FISH positive) and chemotherapy naive metastatic breast cancer which is overexpressed HER2 (IHC 3+ or FISH positive) and have not treated with chemotherapy. 3) Treatment of patients with locally advanced or metastatic breast cancer in whom previous chemotherapy has failed. 4) In combination with capecitabine, treatment of patients with locally advanced or metastatic breast cancer in whom previous chemotherapy has failed. Previous therapy should have included an anthracycline. • Adjuvant breast cancer 1) Adjuvant treatment with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with: -operable node-positive breast cancer - operable node-negative breast cancer with one or more high risk factors, (tumor size ≥2 cm, age <35 years, estrogen/progesterone receptor status negative, tumor grade 2 or 3) 2) Doxorubicin and cyclophosphamide followed by TAT in combination with trastuzumab is indicated for the adjuvant treatment of patients with operable breast cancer whose tumors overexpress HER2/neu. TH regimen (docetaxel/trastuzumab) or TAC regimen (docetaxel/doxorubicin/cyclophosphamide) followed by trastuzumab monotherapy is indicated for the adjuvant treatment of patients with operable breast cancer (primary tumour of ≥1 cm and <7 cm). (TC regimen) **2 Non-Small Cell Lung Cancer :** Treatment of patients with locally advanced or metastatic non-small cell lung cancer, including those who have failed platinum-based chemotherapy. **3 Prostate Cancer :** Treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer in combination with prednisolone. **4 Ovarian Cancer :** 1st line therapy for the treatment of patients with advanced or metastatic epithelial ovarian cancer in combination with carboplatin. **5 Head and Neck Cancer :** In combination with cisplatin and fluorouracil, induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck. **6 Gastric cancer :** Advanced and metastatic adenocarcinoma of the stomach including adenocarcinoma of the gastroesophageal junction, previously untreated. **7 Esophageal cancer :** Advanced or recurrent squamous cell carcinoma of the esophagus not amenable to curative therapy. **[Dosage and Administration] 1 Breast Cancer** • Metastatic and locally advanced breast cancer 1) For the 1st line treatment of breast cancer, docetaxel 75mg/m² is given in combination therapy with doxorubicin (50mg/m²) 2) In combination with trastuzumab for the treatment of HER2 overexpressed and chemotherapy naïve metastatic breast cancer, the recommended dose of docetaxel is 100 mg/m² as a 60-minute infusion every three weeks. Initial docetaxel infusion can be started the day following the first dose of trastuzumab. The docetaxel doses can be administered immediately after completion of the trastuzumab infusion, if the preceding dose of trastuzumab was well tolerated. The recommended initial dose of trastuzumab is 4mg/kg as 90-minute intravenous infusion. The recommended weekly dose of Herceptin is 2 mg/kg, beginning one week after the initial dose. (Refer to the product information of trastuzumab.) 3) For the treatment of breast cancer in whom previous chemotherapy has failed, docetaxel 75-100 mg/m² is administered as a one-hour infusion every three weeks. 4) In combination with capecitabine, for the treatment of locally advanced or metastatic breast cancer in whom previous chemotherapy including anthracycline has failed, the recommended dose of docetaxel is 75mg/m² every three weeks, combined with capecitabine at 1250 mg/m² twice daily (within 30 minutes after a meal) for 2 weeks followed by 1-week rest period. For capecitabine dose calculation according to body surface area, see capecitabine package insert. • Adjuvant breast cancer 1) In the adjuvant treatment of operable node-positive and node-negative breast cancer, the recommended dose of docetaxel is 75 mg /m² administered 1-hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks for 6 cycles(TAC regimen). Prophylactic G-CSF may be used to minimize the risk of hematological toxicities (See Dosage adjustments during treatment). 2) ACT-H regimen (1) AC: cycles 1-4): doxorubicin (A) 60 mg/m² followed by cyclophosphamide (C) 600 mg/m² administered every three weeks for 4 cycles. (2) TH (cycles 5-8): docetaxel (T) 100 mg/m² administered every three weeks for 4 cycles, and trastuzumab (H) administered weekly according the following schedule. - Cycle 5 (starting three weeks after the last cycle of AC): Day 1: trastuzumab 4 mg/kg (loading dose) Day 2: docetaxel 100 mg/m² Days 8 and 15: trastuzumab 2 mg/kg - cycles 6-8: Day 1: docetaxel 100 mg/m² and trastuzumab 2 mg/kg Days 8 and 15: trastuzumab 2 mg/kg three weeks after day 1 of cycle 5 trastuzumab 6 mg/kg is given every three weeks. (3) Trastuzumab is administered for a total duration of 1 year. 3) TCH regimen (1) Docetaxel (T) 75 mg/m² for 1 hour and carboplatin (C) at AUC of 6 mg/mL/min administration over 30 to 60 min every three weeks. Day 2 of cycle 1, Day 1 of cycle 2–6. (2) trastuzumab (H) 4 mg/kg for 90 min in day 1 as loading dose, then weekly administered 2 mg/kg for 30 min as maintenance dose. (3) Trastuzumab 6 mg/kg for 30 min is given every three weeks after completion of adjuvant chemotherapy. Trastuzumab is administered for a total duration of 1 year. 4) TC regimen: TAXOTERE 75mg/m² over 1 hour and cyclophosphamide 600mg/m² as intravenous administration over 30 to 60 minutes on day 1 of a 21 day cycle for a total of four cycles. Premedication with oral dexamethasone 8mg bid or daily is administered commencing 1 day before administering TAXOTERE, and continuing for a total of five doses. **2 Non-Small Cell Lung Cancer :** The recommended dosage of Docetaxel is 75 mg/m² administered as a one-hour infusion every 3 week. Maximum dosage is 75mg/m² at platinum-combined chemotherapy. **3 Prostate Cancer :** The recommended dosage of docetaxel is 75 mg/m² administered as a one-hour infusion every 3 week. Prednisolone 5 mg orally twice daily is administered continuously. **4 Ovarian Cancer :** As the 1st line therapy for advanced or metastatic ovarian cancer, docetaxel 75 mg/m² administered as a one-hour infusion every three week. Then carboplatin 6.0 mg/ml·min (AUC) is intravenously administered during 30–60 min. **5 Head and Neck Cancer :** 1) Induction chemotherapy followed by radiotherapy : For the induction treatment of inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75 mg/m² as a 1 hour infusion followed by cisplatin 75 mg/m² over 1 hour, on day one, followed by fluorouracil as a continuous infusion of 750 mg/m² per day for five days. The regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy. 2) Induction chemotherapy followed by chemoradiotherapy : For the induction treatment of patients with locally advanced (technically unresectable, low probability of surgical cure, and aiming at organ preservation) squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75 mg/m² as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m² administered as a 30-minute to 3-hour infusion, followed by fluorouracil 1000 mg/m²/day as a continuous infusion (from day 1 to day 4). This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemoradiotherapy. **6 Gastric Cancer :** 1) As single agent, the recommended dosage of docetaxel is 75mg/m² administered as a one-hour infusion every three weeks. 2) The recommended dose of docetaxel is 75 mg/m² as a 1-hour infusion, followed by cisplatin 75 mg/m², as a 1-to 3-hour infusion (both on day 1 only), followed by fluorouracil 750 mg/m² per day given as a 24-hour continuous infusion, for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration. Prophylactic G-CSF should be used to mitigate the risk of hematological toxicities. **7 Esophageal Cancer :** The recommended dosage of docetaxel is 70mg/m² administered as one-hour infusion every 3–4 weeks, and the dosage may be reduced or increased depending on the condition of patients **<Premedication Regimen>** All patients should be premedicated prior to TAXOTERE administration in order to minimize fluid retention and severe hypersensitivity reaction. Such premedication consisting of oral corticosteroids such as dexamethasone 16 mg per day (ex, 8mg bid) for 3 days starting one day prior to TAXOTERE administration. should be used unless it is contraindicated. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities. **<Dosage adjustments during treatment>** Frequent monitoring of neutrophil counts should be performed during TAXOTERE therapy. Dosage should be adjusted if necessary depending on neutrophil counts. **[Precautions] <Contraindications>** 1) Hypersensitivity reactions to TAXOTERE or Polysorbate 80. 2) Patients with baseline neutrophil count of <1,500 cells/mm³. 3) Patients with severe liver impairment. 4) When combined with other medicinal products, contraindications for those products also apply (severe renal impairment, hypersensitivity to paraplatin, Pe-compounds and/or mannaditol). 5) Patients with complications of infections (infections could be worsened or fatal) 6) Patients who are suspected to have infectious fever (infections could be worsened or fatal) 7) Patients who have severe myelosuppression (severe infection could be occur or fatal) **<Special Precautions in Use>** 1) Patients with myelosuppression 2) Patients with liver impairment (See 5. General precautions) 3) Patients with renal impairment 4) Patients with pneumonia interstitialis or pulmonary fibrosis 5) Patients with edema 6) Patients [both men and women] having contraceptive measures must be taken during treatment, and for men at least 6 months after cessation of therapy.) ※ Please refer to package insert or homepage for the details. sanofi -aventis Korea Co., Ltd. 235, Banpo-daero, Seocho-gu, Seoul T.02-2136-3000 F.02-2136-3249 www.sanofi.co.kr

[제품명] 허쥬마주 150mg,440mg(트라스투주맙)단클론항체, 유전자재조합 **[주성분]** 트라스투주맙 **[효능·효과]** HER2 양성 전이성 유방암, HER2 양성 조기 유방암, 전이성 질환으로 이전에 항암치료를 받은 적이 있는 HER2 양성 전이성 위 선암이나 위식도 접합부 선암 **[용법·용량] 유방암 · 전이성 유방암** : 이 약 단독요법 및 파클리탁셀, 도세탁셀, 아로마타제 억제제와의 병용요법 시 이 약의 권장용량은 다음과 같다. **1) 1주 요법**—초기부하용량 : 권장 초기부하용량은 4mg/kg이다. 유지용량 : 권장 유지용량은 매주 2mg/kg이며 초기부하용량 투여 1주일 후부터 투여를 시작한다. **2) 3주 요법**—초기부하용량 : 권장 초기부하용량은 8mg/kg이다. 유지용량 : 권장 유지용량은 6mg/kg이며 초기부하용량 투여 3주 후부터 투여를 시작한다. 도세탁셀과 파클리탁셀의 병용요법 : 이 약의 최초 투여시에는 이 약 투여 다음날에 파클리탁셀 또는 도세탁셀을 투여한다. 최초 투여에 내약성이 우수한 경우, 이후 투여시에는 이 약 투여후 즉시 파클리탁셀 또는 도세탁셀을 투여할 수 있다. 아로마타제 억제제와의 병용요법 : 이 약과 아로마타제 억제제는 첫날에 모두 투여한다(투여순서는 상관없음). **• 조기 유방암 : 1) 3주 요법** : 초기 부하용량으로 8mg/kg을 투여하고 이후 매 3주마다 유지용량으로 6mg/kg을 투여한다. **2) 1주 요법** : 인트라싸이클린과 싸이클로포스파미드 병용 화학요법실시후, 초기부하용량으로 4mg/kg을 투여하고 이후 1주마다 2mg/kg을 유지용량으로 투여한다. 이때는 파클리탁셀과 병용투여한다. **전이성 위암 : 1) 3주 요법** : 초기 부하용량으로 8mg/kg을 투여하고 이후 매 3주마다 유지용량으로 6mg/kg을 약 90분에 걸쳐 점적주입한다. 초기 부하 용량에 내약성이 우수한 경우 유지용량은 30분에 걸쳐 주입할 수 있다. **[사용상의 주의사항] 1. 경고** : 1) 심장독성 : 트라스투주맙 투여 시 울혈성 심부전(뉴욕심장학회(NYHA)등급 Ⅱ-Ⅳ등급) 또는 무증상 심기능 장애의 위험이 증가할 수 있다. 2) 주입관련 반응, 알러지성 반응 및 과민반응 : 주입관련 반응의 발생 위험을 감소시키기 위해 전 처치를 할 수도 있다. 3) 폐 이상반응 : 드물게 증증 폐 이상반응이 나타 후 조사에서 보고되었으며 이는 致死로 귀결되었 수도 있다. **2. 다음환자에게 투여하지 말 것.** 1) 트라스투주맙, 설치류 유래 단백 또는 트라스투주맙의 구성성분에 과민반응 병력이 있는 환자 2) 진행성 악성종양에 의한 중증 안정 시 호흡곤란 또는 산소보충이 필요한 환자 **※ 제품에 대한 자세한 정보는 최신의 제품설명서를 참고하시길 바라며 홈페이지를 통해 확인하실 수 있습니다.**

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