

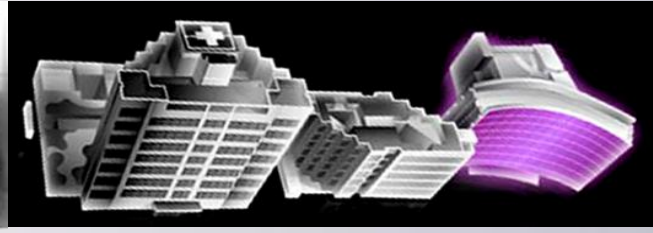

Individualized Overall Treatment Programs for Patients with Loco-regional Recurrence

2011. 10. 6

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Contents

- Definition of Loco-regional Recurrence (LLR)
- Pattern of LLR
- Prognosis after LRR
- Treatment strategy for LLR
- Molecular subtypes and LLR
- Individualized treatment strategy for LLR

Definition of Loco-regional Recurrence

- LRR = “local recurrence” + “regional recurrence”
  - discrimination of ‘local’ and ‘regional’: not easy
  - different pattern of LRR according to the initial local treatment
    (1) BCS vs Mastectoy
    (2) with or without radiation
- Local Recurrence
  - local treatment failure
  - chest wall, skin, scar, ipsilateral breast tumor recurrence (IBTR)
- Regional Recurrence
  - regional treatment failure
  - internal mammary, supraclavicular, ipsilateral axillary nodes

IBTR vs. ipsilateral second tumor

- Factors suggesting a second tumor
  - ✓ A long interval of time since the first tumor
  - ✓ A different location in the breast
  - ✓ Different tumor biology (ER/PR status, HER2-receptor status)

Incidence of LLR

- Factors
  - initial tumor stage, tumor biology, previous treatment
  - sensitivity of the diagnosis
- 10-year incidence of LRR
  - 13% (IQR 9–26%) after mastectomy
  - 12% (IQR 7–15%) after breast conserving therapy
- 5-year overall survival rates from the time of recurrence
  - 81% after IBTR
  - 68% after isolated chest wall recurrence
- LLR: often with simultaneous or antecedent distant metastases
  - About 10% of IBTR after BCS & 35% of LRR after mastectomy

  → "Is it isolated LRR or a prodrome of systemic metastasis?"

Clemons M, Cancer Treatment Reviews 2001; 27: 83–97

Sites of LRR after BCS

- 1,312 early stage breast cancer pts
  - BCS & axillary LN sampling or dissection with adj. radation to the breast ± ipsilateral lymphatics
- LRR: 108 events (8.2%)

Site	Ipsilat Breast	Ipsilat Axilla	Ipsilat Breast & Axilla	contralat Breast	Ipsilat Axilla & Bilat Breast	Bilat Breast	Total
LRR events	36	25	10	35	1	1	108
	33.3%	23.1%	9.3%	32.4%	0.9%	0.9%	100.0%

Montgomery DA, Glasgow Royal Infirmary, Scotland. Br J Cancer. 2007 Jun 18;96(12):1802-7.

Sites of LRR after BCS

- retrospective study, 764 consecutive pts with invasive cancer (BCS without neoadjuvant chemotherapy (1995-2008))
- median follow-up time: 41.5 months (range = 3–158)
- LRR: 30 events (3.9%)

Site	IBTR	Axillary LN	Supraclavicular LN	Chest wall & skin	Internal Mammary	Total
LRR events	12	8	6	3	1	30
	40.0%	26.7%	20.0%	10.0%	3.3%	100.0%

Li S, Fudan University, Shanghai. Ann Surg Oncol. 2011 Sep;18(9):2492-9.

Sites of LRR after BCS & Mastectomy

- 895 tamoxifen-treated node negative and ER positive patients
  - 668 from NSABP B-14 (1982-88)
  - 227 from NSABP B-20 (1988-93)
- Median follow-up time for LRR: 13.9 & 10.6 years respectively

the First LLR Sites Among Tamoxifen-Treated Patients
From NSABP Trials B-14 & B-20 According to Type of Initial Treatment (N=895)

Type of Initial Treatment	Group Total (No)	Local Recurrence			Regional Recurrence			Total
		IBTR	Chest Wall	Scar	Axilla	Supra-clavicular	Local & Regional	
Lumpectomy + RTx	390	34	3	0	1	3	1	42 (10.7%)
		81.0%	7.1%	0.0%	2.4%	7.1%	2.4%	100.0%
Mastectomy	505	0	17	1	9	3	1	31 (6.1%)
		0.0%	54.8%	3.2%	29.0%	9.7%	3.2%	100.0%

Mamounas EP, J Clin Oncol 2010 Apr;28(10):1677-83.

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Mamounas EP, J Clin Oncol 2010 Apr;28(10):1677-83.

Pattern of LRR after BCS & Mastectomy

- Local Recurrence after BCS
  - fairly occur at a constant rate during the first decade of treatment
  - IBTR presents as a mass, thickening at the lumpectomy site
  - new abnormality on mammography / ultrasound

- Local Recurrence after mastectomy
  - most local recurrences within 4 years after surgery
  - chest wall recurrence as an asymptomatic nodule under the skin
  - typically near the mastectomy scar

- Regional recurrences
  - axillary, supraclavicular, internal mammary lymph nodes
  - with or without simultaneous local recurrence

Punglia RS, N Engl J Med. 2007 Jun 7;356(23):2399-405.

Prognosis after LRR in simple mastectomy

- prospective study for staging of patients with first recurrence of breast cancer
- 140 patients with simple mastectomy who experienced LRR (1983–1985)
- Median follow up: 10.4 years

- 78 pts → distant metastases to soft tissue (32%), bone (45%), viscera (40%)
- Median time to dissemination (*p=0.05*)
  - regional node recurrence: 3.7 years
  - chest wall recurrence only: 6.5 years

- Specific time sequence in the anatomical distribution: not observed
- Anatomical site of recurrence by prognostic factors: not predicted

- 1/3 of pts treated with local treatment only
  → survive 10 years without distant metastases

Kamby C, Finsen Centre, Denmark. Breast Cancer Res Treat. 1997 Sep;45(2):181-92.

Prognosis after LRR in BCS a/t N status

Node negative pts

- **3,799 women**
- **NSABP B-13, B-14, B-19, B-20, B-23**
- **BCS + RTx ± Adj. systemic therapy**
- 12-yr cumulative incidence
  (in Adj. systemic therapy pts)
  - IBTR: 6.6%, other LRR: 1.8%
- LRR occurred within 5 years
  - IBTR: 37.1%, other LRR: 72.7%
- 5-year OS rates
  - IBTR: 76.6%, other LRR: 34.9%
- early LRF had worse OS
- mortality related factor
  - Older age, BMI, T, occurrence of LRR, ER

Node positive pts

- **2,669 women**
- **NSABP B-15, B-16, B-18, B-22, B-25**
- **BCS + RTx + Adj. systecmic therapy**
- 10-yr cumulative incidence
  - IBTR: 8.7%, other LRR: 6.0%
- Most LRR occurred within 5 years
  - IBTR: 62.2%, other LRR: 80.6%
- 5-year OS rates
  - IBTR: 59.9%, other LRR: 24.1%
- LRR related factor
  - age, T, N, ER, PR
- Hazard ratios for mortality
  - IBTR: 2.58 (95% CI: 2.11-3.15)
  - other LRR: 5.85 (95% CI: 4.80-7.13)

Anderson SJ, J Clin Oncol. 2009 May 20;27(15):2466-73.
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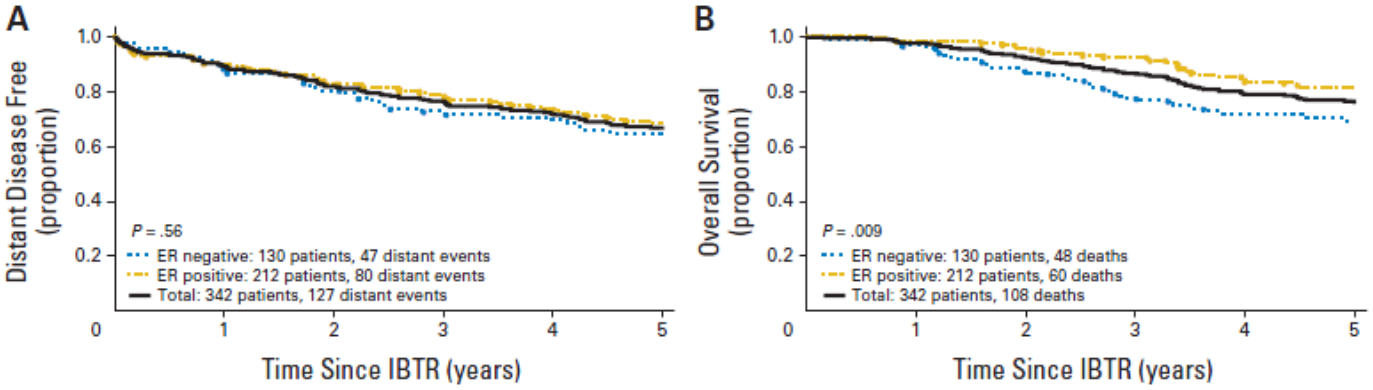
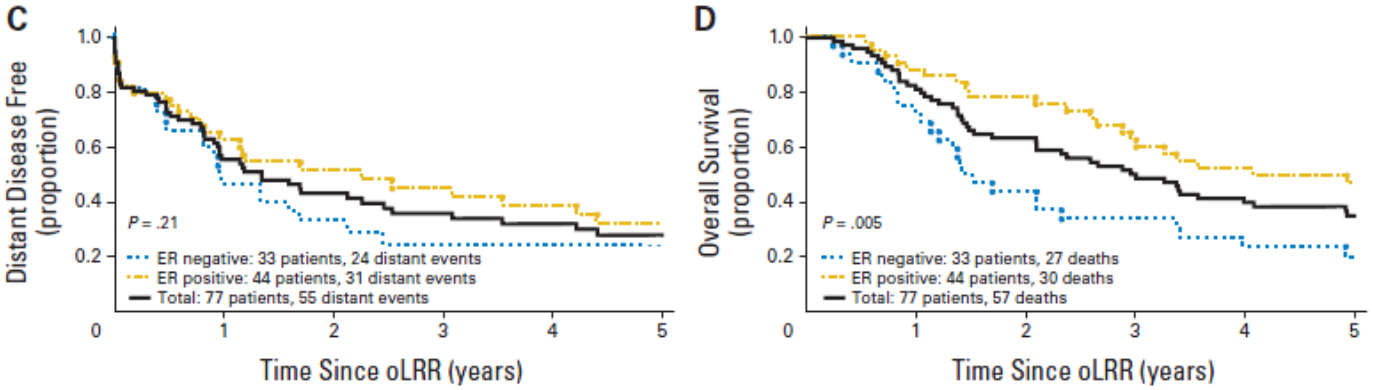
Anderson SJ, J Clin Oncol. 2009 May 20;27(15):2466-73.
Wapnir IL, J Clin Oncol. 2006 May 1;24(13):2028-37.

Survival after LRR in BCS N0 pts (by ER)

IBTR



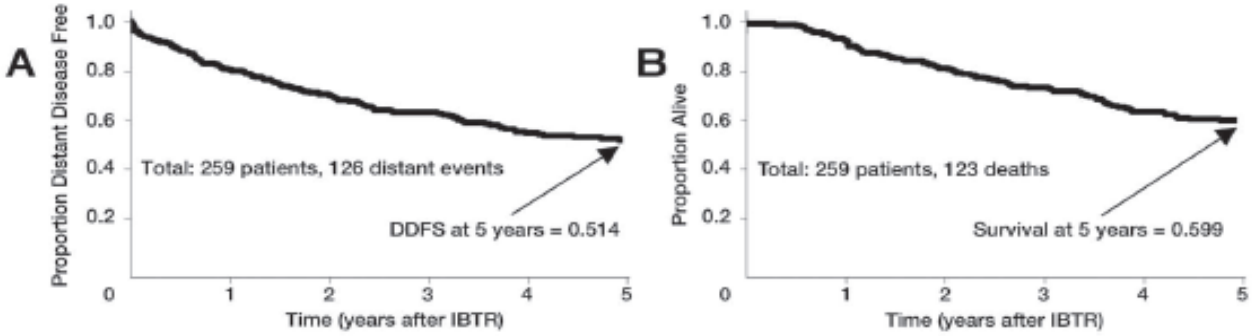
other LRR



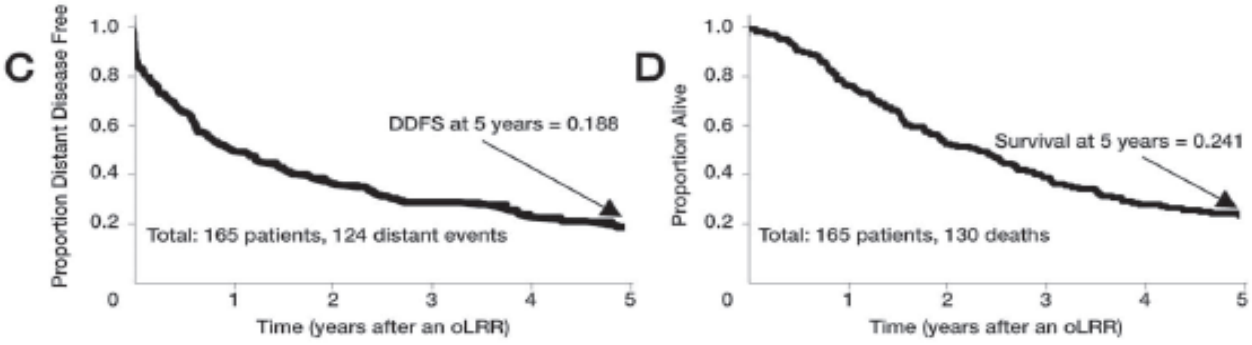
Anderson SJ, J Clin Oncol. 2009 May 20;27(15):2466-73.

Survival after LRR in BCS N(+) pts

IBTR



other LRR



Wapnir IL, J Clin Oncol. 2006 May 1;24(13):2028-37.

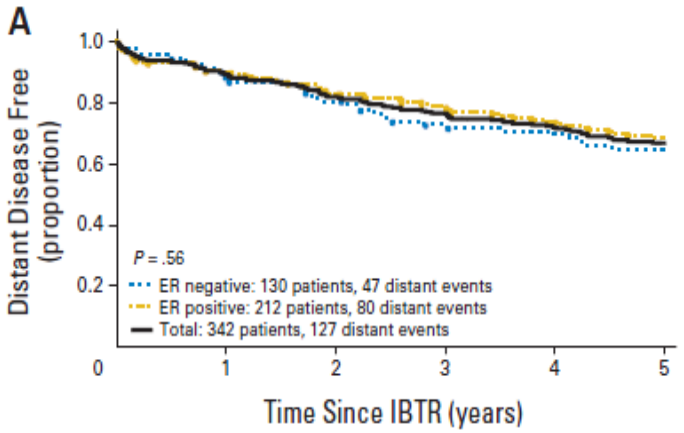
Hypotheses regarding the behavior of LRR

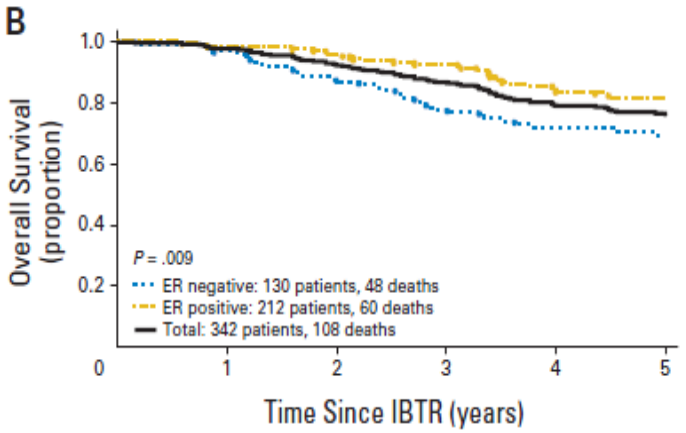
- Halstedian theory
  - breast cancer cells spread over time in a contiguous manner away from the primary site through lymphatics
  - complete local control
- Fisherian theory (systemic theory)
  - breast cancer is a systemic disease from the time of primary diagnosis
  - LN status/LRR: markers of risk rather than source of distant metastases
  - focus on systemic therapy
- "Alternative" or "Spectrum" theory
  - breast cancer is a heterogeneous disease
  - from what remains local disease to systemic one when first detectable

- treatment of LRR can be beneficial or useless? According to what?

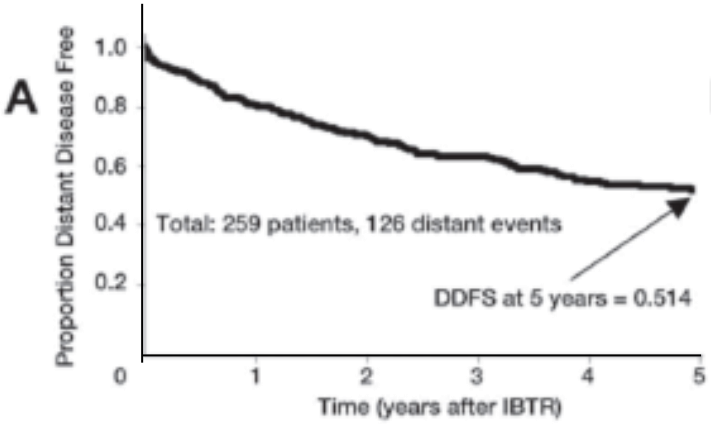
Survival after IBTR in BCS

Node (-)





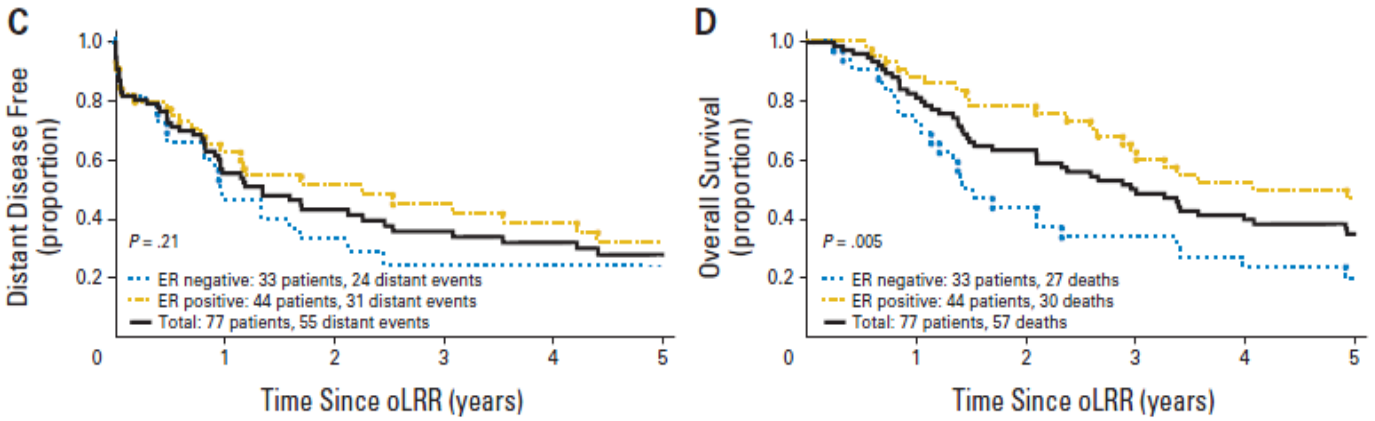
Node (+)



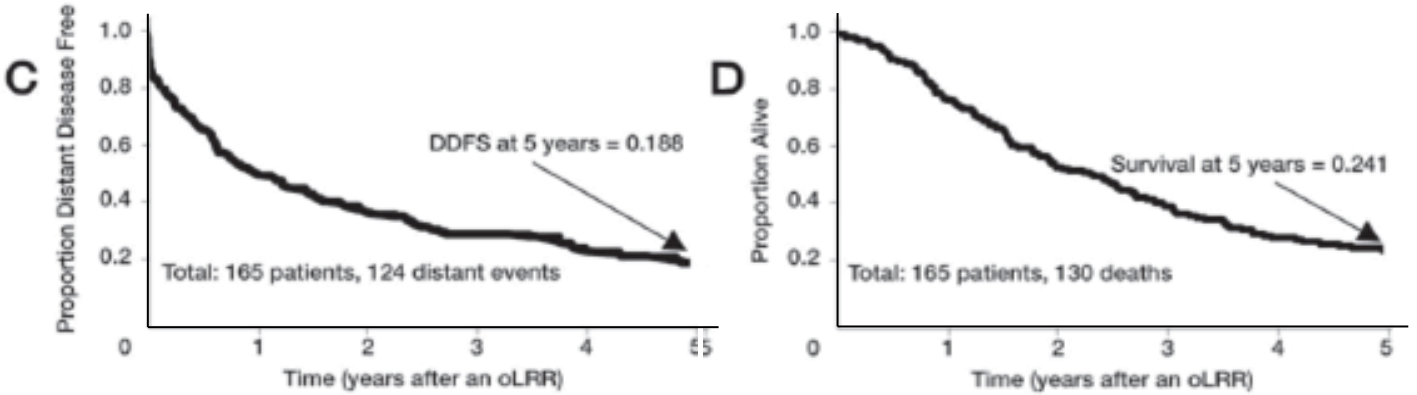
Anderson SJ, J Clin Oncol. 2009 May 20;27(15):2466-73.
Wapnir IL, J Clin Oncol. 2006 May 1;24(13):2028-37.

Survival after other LRR in BCS

Node (-)



Node (+)



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Wapnir IL, J Clin Oncol. 2006 May 1;24(13):2028-37.

What is the benefit of LRR treatment?

- Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis
  - about one breast cancer death over the next 15 years would be avoided for every four LRR avoided
  - about 25% of local recurrences, the cancer cells in the recurrent tumor have acquired the ability or have the opportunity to spread distantly, leading to an increased risk of death from metastatic disease.
  - Who will be "the one in the four LRR"? ("four-to-one relationship")

- Potential benefit from the local treatment should be considered in the treatment of LRR.
- The time from the initial treatment to LRR, receptor conversion in breast cancer recurrence should be also considered for the treatment of patients with LRR with local or systemic therapy or both.

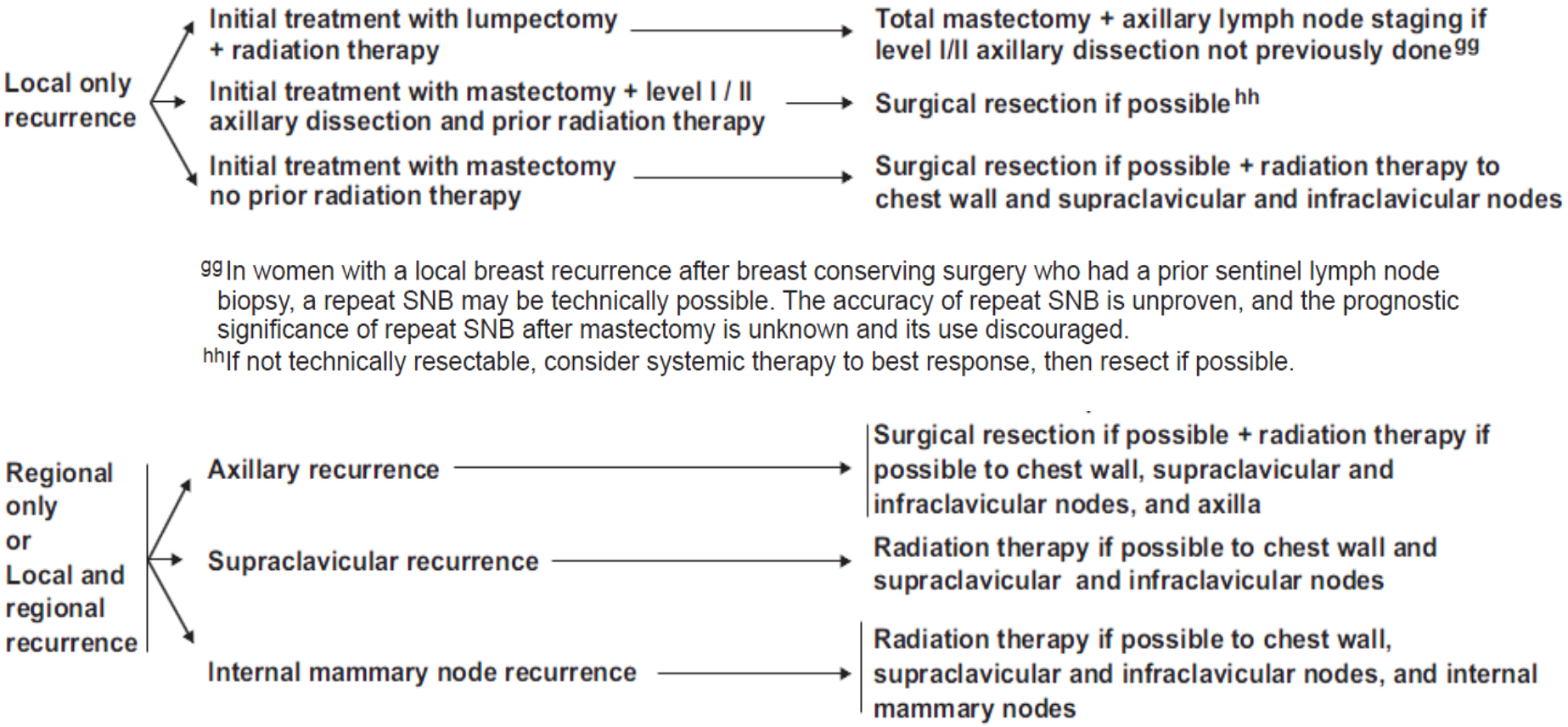
How to treat LLR?

- The pattern of LRR: distinct according to the types of initial surgery

- Treatment of LRR: broadly divided into local and systemic therapy
  - Local therapy includes surgical resection and radiation therapy.
  - Systemic therapy can be combined, and chemotherapy, hormonal therapy and targeted therapy can be considered.

- Treatment recommendations after LRR: not so well defined

NCCN Guidelines Version 2.2011



NCCN Practice Guidelines in Oncology: Breast Cancer 2011: http://www.nccn.org

IBTR after BCS

- the most subsequent area of local recurrences
- Salvage mastectomy: about 90% of IBTR is surgically operable
- Conservative re-excision without radiotherapy

  : may result in a poorer outcome
- Radiation therapy

  : not always possible b/o severe toxicities from cumulative radiation dose
- 5 year OS after IBTR: almost 60% to 80%

Chest wall recurrence after mastectomy

- Surgery (Wide Excision)
  - simple excision for the small subcutaneous recurrence
  - extensive surgery for the isolated chest wall recurrence

- Radiation therapy
  - surgical excision followed by radiotherapy
    > surgical excision alone
    > radiotherapy alone
  - problem: toxicities from cumulative radiation dose

Axillary/Regional Lymph Nodes Recurrence

- Axillary LN recurrence: the second most common site of LRR after BCS
- distant metastases chances at the LRR according to the initial N stage
  - 8% incidence of distant metastases at the LRR with 0 node (N0)
  - 36% for those with 1 to 3 positive nodes (N1)
  - 50% for those with 4 of more positive nodes (N2~N3)
- Axillary node dissection if level I/II dissection is not done before
- Surgical resection if possible & Consider Radiation to regional area

Today's topic is "Individualized…"

- "Individualized overall treatment programs for patients with loco-regional recurrence"

- "Individualized" = "personalized, tailored"
- "Individualized" ≠ "occasionally, by experience"

- Does molecular subtypes predict LLR or its prognosis in breast cancer?

Molecular subtypes in LRR after BCS (1)

- retrospective study, 596 pts, stage I-II (1994-2002)
- treated with BCS without neoadjuvant chemotherapy
- median follow-up time: 79 months (range = 5–147)
- define subtypes with IHC & FISH
- LRR as the first site of recurrence (*p= 0.19).*
  : luminal (6.4%), TN (10.5%), HER2 (10.8%) subtypes
- distant metastases as the first sign of recurrence (*p= 0.90*)
  : luminal (7.6%), TN (6.7%), HER2 (8.4%) subtypes
- After BCT in Korean women with early stage breast cancer, the patterns of recurrence were not different among the molecular subtypes, although TN and HER2 subtypes were associated with younger age, higher N/G, poorer histologic grade.

Noh JM, Sungkyunkwan University School of Medicine. J Breast Cancer. **2011** Mar;14(1):46-51.

Molecular subtypes in LRR after BCS (2)

- retrospective study, 764 pts with invasive breast cancer (1995-2008)
- treated with BCS without neoadjuvant chemotherapy
- median follow-up time: 41.5 months (range = 3–158)
- define molecular subtypes with IHC only

- In univariate analysis for LRR, lymph node status, HER2/neu status, and molecular subtype were significantly associated with local and regional relapse
- In multivariate analysis, lymph node status was the only one independent predictive factor for LRR (P = .0049, HR: 2.27 [95%CI: 1.28–4.03])

Li S, Fudan University, Shanghai. Ann Surg Oncol. **2011** Sep;18(9):2492-9.

Molecular subtypes in LRR after mastectomy

- retrospective study, 1,195 pts, stage I-II (2004-2008)
- all were treated with MRM without neoadjuvant chemotherapy
- median follow-up time: 44 months (range = 15–76)
- define subtypes with IHC & FISH/SISH

- In univariate analysis, the intrinsic subtypes of breast cancer had a signifi cant effect on LRR (p = 0.002)
- In multivariate analysis, only extranodal invasion and ER status were signi ficant predictors of LRR
- In multivariate analysis, intrinsic subtypes did not reveal a significant relat ionship with LRR (p = 0.57; HR: 2.9 [95%CI: 0.2–4.7])

Mersin H, Ankara Oncology Training & Research Hospital. World J Surg. **2011** Oct;35(10):2196-2202.

Molecular subtypes regarding LRR in PMRT

- retrospective study, 582 stage II-III pts (1999-2009)
- treated with post-mastectomy radiation (PMRT)
- median follow-up time: 44.7 months
- define ER/PR/Her-2 status with IHC & FISH
- The cumulative 5-year incidence of LRR as first site of failure: 6.2%
- 5-yr cumulative incidence of LRR
  - ER negative (8.6%) vs ER positive (4.4%) (*P = 0.017*)
  - PR negative (8.5%) vs PR positive (3.4%) (*P = 0.011*)
  - HER2 positive (*86% received trastuzamab*) vs HER2 negative : 1.7% vs 7.5% (*P = 0.032*)
  - TN subtype (11.8%) vs other combinations (3.9%) (*P<0.001*)
- In multivariate analysis, the prognostic value of the triple negative and HER2 negative subtypes was maintained.

Panoff JE, University of Miami School of Medicine, Breast Cancer Res Treat. **2011** Aug;128(3):899-906.

Molecular subtypes regarding LRR in NAC

- retrospective study, 331 patients
  - NAC plus lumpectomy & WBRT (n = 155)
  - NAC plus mastectomy with (n = 122) or without (n = 50) adjuvant RTx
- median follow-up time: 43 months (range = 10–104)
- define subtypes with IHC & FISH/SISH

- molecular class (p = 0.003) and pCR (p = 0.004)
  → predicted distant recurrence, DFS, overall survival
- only the omission of adjuvant RTx following mastectomy (*p = 0.006*)
  → predicted LRR
- "More work is needed to define if molecular class can predict patients at risk for locoregional recurrence."

Vargo JA, Magee-Womens Hospital of UPMC, Pittsburgh, Oncology. **2011**;80(5-6):341-9.

Breast Cancer Subtypes and the Risk of LLR

- British Columbia cancer agency cohort. 2,985 tumors (1986-92)
- median age: 59 years-old
- median follow-up time for both LR and RR: 12 years
- ER, PR, HER2, Ki-67, EGFR, and CK5/6s by IHC & Hercept test/FISH
  - ✓ luminal A (ER positive or PR positive and Ki-67<14%)
  - ✓ luminal B (ER positive or PR positive and Ki-67≥14%)
  - ✓ luminal-HER2 (ER positive or PR positive and HER2 positive)
  - ✓ HER2 enriched (ER negative, PR negative, and HER2 positive)
  - ✓ Basal like (ER negative, PR negative, HER2 negative, and EFGR positive or CK5/6 positive)
  - ✓ TNP-nonbasal (ER, PR, HER2, EGFR, CK5/6s, all negative)
- BCS (42%) & mastectomy (58%)
- 25% of mastectomy patients received postoperative radiotherapy

Voduc KD, British Columbia Cancer Agency, Canada. J Clin Oncol. **2010** Apr 1;28(10):1684-91.

LR and RR after BCS

- Univariate analysis
  - For both LR and RR, luminal A
    → the most favorable prognosis with LR/RR rates of 8%/3% at 10 yrs
  - highest rates of LR & and RR
    in HER2-enriched and basal-like (LR 21%/14%, RR 16%/14%)

- Multivariable analysis for LR
  - young age (<55) at diagnosis, HER2-enriched subtype
  - anthracycline-based chemotherapy: protective
- Multivariable analysis for RR
  - young age (<40) , LN > 3
  - HER2-enriched and basal-like subtypes

Voduc KD, Breast cancer subtypes and the risk of LLR. J Clin Oncol. **2010** Apr 1;28(10):1684-91.

LR and RR after Mastectomy

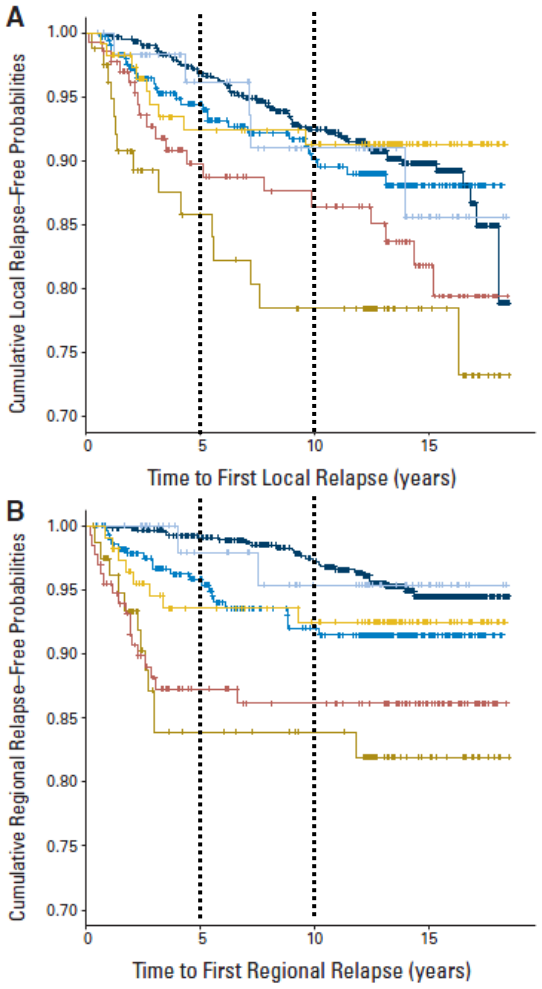
- Univariate analysis
  - luminal A tumors again had the best prognosis
    → lowest LR & RR: 8% & 4% at 10 yrs
  - All non–luminal A subtypes exhibited a greater risk of LR and RR.

- Multivariable analysis for LR
  - larger T, high N/G, N (+), and all non–luminal A subtypes except TNP-nonbasal
  - Chemotherapy and hormonal therapy: protective
- Multivariable analysis for RR
  - All of the non–luminal A subtypes

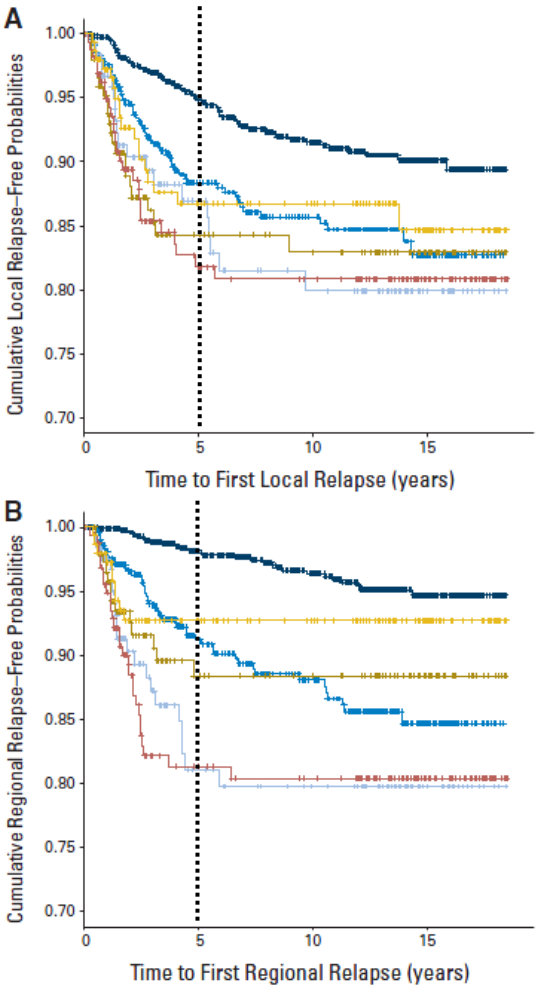
Voduc KD, Breast cancer subtypes and the risk of LLR. J Clin Oncol. **2010** Apr 1;28(10):1684-91.

British Columbia cancer agency study

LRR after BCS



LRR after Mastectomy



Violet line, luminal A
dark blue, luminal B
light blue, luminal HER2
gold, TNP-nonbasal
red, basal
beige, HER2 enriched.

Voduc KD, Breast cancer subtypes and the risk of LLR. J Clin Oncol. **2010** Apr 1;28(10):1684-91.

Molecular Predictors of LLR
- temporary conclusion -

- Molecular profiling is integrated into risk assessment and clinical decision making; it relates to systemic Mx of breast cancer.
- However, the application of molecular profiling of breast cancers to LRR risk assessment and management is underdeveloped yet.

- luminal A tumors may be at low risk for both local relapse as well as systemic disease.
- However, molecular profiling for the survival may differ from that for the LRR.
- Susceptibility for radiation, chemotherapy and targeted therapy needs to be taken into consideration in evaluation of molecular profiling in LLR risk assessment.

Haffty BG, Molecular predictors of LRR in breast cancer. J Clin Oncol. 2010 Apr 1;28(10):1627-9.

Individualized treatment strategy for LLR
- summary -

- For operable breast, chest wall, and axillary recurrences

  → excision can be strongly deliberated with tumor-free margins
- For IBTR after BCS & RTx → standard treatment: mastectomy
- Breast conserving re-excision can be cautiously considered in highly selective cases.
- Radiation can be considered, avoiding cumulative toxicities.
- Systemic therapy (chemotherapy, hormonal therapy, targeted therapy, bisphosphonates, or combination of these) can be applied according to the molecular characteristics of recurred tumor in high suspicion of prodrome of systemic metastasis.
- Molecular subtypes related to the LLR needs to be further elucidated.


SAMSUNG
삼성서울병원

Thank you very much for your attention.

a part, “Portrait of a Beauty”, Shin Yun-Bok (1758~?), Korea