Surgical Issues According to The Molecular Subtypes of Tumor

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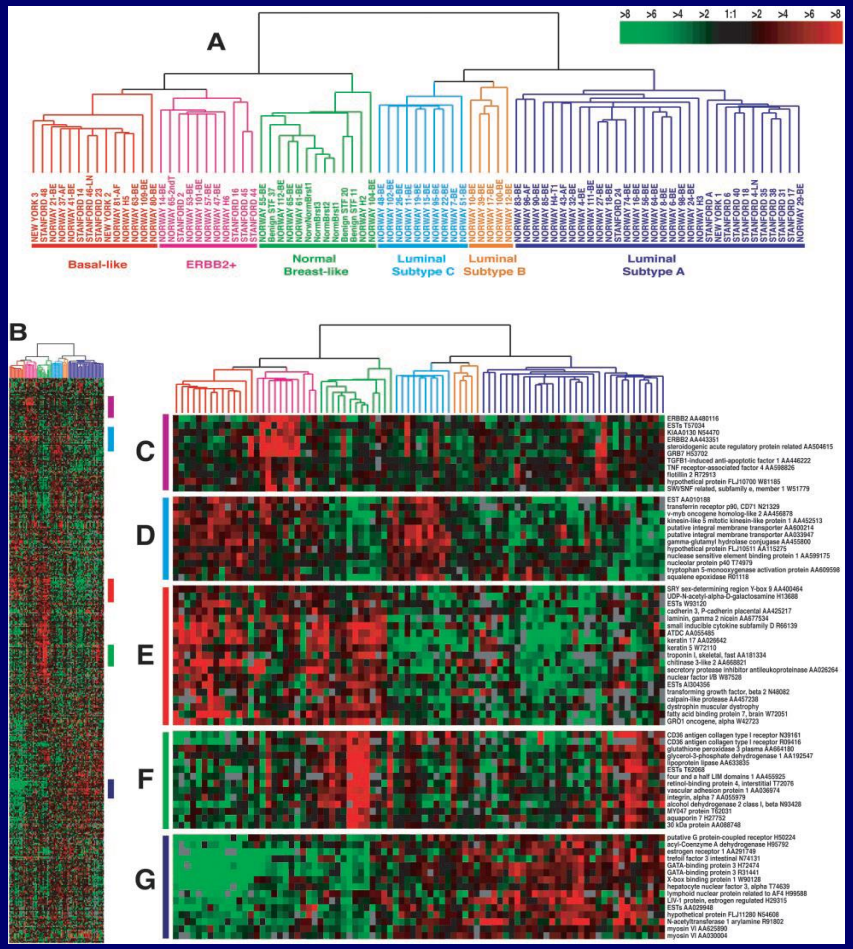
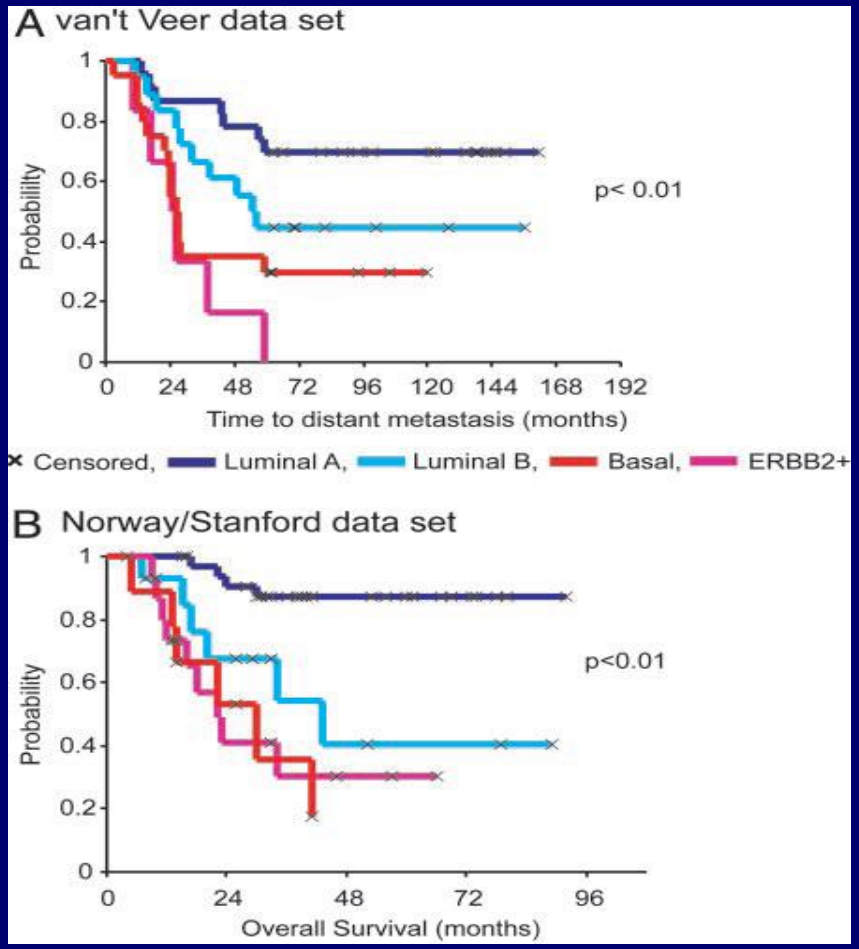
KIRAMS

Gene expression patterns of breast carcinomas distinguish tumor subclasses





Sørlie T and Perou CM et al. PNAS 2001

Sørlie T et al. PNAS 2003

Molecular Subtypes (*St.Gallen 2013)*

Intrinsic subtype	Clinico-pathologic surrogate definition	Notes
Luminal A	**'Luminal A-like'** *all of:* ER and PgR positive HER2 negative Ki-67 'low'[a] Recurrence risk 'low' based on multi-gene-expression assay (if available)[b]	The cut-point between 'high' and 'low' values for Ki-67 varies between laboratories.[a] A level of <14% best correlated with the gene-expression definition of Luminal A based on the results in a single reference laboratory [23]. Similarly, the added value of PgR in distinguishing between 'Luminal A-like' and 'Luminal B-like' subtypes derives from the work of Prat et al. which used a PgR cut-point of ≥20% to best correspond to Luminal A subtype [24]. Quality assurance programmes are essential for laboratories reporting these results.
Luminal B	**'Luminal B-like (HER2 negative)'** ER positive HER2 negative and *at least one of:* Ki-67 'high' PgR 'negative or low' Recurrence risk 'high' based on multi-gene-expression assay (if available)[b]	'Luminal B-like' disease comprises those luminal cases which lack the characteristics noted above for 'Luminal A-like' disease. Thus, either a high Ki-67[a] value or a low PgR value (see above) may be used to distinguish between 'Luminal A-like' and 'Luminal B-like (HER2 negative)'.
	'Luminal B-like (HER2 positive)' ER positive HER2 over-expressed or amplified Any Ki-67 Any PgR	
Erb-B2 overexpression	**'HER2 positive (non-luminal)'** HER2 over-expressed or amplified ER and PgR absent	
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative	There is an 80% overlap between 'triple-negative' and intrinsic 'basal-like' subtype. Some cases with low-positive ER staining may cluster with non-luminal subtypes on gene-expression analysis. 'Triple negative' also includes some special histological types such as adenoid cystic carcinoma.

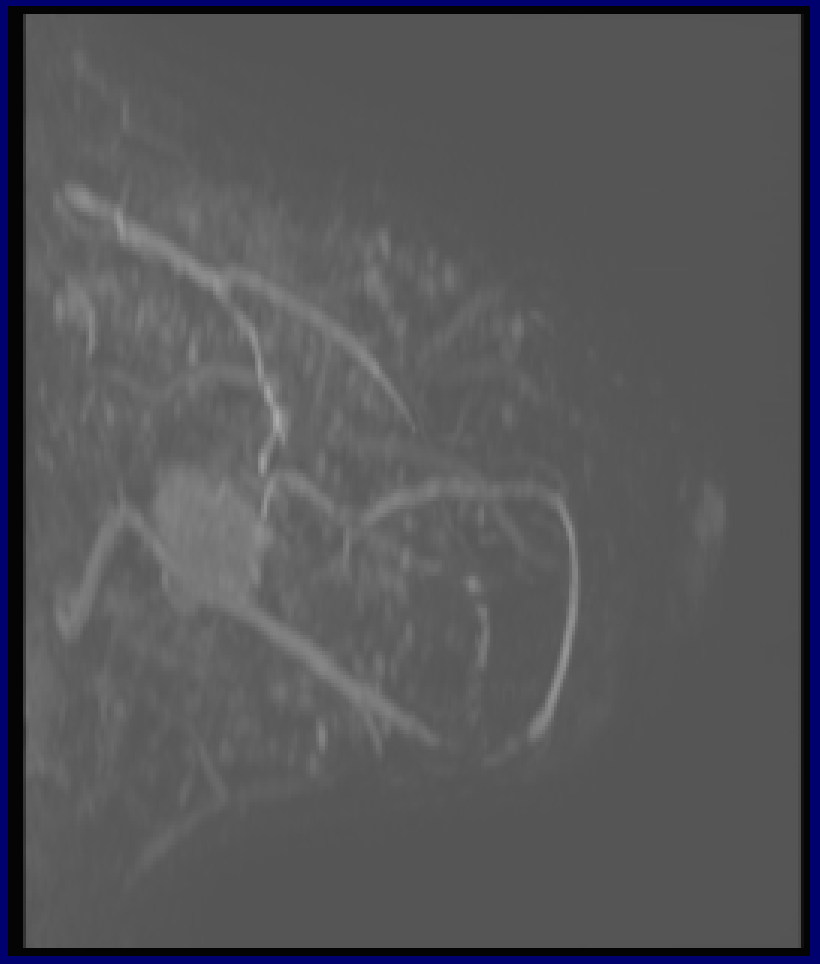
Systemic treatment recommendations *(St. Gallen 2013)*

'Subtype'	Type of therapy	Notes on therapy
'Luminal A-like'	Endocrine therapy is the most critical intervention and is often used alone.	Cytotoxics may be added in selected patients. Relative indications for the addition of cytotoxics accepted by a majority of the Panel included: (i) high 21-gene RS (i.e. >25), if available; (ii) 70-gene high risk status, if available; (iii) grade 3 disease; (iv) involvement of four or more lymph nodes (a minority required only one node). The Panel was almost equally divided as to whether young age (<35 years) *per se* was an indication to add cytotoxics. Studies suggest a wide geographical divergence in the threshold indications for the inclusion of cytotoxics for the treatment of patients with luminal disease [96].
'Luminal B-like (HER2 negative)'	Endocrine therapy for all patients, cytotoxic therapy for most.	
'Luminal B-like (HER2 positive)'	Cytotoxics + anti-HER2 + endocrine therapy	No data are available to support the omission of cytotoxics in this group.
'HER2 positive (non-luminal)'	Cytotoxics + anti-HER2	Threshold for use of anti-HER2 therapy was defined as pT1b or larger tumour or node-positivity.
'Triple negative (ductal)'	Cytotoxics	
'Special histological types'[a]		
A. Endocrine responsive	Endocrine therapy	
B. Endocrine non-responsive	Cytotoxics	Adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).

Q> **Surgical treatment of breast cancer: Should it be different according to the molecular subtypes of tumor?**

Case

- F/49
- Rt. OUQ 2.9cm single lesion with axillary L.N metastasis
- Gun Bx: IDC
- BCS with AD was performed on 2012/12



Case

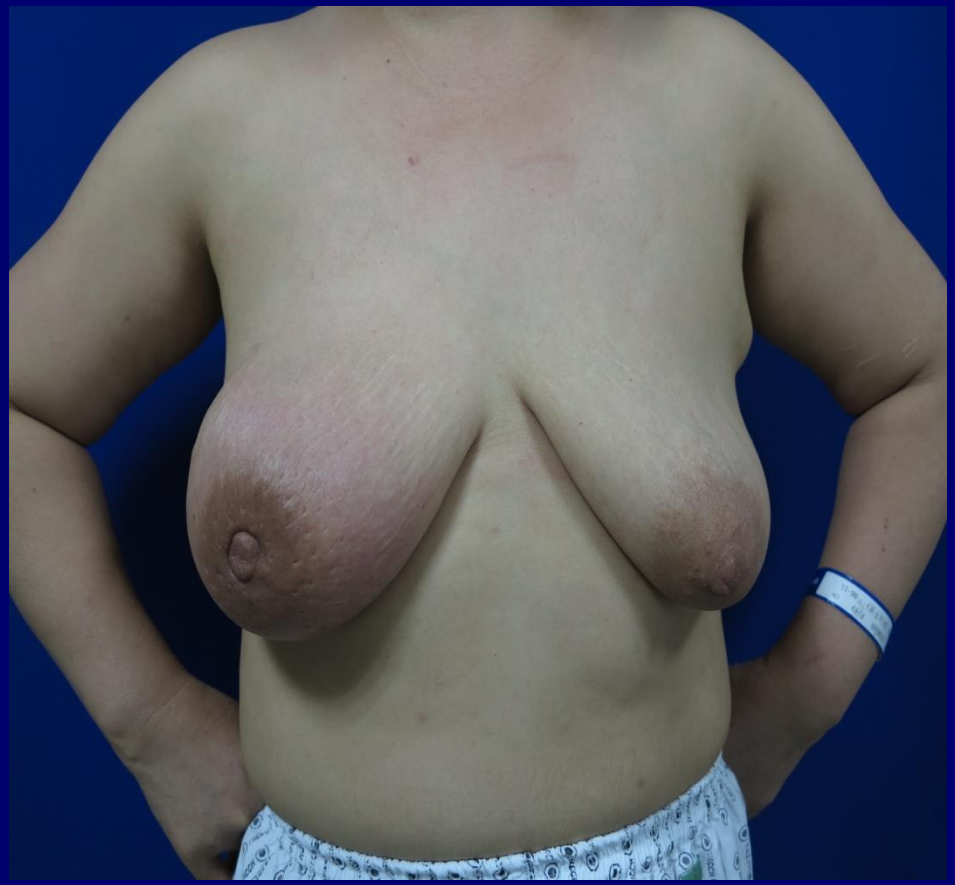
- Breast, right, breast-conserving surgery:
- Invasive ductal carcinoma
- with 1) tumor size of invasive component: 2.2x1.6cm
- 2) histologic grade: 3/3
- a) tubule formation: 3/3
- b) nuclear pleomorphism: 3/3
- c) mitotic count: 3/3 (28/10HPF)
- 3) ductal carcinoma in situ: (-)
- 4) ly(+), n(-), v(-)
- 5) clear resection margins (deep, medial, lateral, superior and inferior)

- Lymph node, right axillary, dissection:
- Metastatic ductal carcinoma in three out of 18 lymph nodes

ER/PR/HER2: -/-/-, Ki67: 20%

Case

- Adjuvant AC->Paclitaxel followed by RT was planned
- At 5 months after surgery (during the course of adjuvant chemotherapy), ill-defined erythematous lesion with inflammation developed in ipsilateral breast
- No sign of improvement after 2wks of antibiotics.



Cases

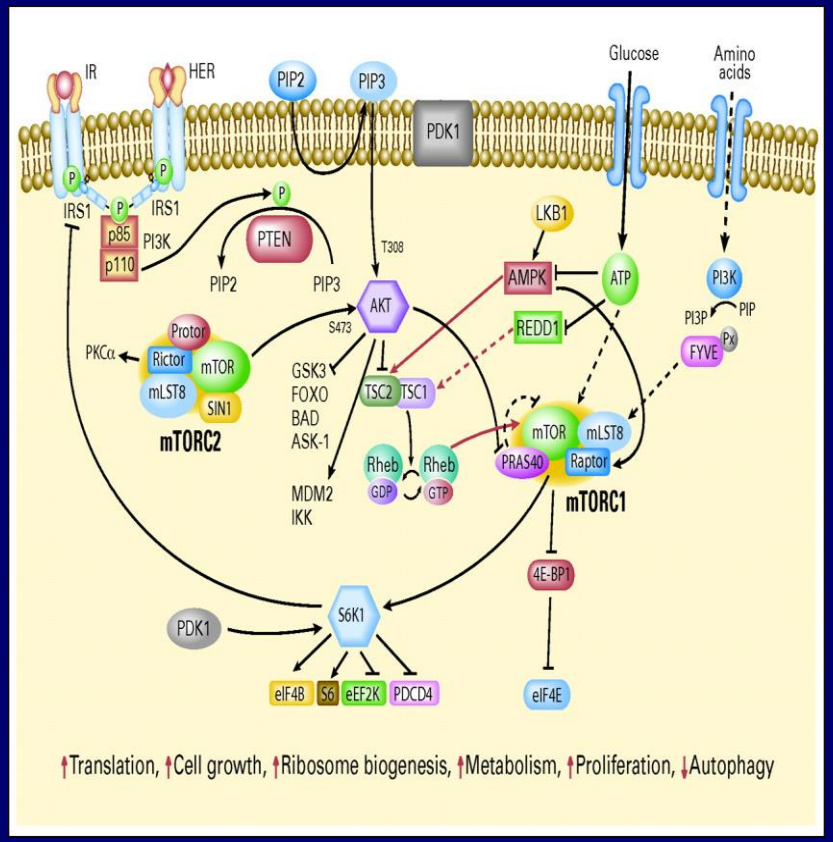
- Breast, right, total mastectomy:
- Invasive ductal carcinoma, almost entire parenchyma
- with 1) size of invasive component: up to 8x8x4.5cm
- 2) histologic grade: 3/3
- a) tubule formation: 3/3
- b) nuclear pleomorphism: 3/3
- c) mitotic count: 3/3 (61/10HPF)
- 3) ly(+), n(-), v(+)
- 4) no involvement of deep resection margin
- 5) involvement of nipple
- 6) no involvement of major lactiferous duct

ER/PR/HER2: -/-/-, Ki67: 40%

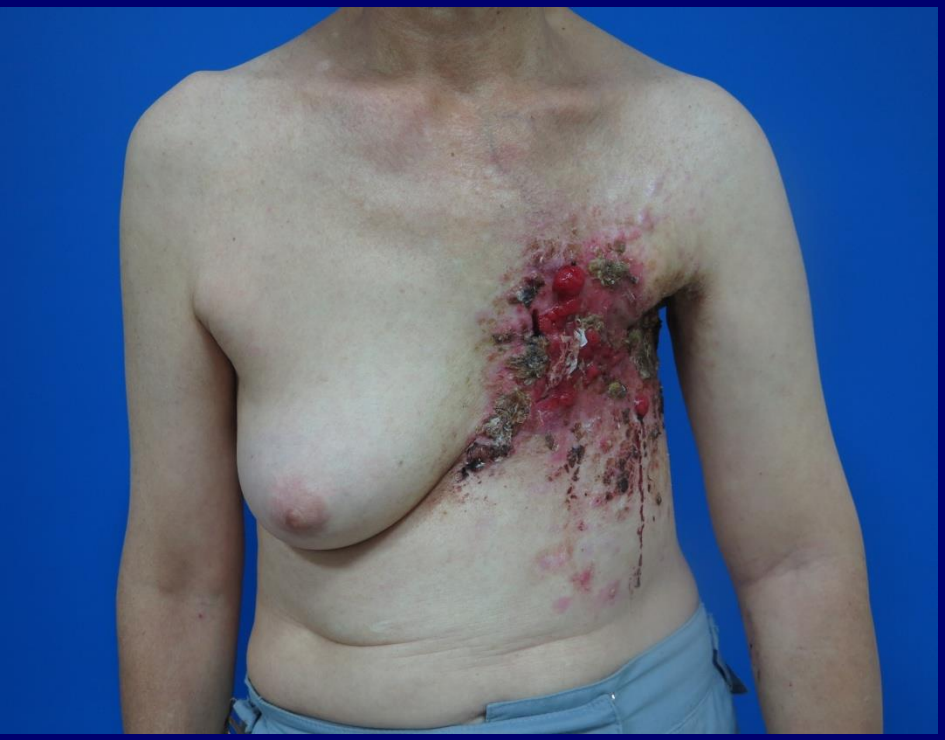
Loco-Regional Recurrence

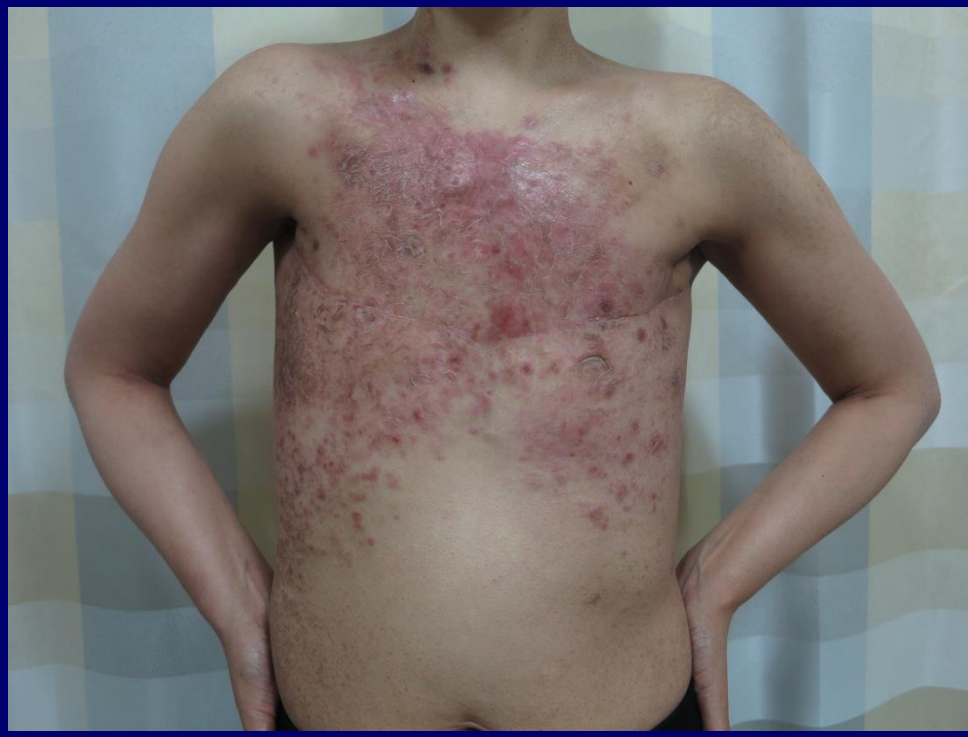
- Local factors?

- Biological Factors?



Locoregional Recurrence (LRR) after Mastectomy

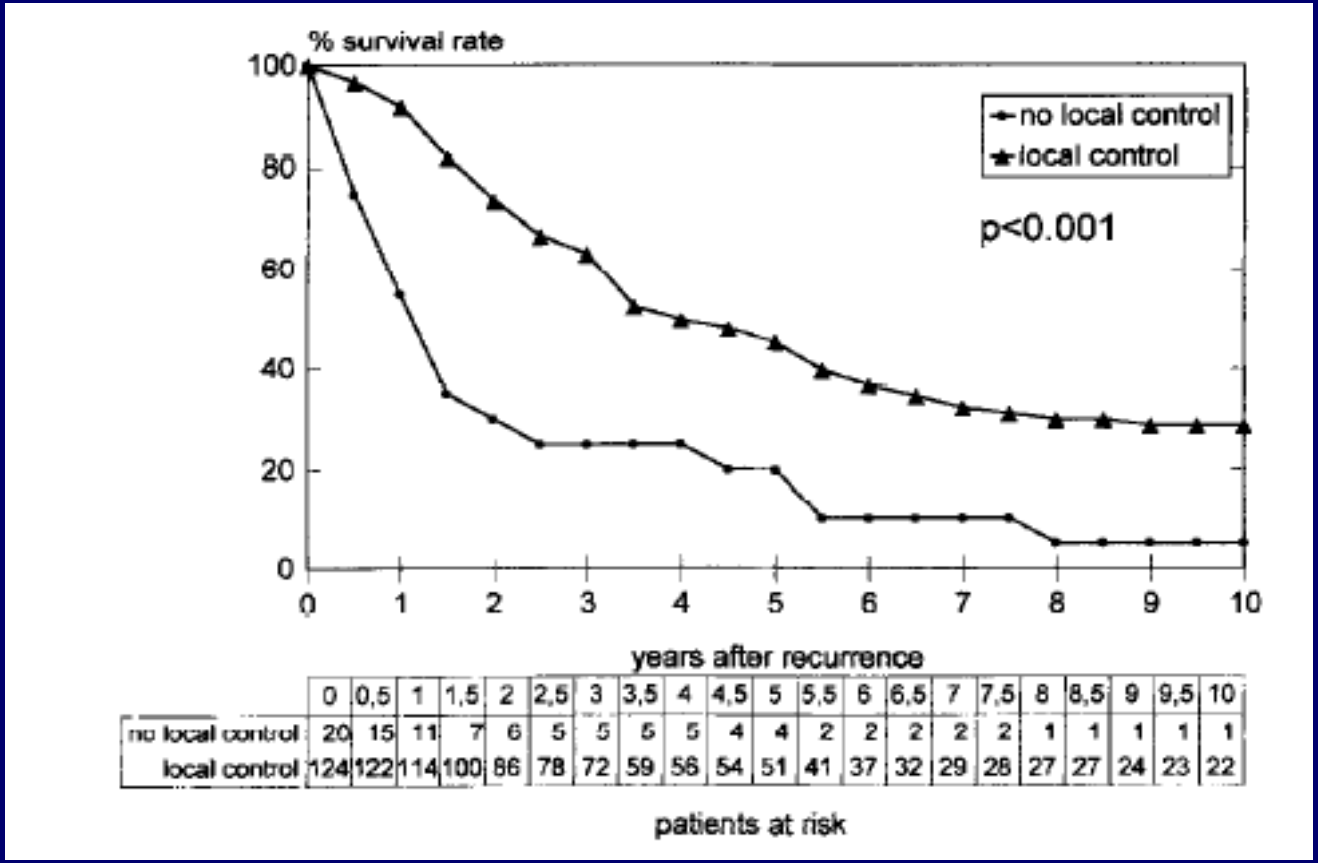




Locoregional Recuurence (LRR) after Mastectomy

- Usually fatal
- Subgroups with favorable prognosis exist
  - Axillary node or single chest wall lesion
  - Long disease-free interval
  - pT1N0 primary tumor

Prognosis of LRR after Mastectomy

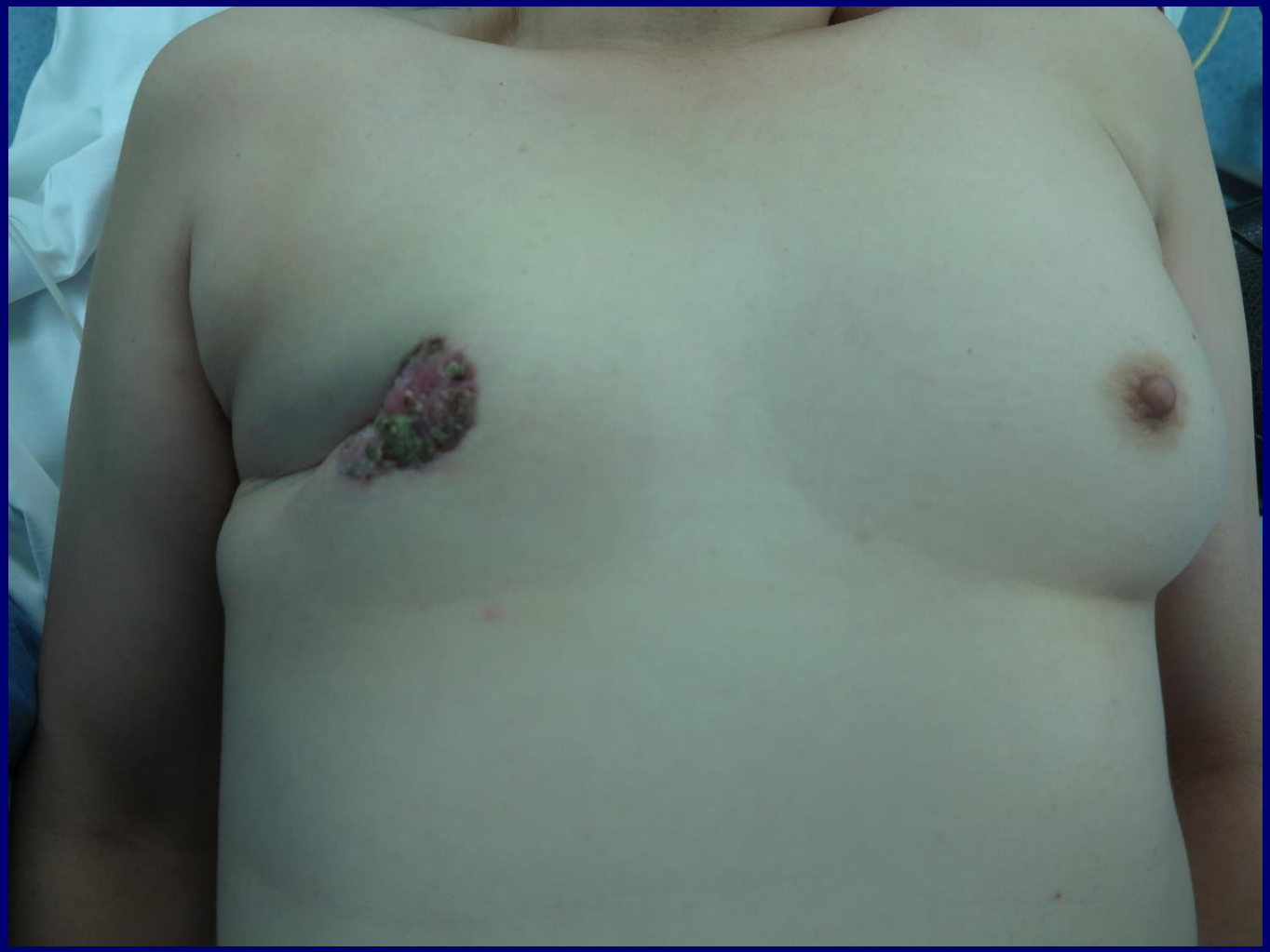


	0	0,5	1	1,5	2	2,5	3	3,5	4	4,5	5	5,5	6	6,5	7	7,5	8	8,5	9	9,5	10
no local control	20	15	11	7	6	5	5	5	5	4	4	2	2	2	2	2	1	1	1	1	1
local control	124	122	114	100	86	78	72	59	56	54	51	41	37	32	29	28	27	27	24	23	22

patients at risk

Willner et al. Int J Radiat Oncol Biol Phys 1997

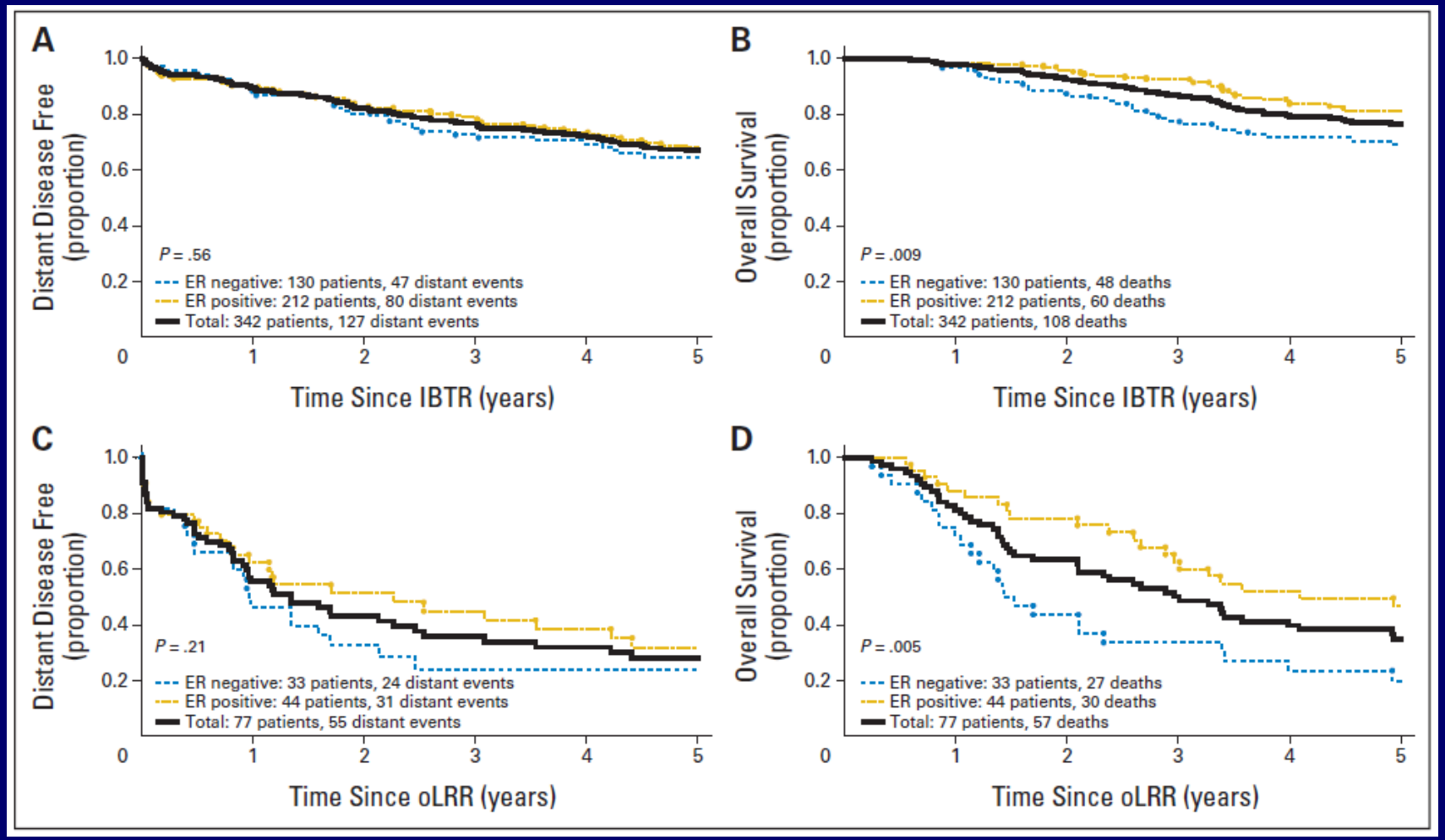
IBTR or LRR after BCT



IBTR or LRR after BCT

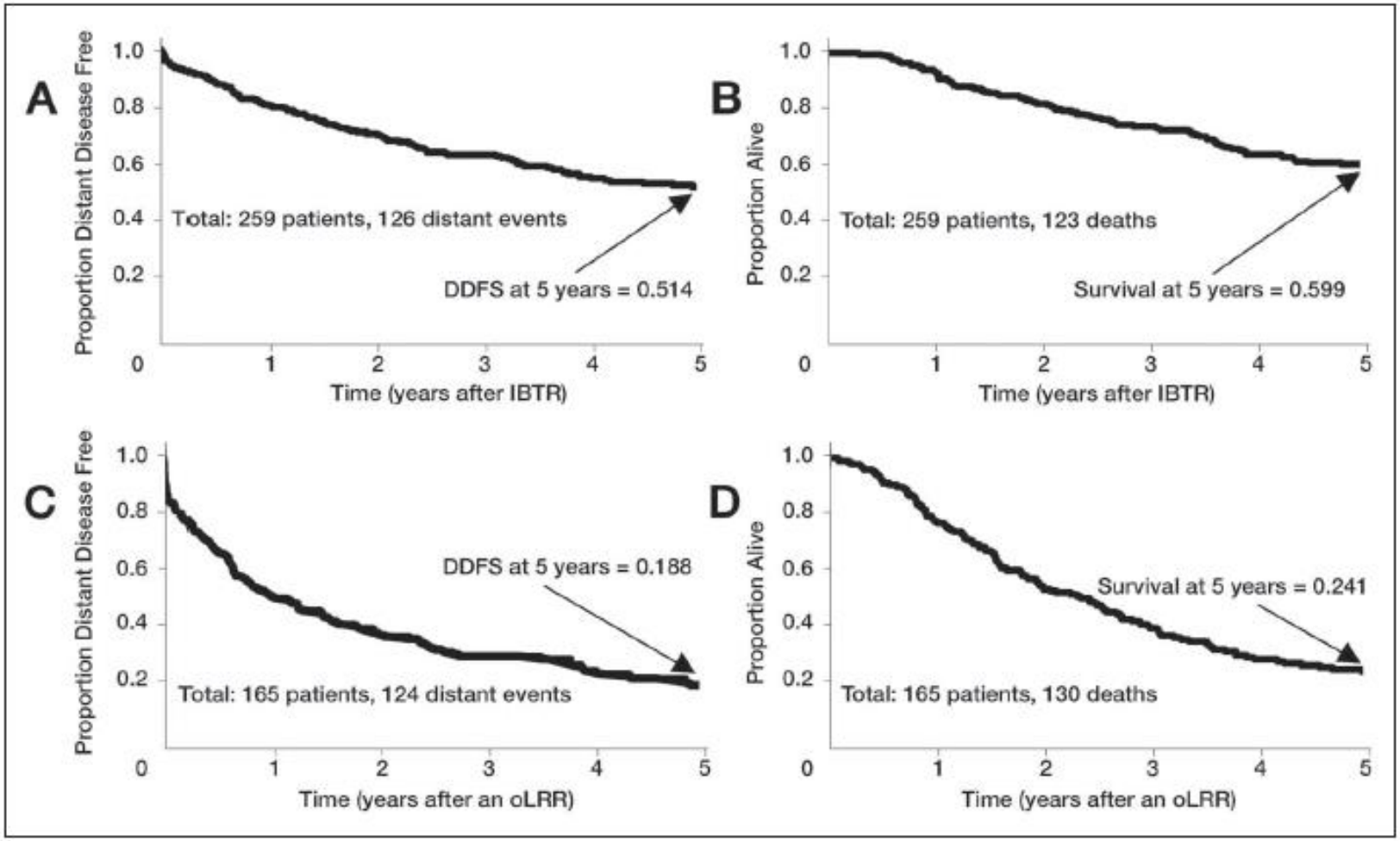
- IBTR predicts survival, but does not always mean treatment failure.

Prognosis after IBTR or other LRR in 5 NSABP L/N - adjuvant trials



Wolmark N et al, J Clin Oncol 2008

Prognosis after IBTR or other LRR in 5 NSABP L/N + adjuvant trials



Wolmark N et al, J Clin Oncol 2006

IBTR or LRR after BCT

- Is IBTR a marker or a cause of distant metastasis?

IBTR is a marker of risk for, not a cause of, distant metastasis

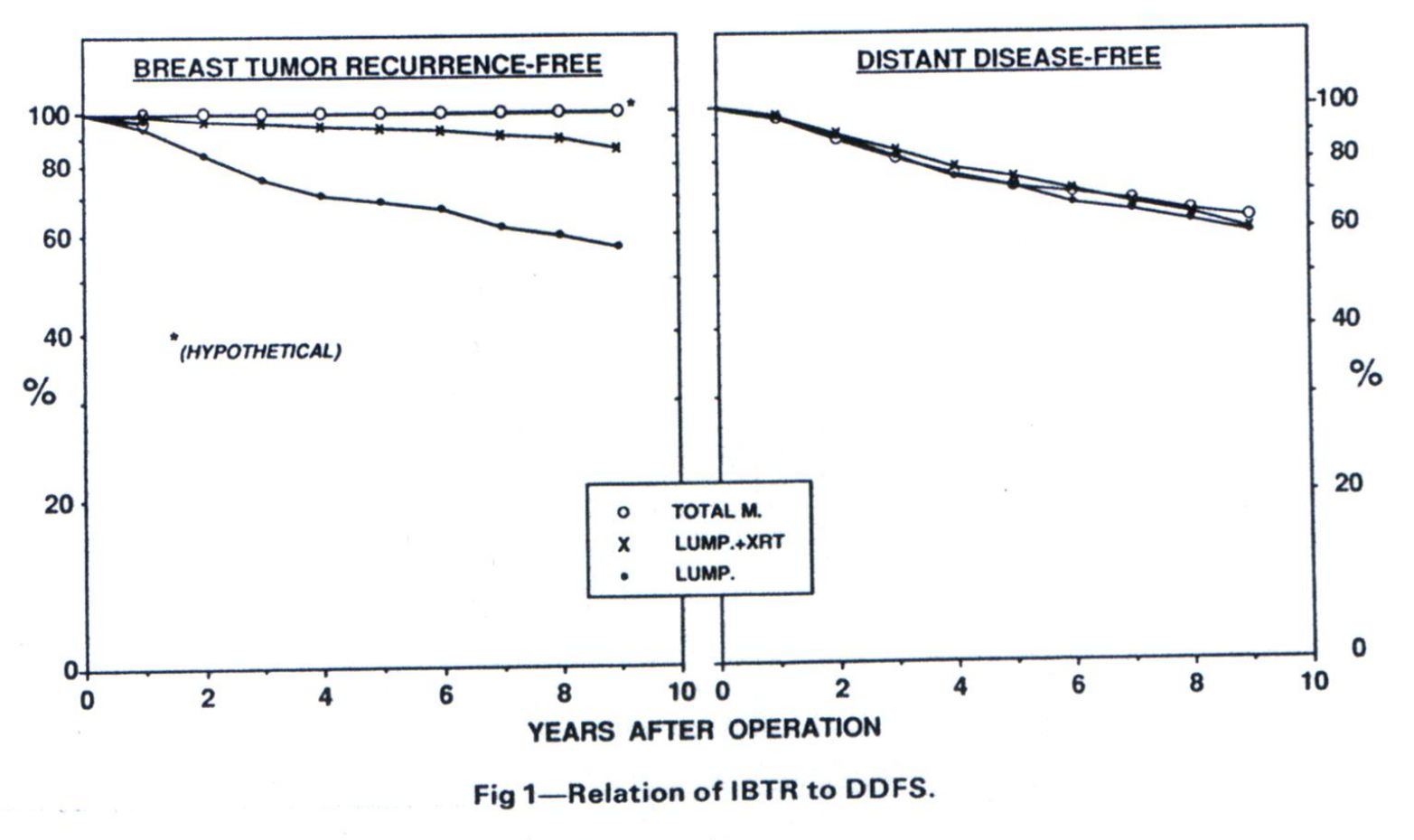


Fig 1—Relation of IBTR to DDFS.

Fisher et al. Lancet 338,1991

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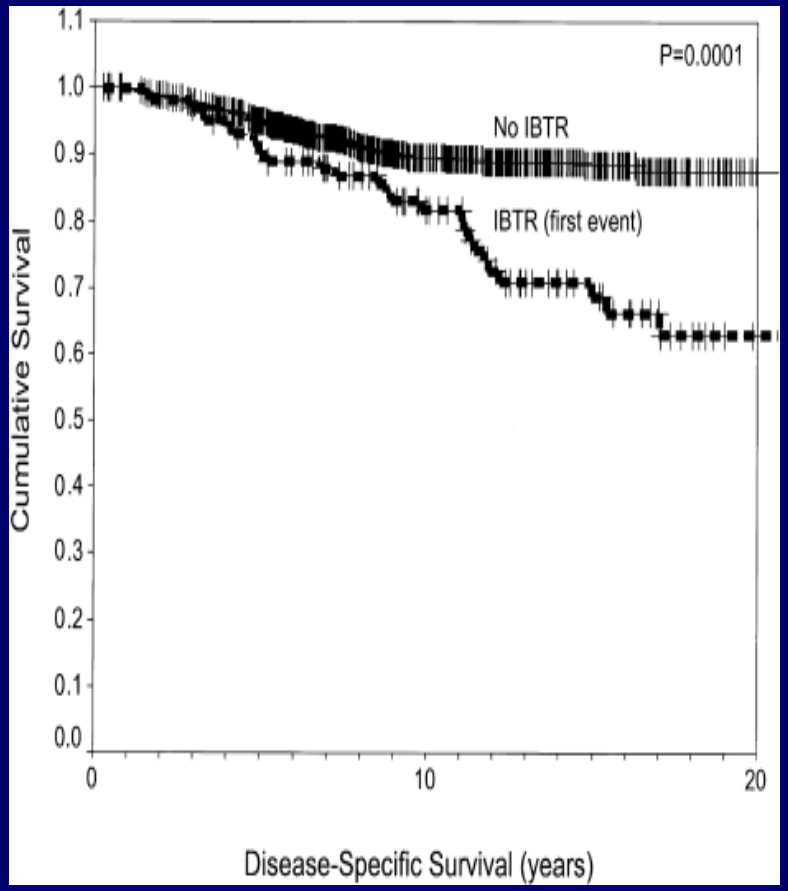
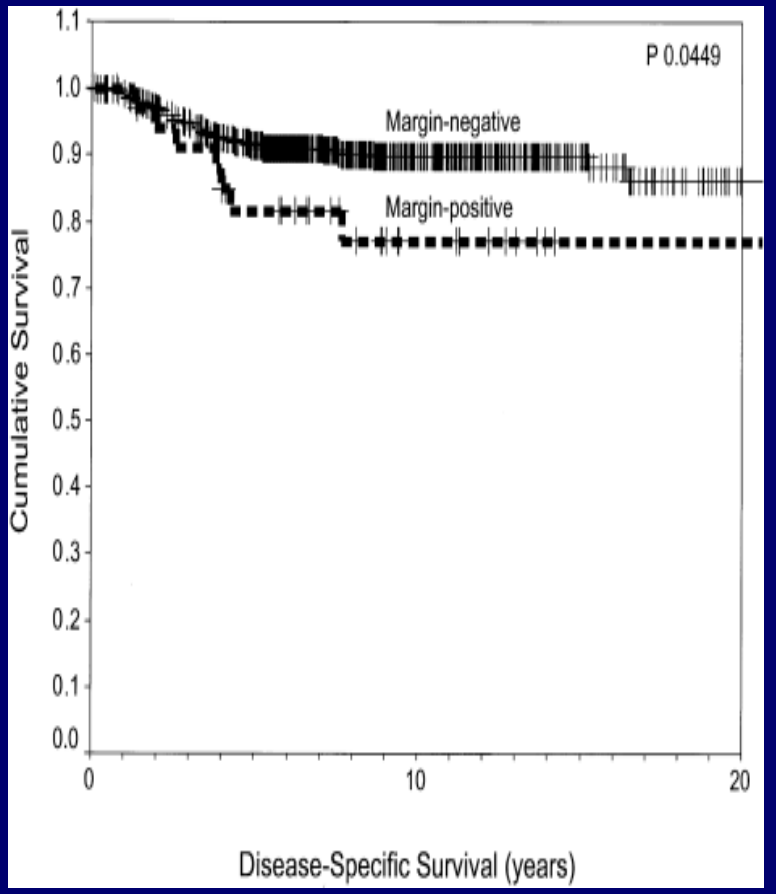
IBTR may be responsible for an increase in distant disease.





Meric et al. Cancer 97,2003

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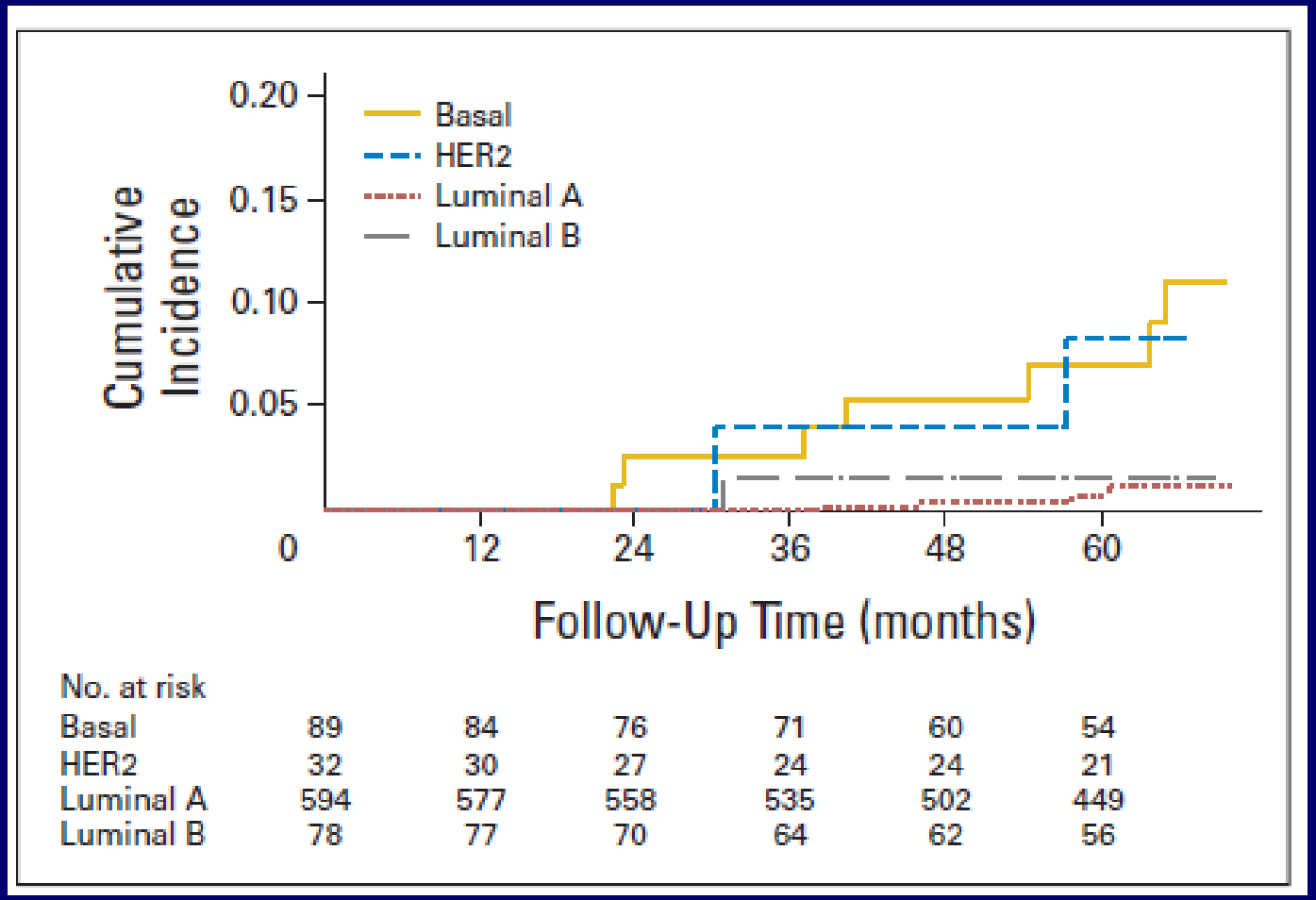
- Currently available data cannot definitely resolve whether IBTR is simply a marker of risk for or a direct cause of distant metastasis.

- It had long been thought that local factors and tumor burden were major determinants of IBTR.

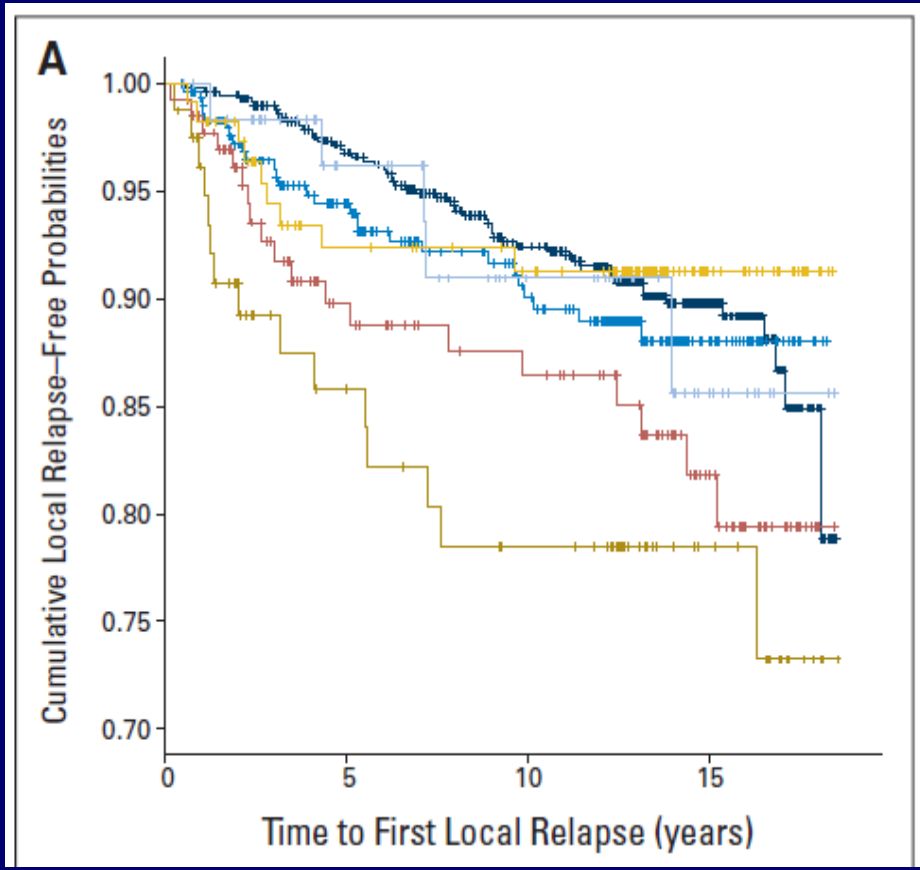
Breast Cancer Subtype Is Associated with IBTR after BCT

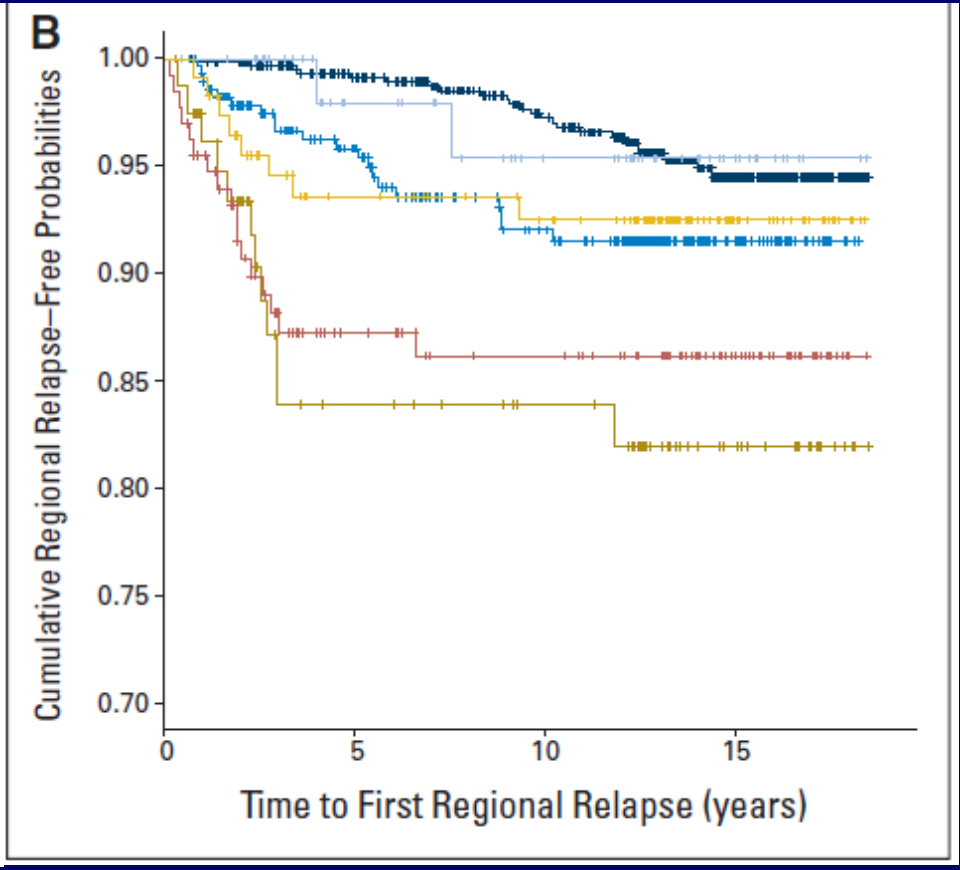


No. at risk						
Basal	89	84	76	71	60	54
HER2	32	30	27	24	24	21
Luminal A	594	577	558	535	502	449
Luminal B	78	77	70	64	62	56

Nguyen PL et al. J Clin Oncol 2008

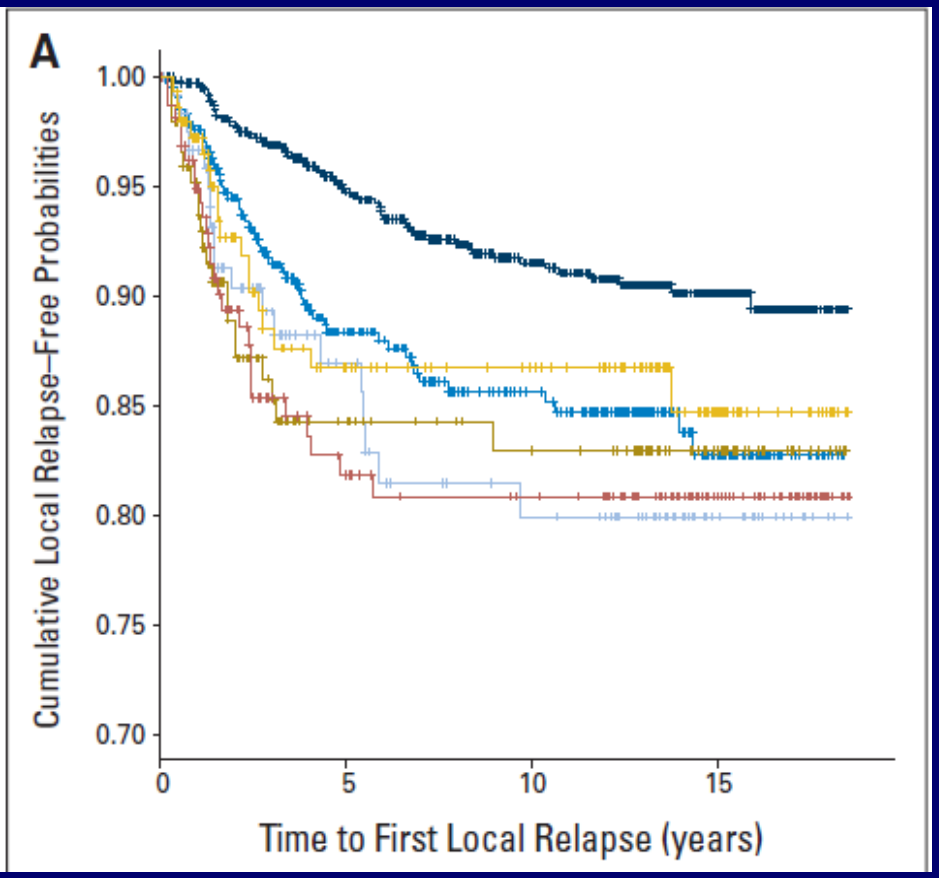
Breast Cancer Subtype Is Associated with LRR after BCT

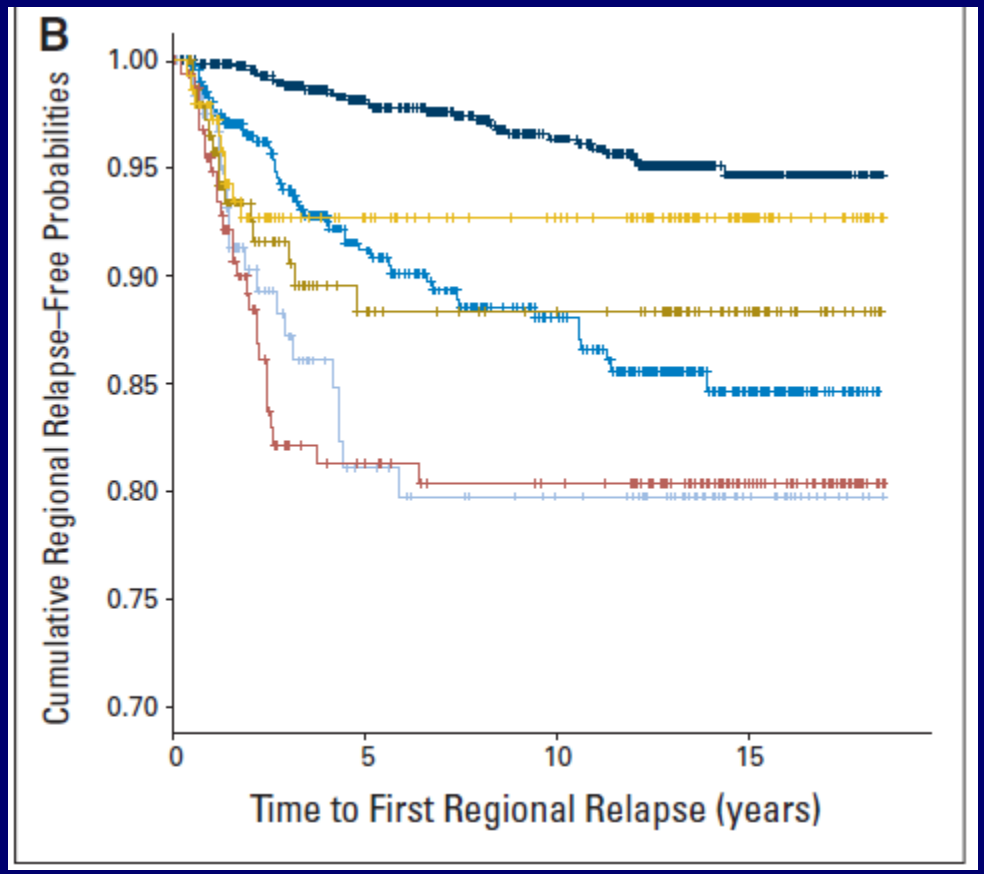




Voduc KD et al. J Clin Oncol 2010

Breast Cancer Subtype Is Associated with LRR after mastectomy

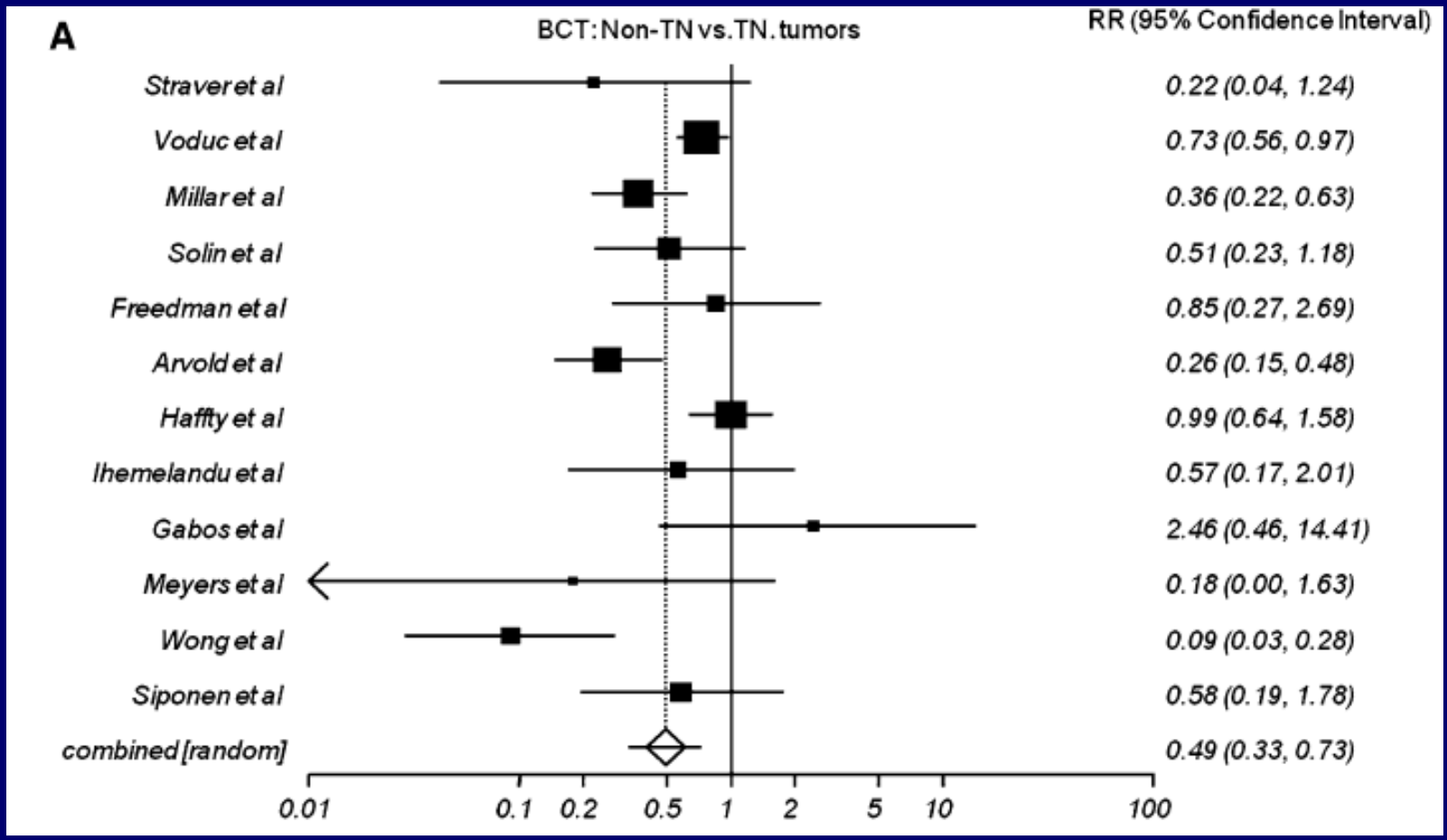




Voduc KD et al. J Clin Oncol 2010

Incidence of LRR following BCT (Results of meta-analysis I)

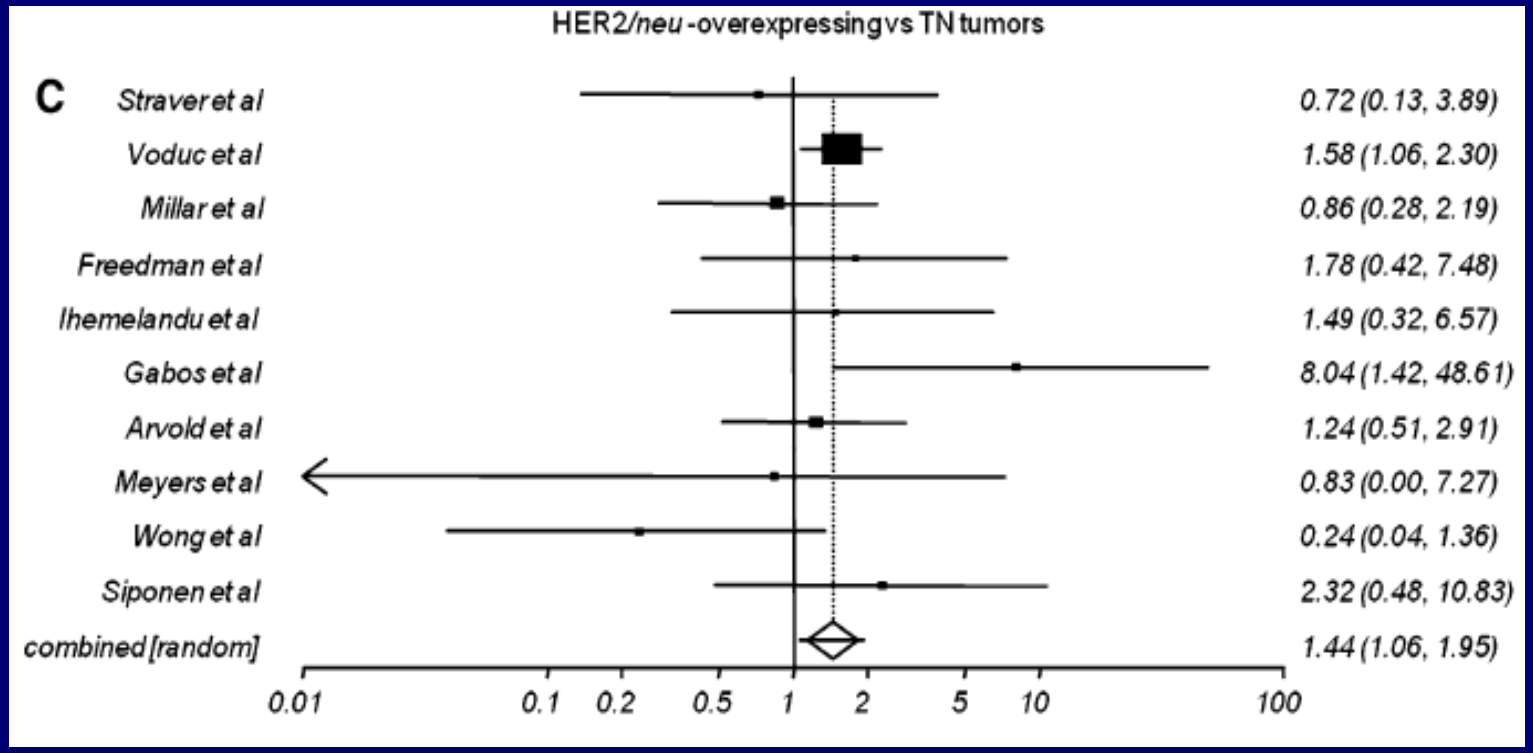
- TNBC > non-TNBC



Lowery AJ et al. Breast Cancer Res Treat 2012

Incidence of LRR following BCT (Results of meta-analysis II)

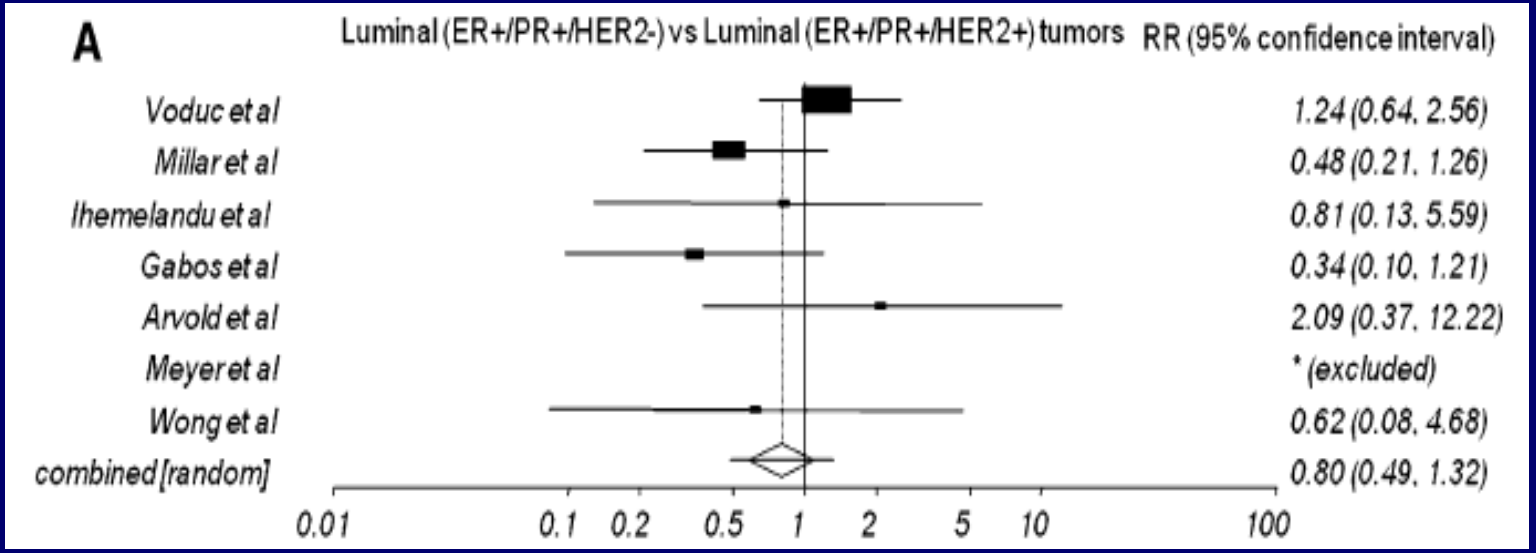
- HER2+ > TNBC > Luminal



Lowery AJ et al. Breast Cancer Res Treat 2012

Incidence of LRR following BCT (Results of meta-analysis III)

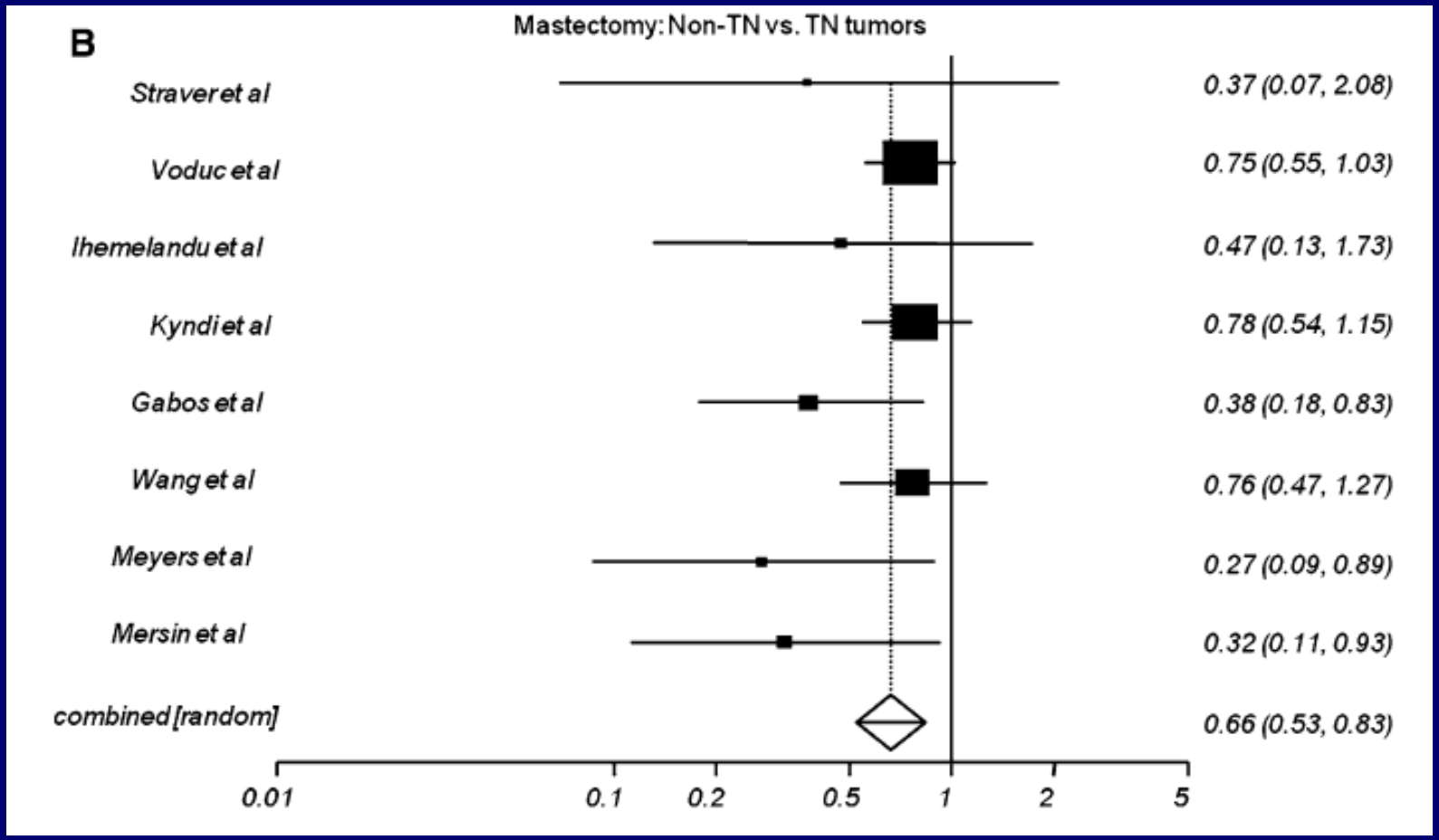
- Luminal A (HER2-) = Luminal B (HER2+)



Lowery AJ et al. Breast Cancer Res Treat 2012

Incidence of LRR following Mastectomy (Results of Meta-analysis I)

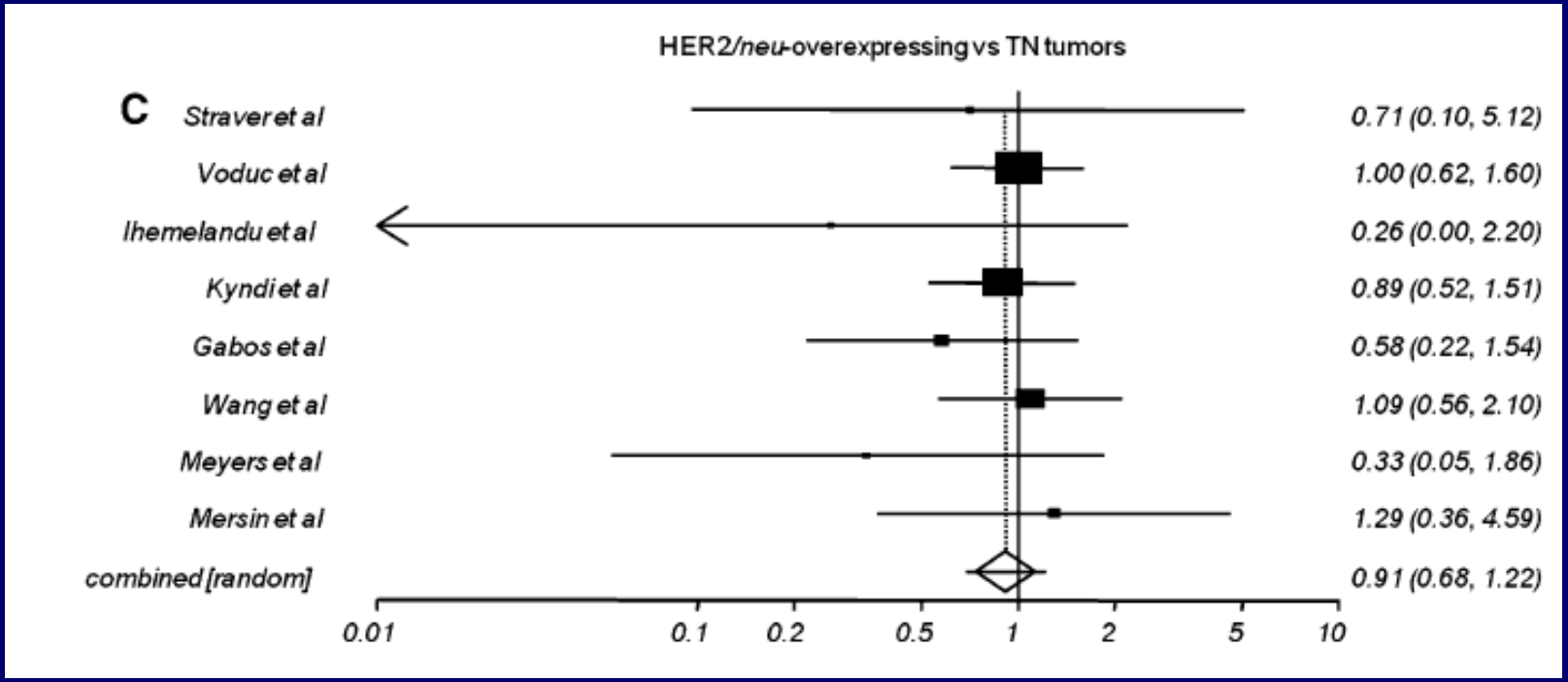
- TNBC > non-TNBC



Lowery AJ et al. Breast Cancer Res Treat 2012

Incidence of LRR following Mastectomy (Results of Meta-analysis II)

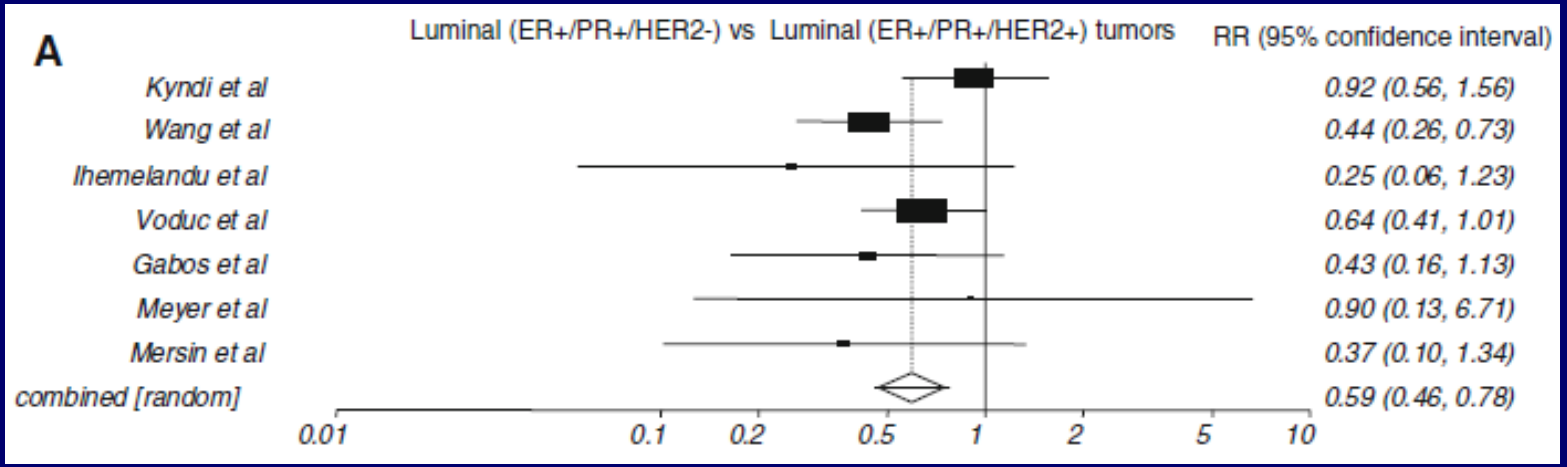
- HER2+ = TNBC > Luminal



Lowery AJ et al. Breast Cancer Res Treat 2012

Incidence of LRR following Mastectomy (Results of Meta-analysis III)

- Luminal B (HER2+) > Luminal A (HER2-)



Lowery AJ et al. Breast Cancer Res Treat 2012

Incidence of LRR (Summary of Meta-analysis III)

- After BCT
  - HER2+ > TNBC > Luminal B = Luminal A
- After Mastectomy
  - HER2+ = TNBC > Luminal B > Luminal A

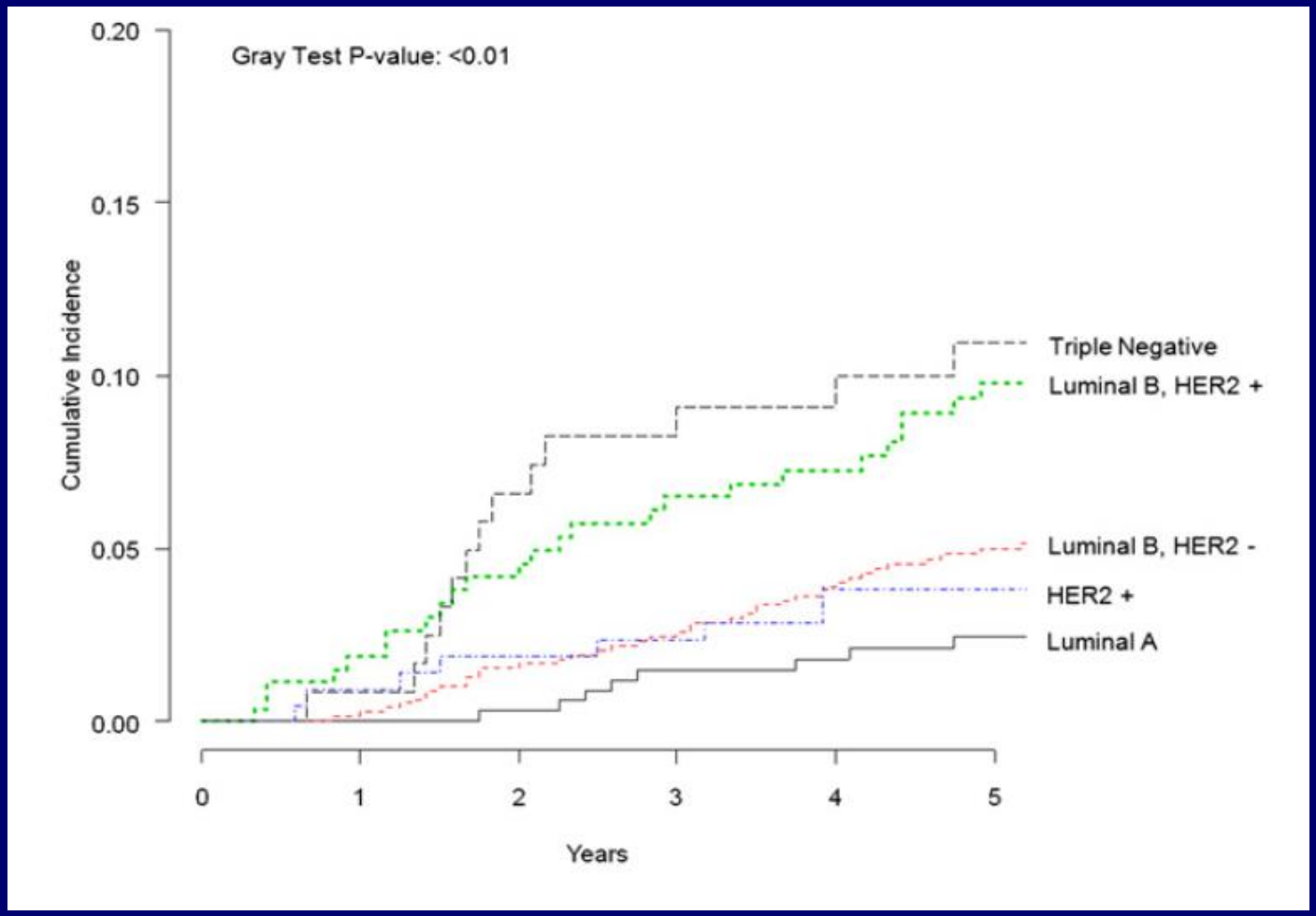
Lowery AJ et al. Breast Cancer Res Treat 2012

Incidence of LRR following Mastectomy vs. BCT (Results of Meta-analysis)

- In Luminal and HER2+ types
  - BCT > Mastectomy
- In TNBC
  - BCT = Mastectomy

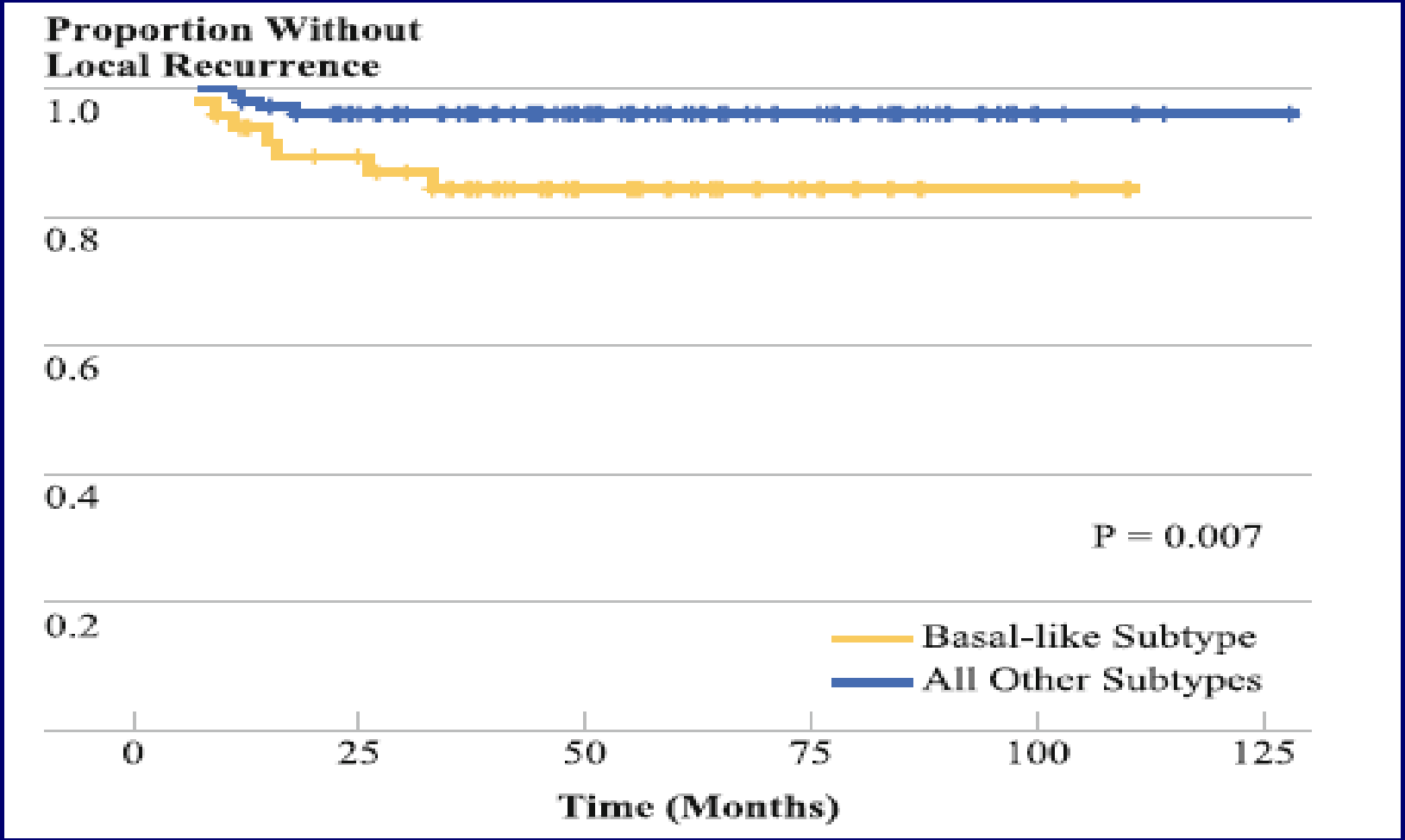
Lowery AJ et al. Breast Cancer Res Treat 2012

Breast cancer subtype affects LLR after immediate breast reconstruction



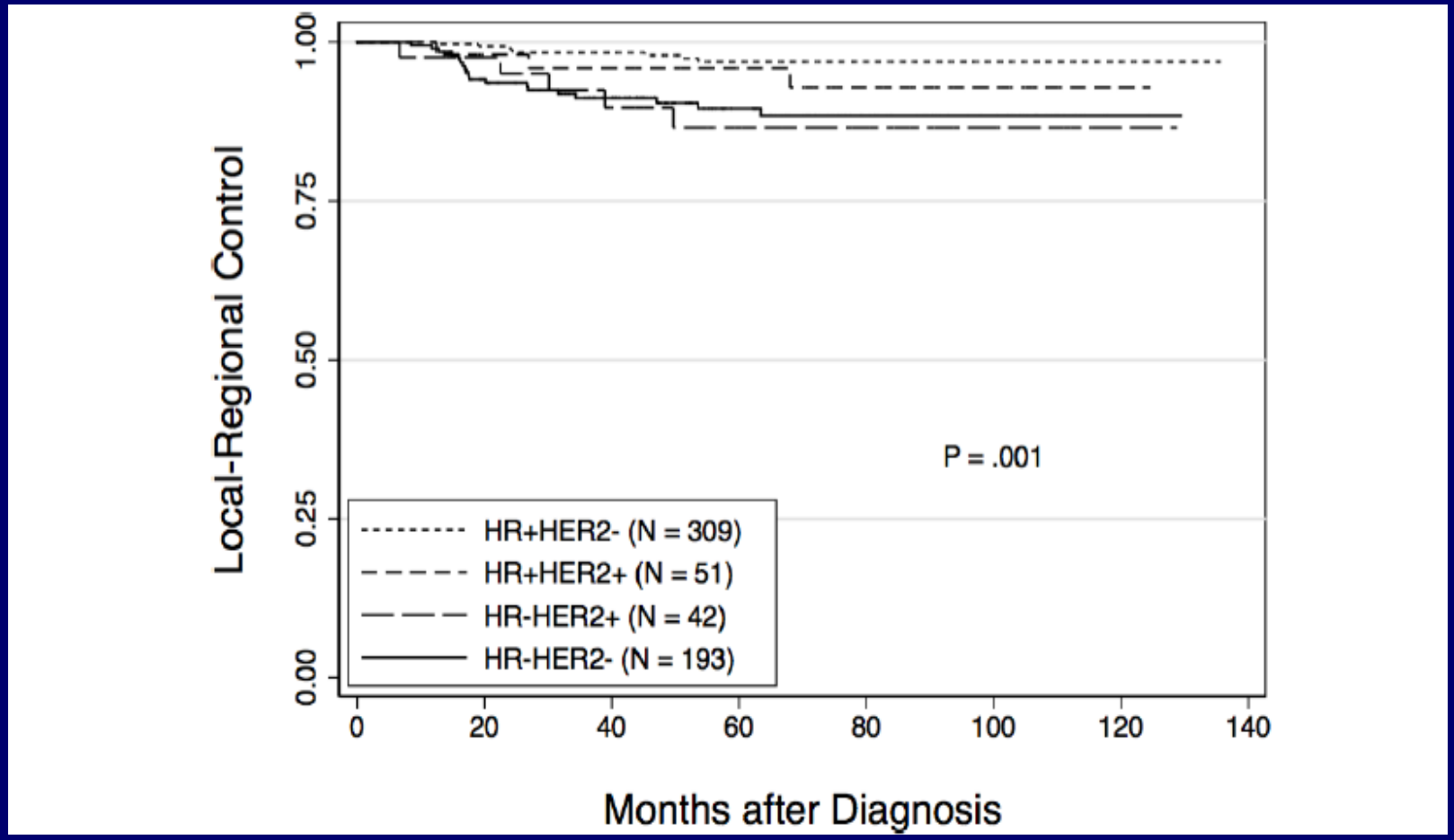
Kneubil MC et al. Eur J Surg Oncol 2013

TNBC is more likely to develop LLR following neoadjuvant CTx



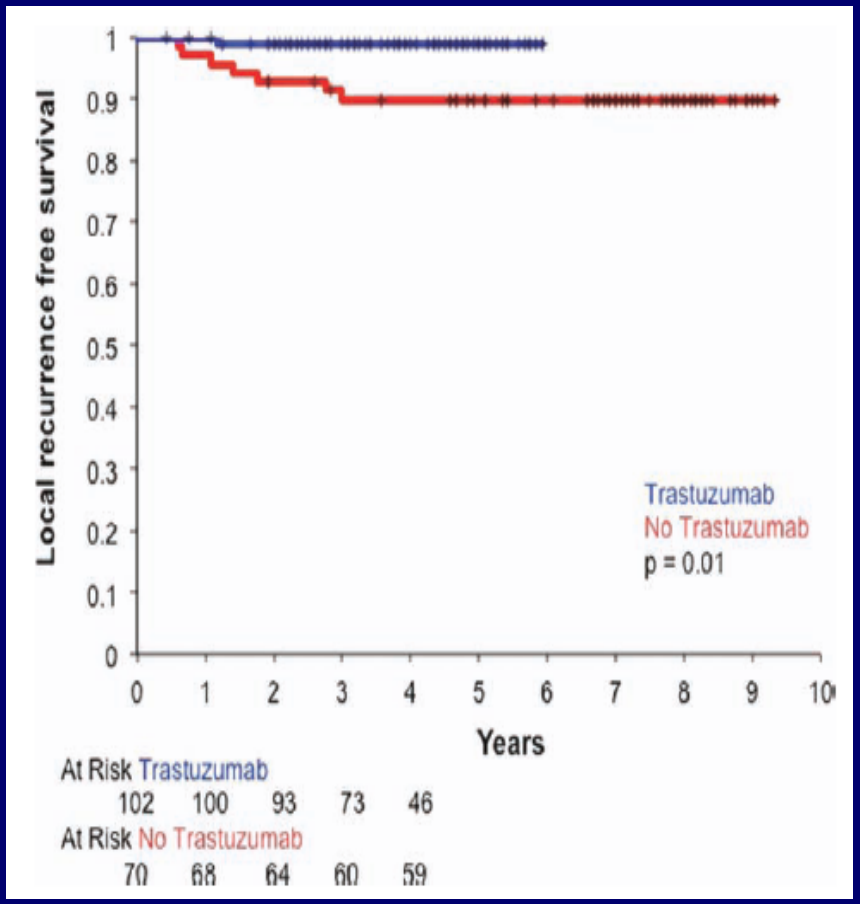
Meyers MO et al. Ann Surg Oncol 2011

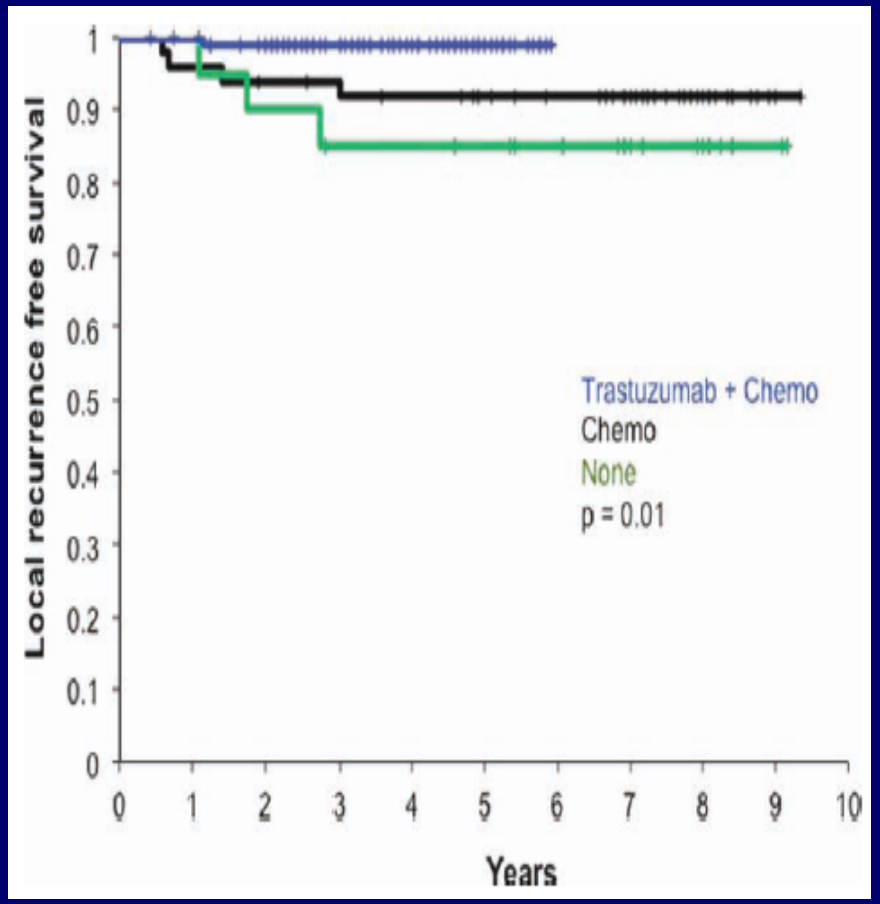
Luminal Type tumors show good Locoregional control following neoadjuvant CTx



Candle AS et al. Breast Cancer Res 2012

Adjuvant Trastuzumab reduces LRR in women with HER2+ tumor after BCT (MSKCC)

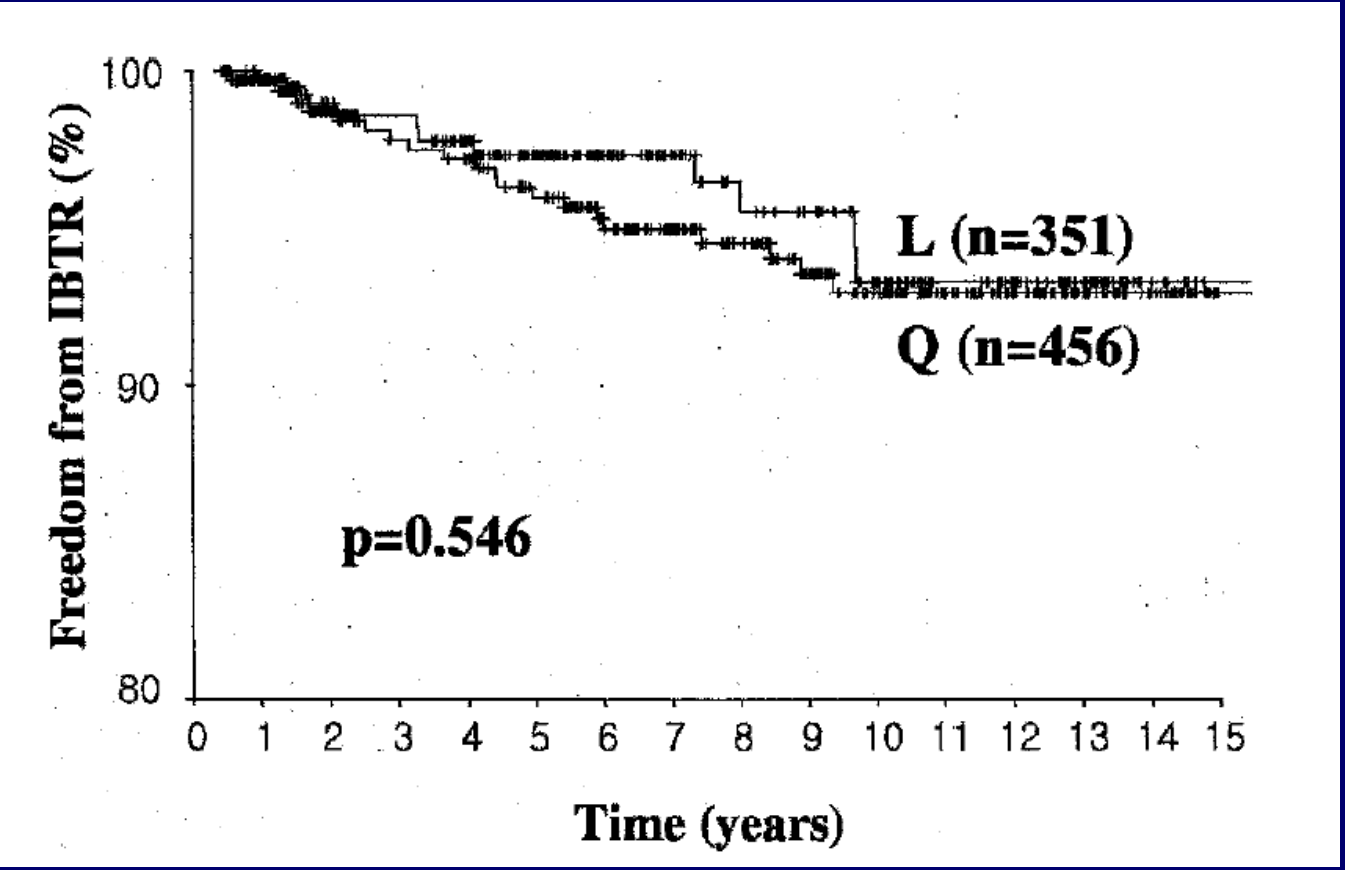




Kiess AP et al. Cancer 2012

Korean Data Relevant to These Issues:

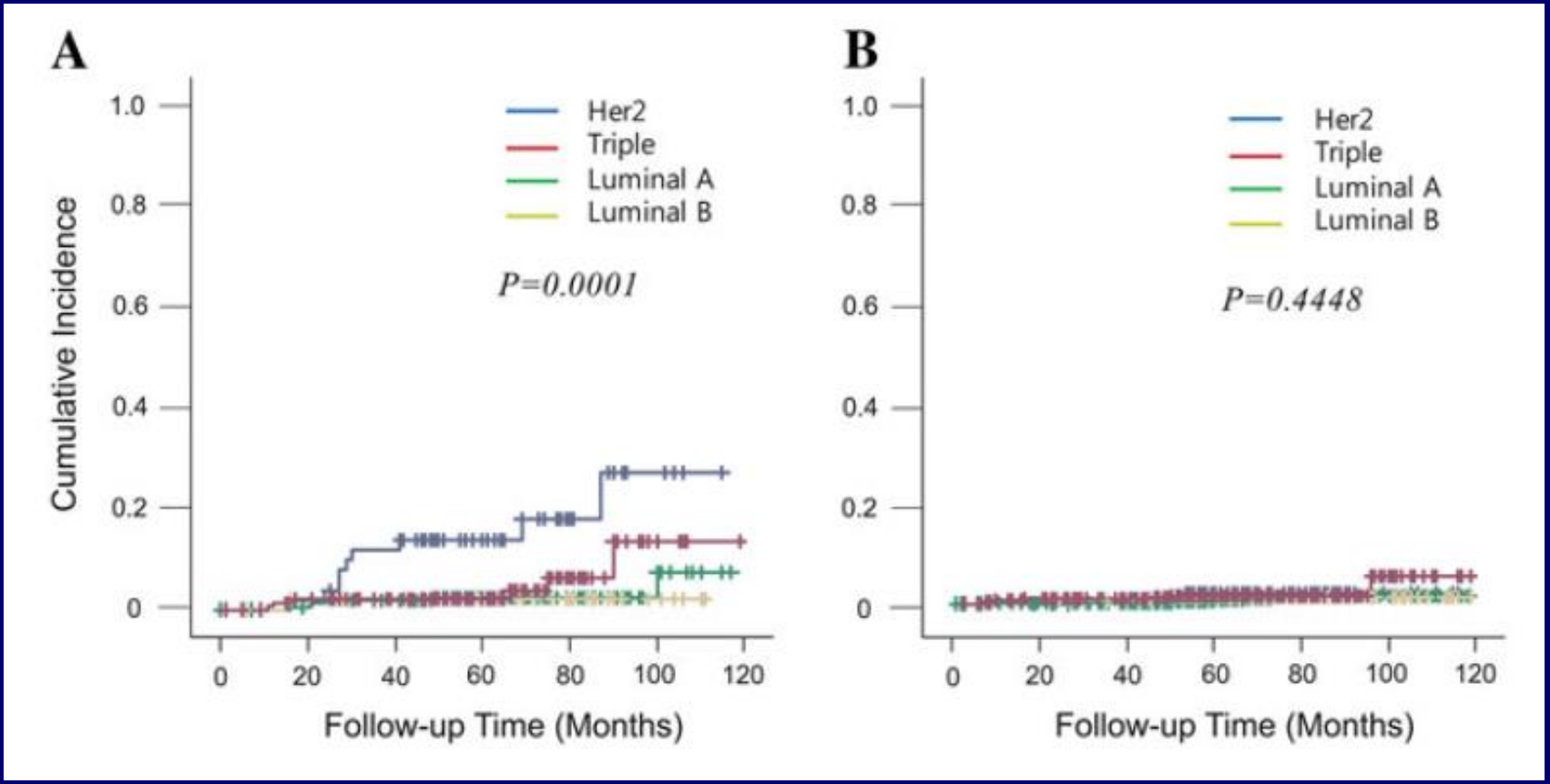
Extent of resection (Q vs. L) is not associated with IBTR if clear margin can be achieved (KCCH database)



Noh WC et al: World J Surgery 2006

Korean Data Relevant to These Issues:

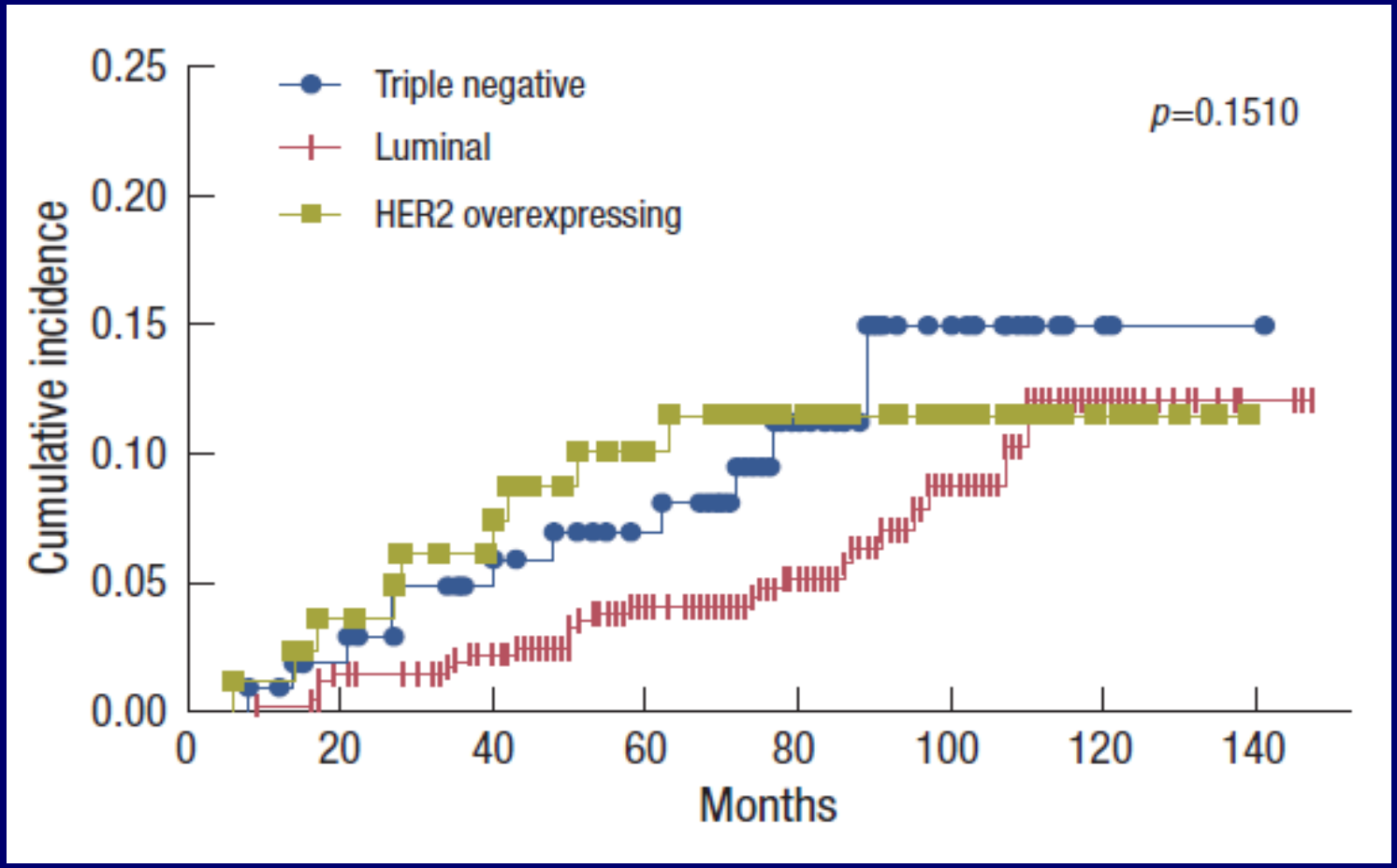
Young Age (<40) is associated with IBTR after BCT in patients with HER2+/ER- subtype (AMC and SNUH database)



Kim HJ et al. Breast Cancer Res Treat 2011

Korean Data Relevant to These Issues:

LRR rates were not different among the molecular subtypes (SMC database)



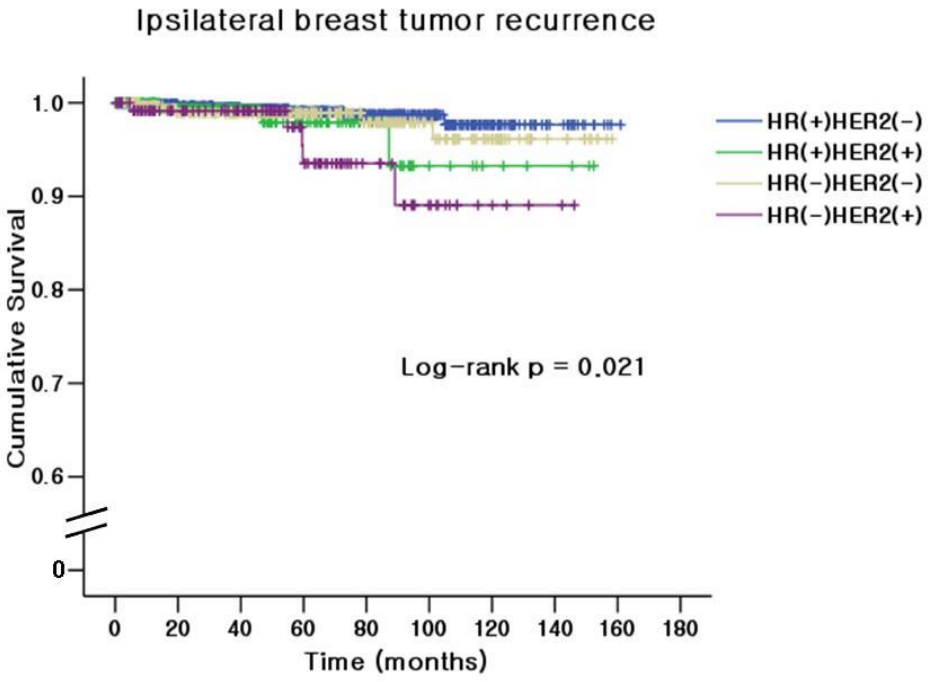
Noh JM et al. J Breast Cancer2011

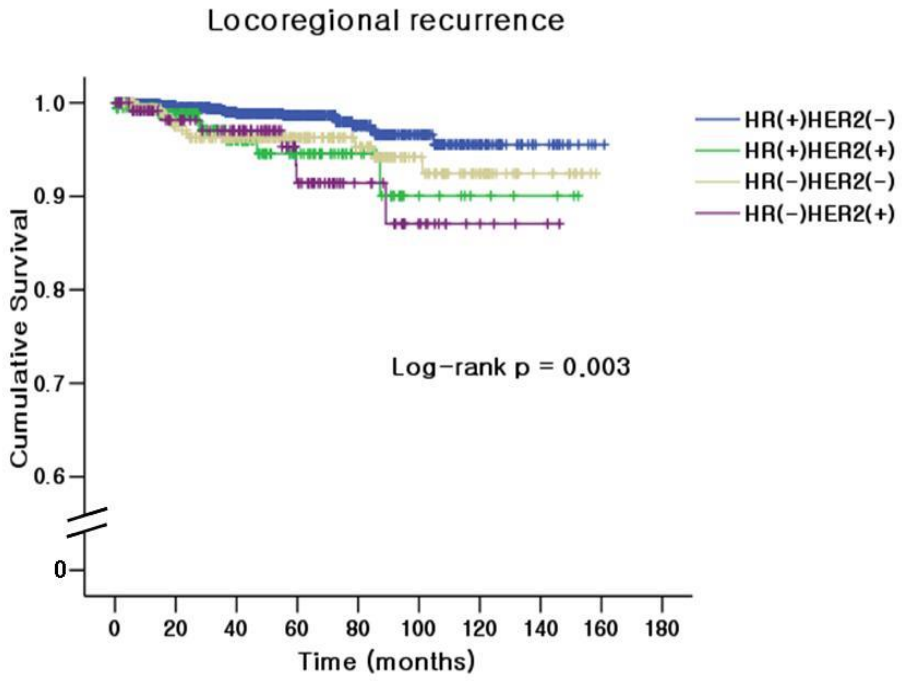
IBTR and locoregional recurrence after BCT according to the subtypes

- Korea Cancer Center Hospital (KCCH)
- 1983 ~ 2012
- Stage I~III invasive breast Ca
- BCS: 1896 (37.6% of total cases)
- BCS with known HR/HER2 status: 1752
  - HR(+)HER2(-): 1120 (63.9%)
  - HR(+)HER2(+): 185 (10.6%)
  - HR(-)HER2(-): 324 (18.5%)
  - HR(-)HER2(+): 123 (7.0%)

- Ipsilateral breast tumor recurrence: 22 (1.3%)
- Locoregional recurrence: 43 (2.5%)

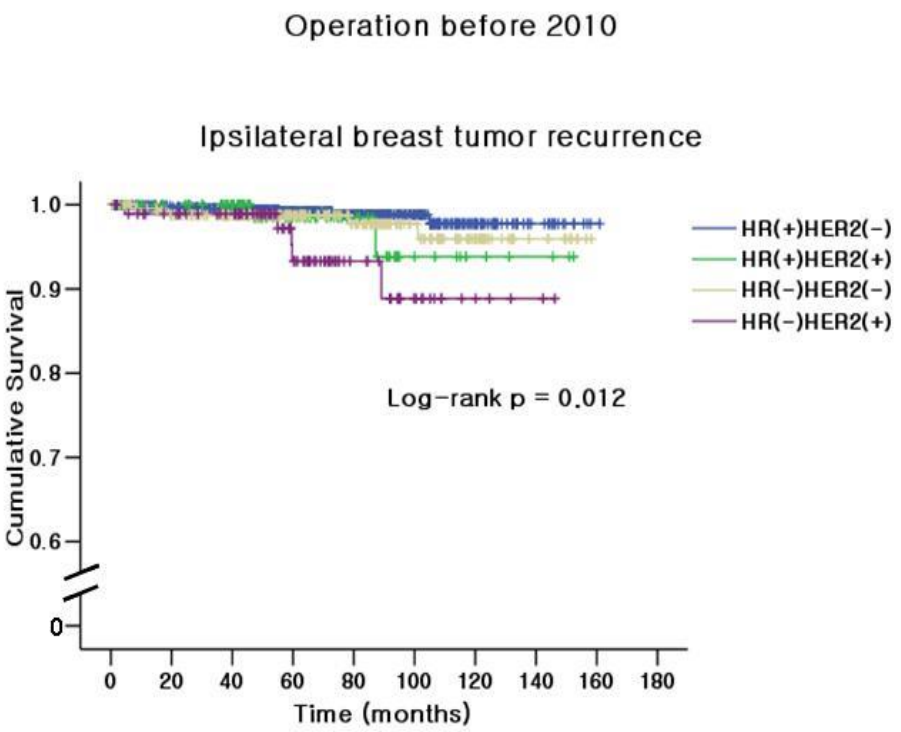
IBTR and LRR after BCT according to the subtypes (KCCH database)

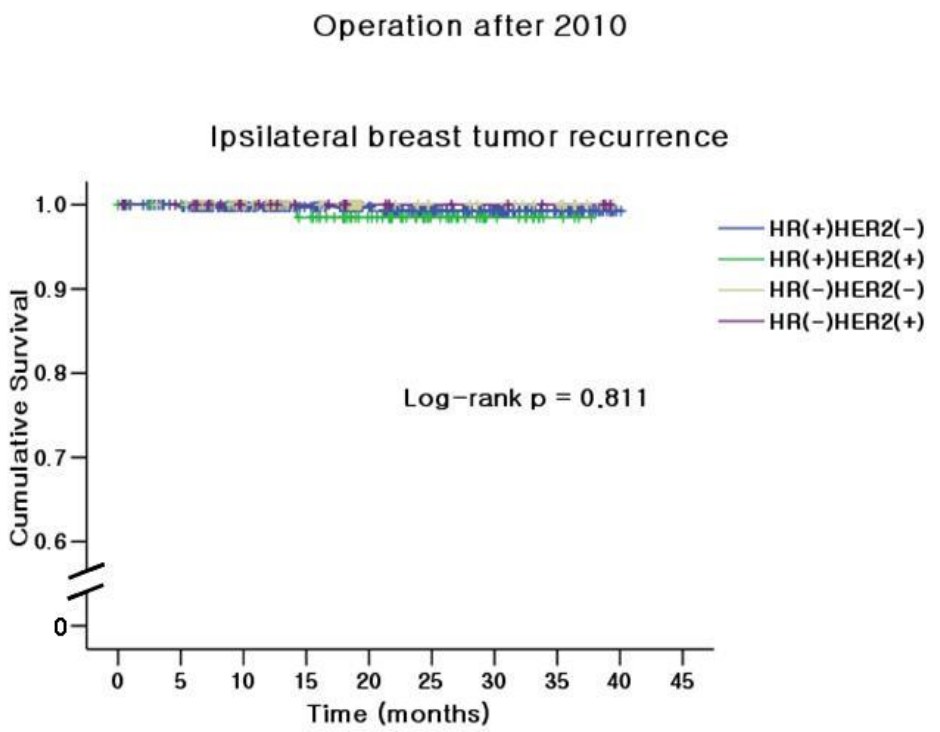




Data unpublished

IBTR after BCS according to subtype (Before and after Trastuzumab era)





IBTR: 19/1166 (1.6%)

IBTR: 3/586 (0.5%)

Data unpublished

2013 St Gallen Consensus Meeting Statements

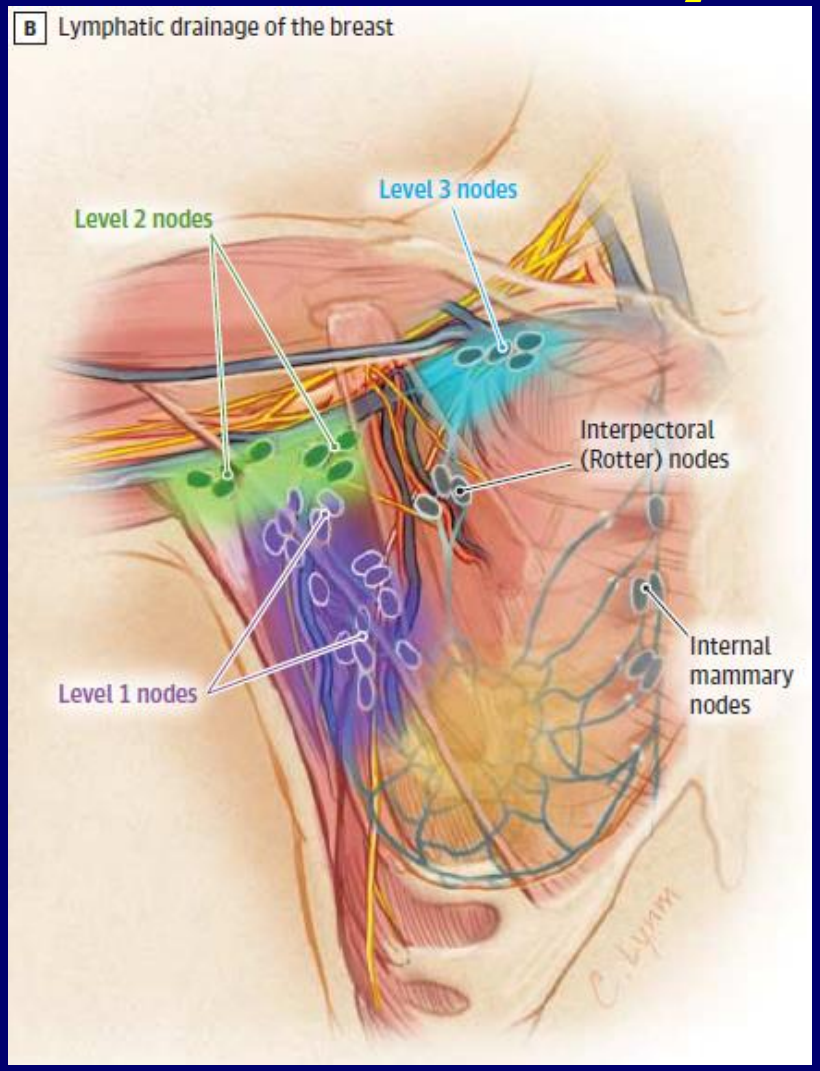
- Although the risk of LRR is related with the biologic subtypes of disease, there is no evidence that more extensive surgery will overcome this risk.

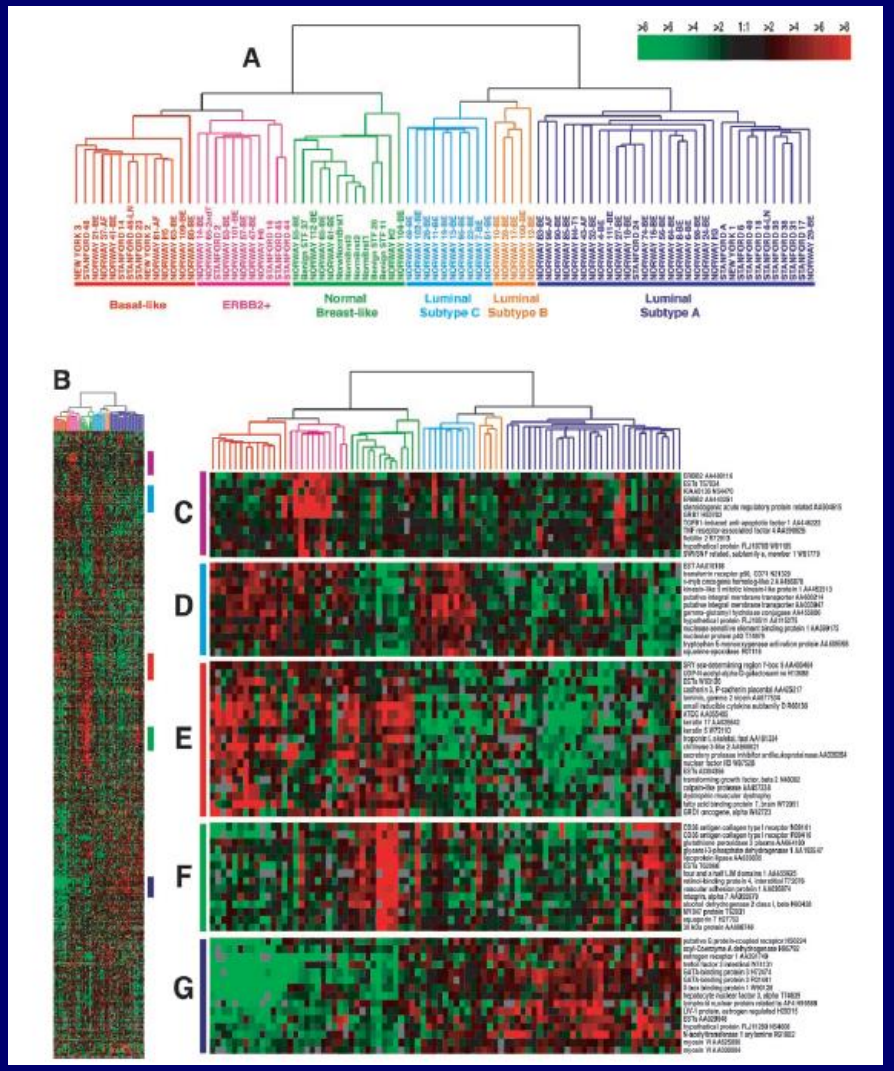
- Effective systemic therapy decreases LRR.

Local control is a result of complex interaction among

- Local treatment (surgery, RT)
- Tumor burden
- Biologic subtypes of tumor
- Systemic therapy

Molecular Subtypes and Axillary Interventions

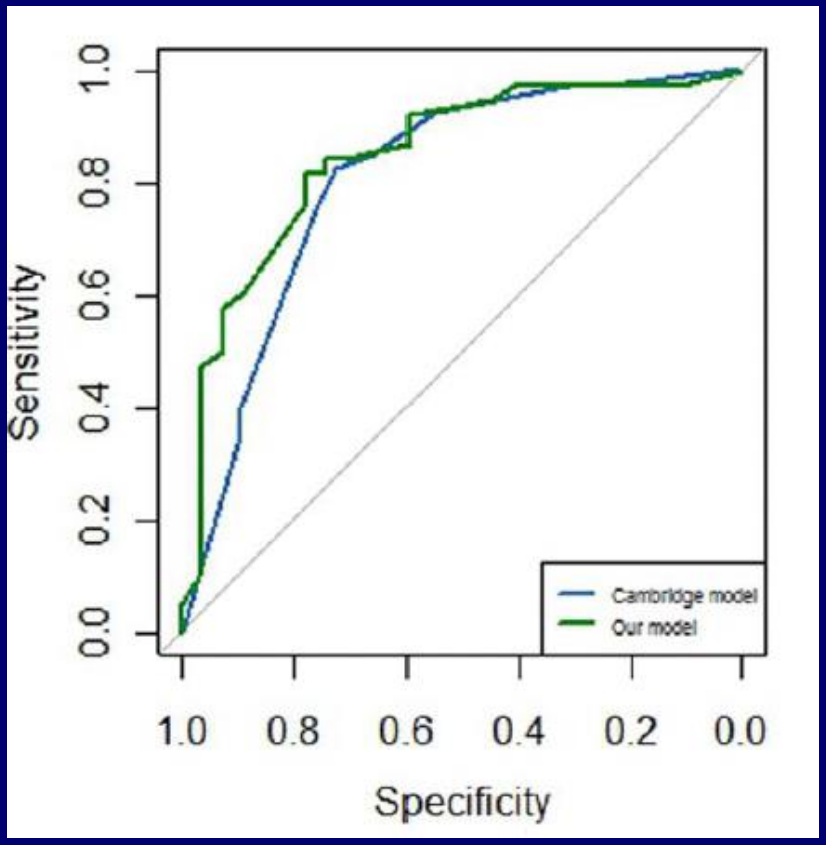


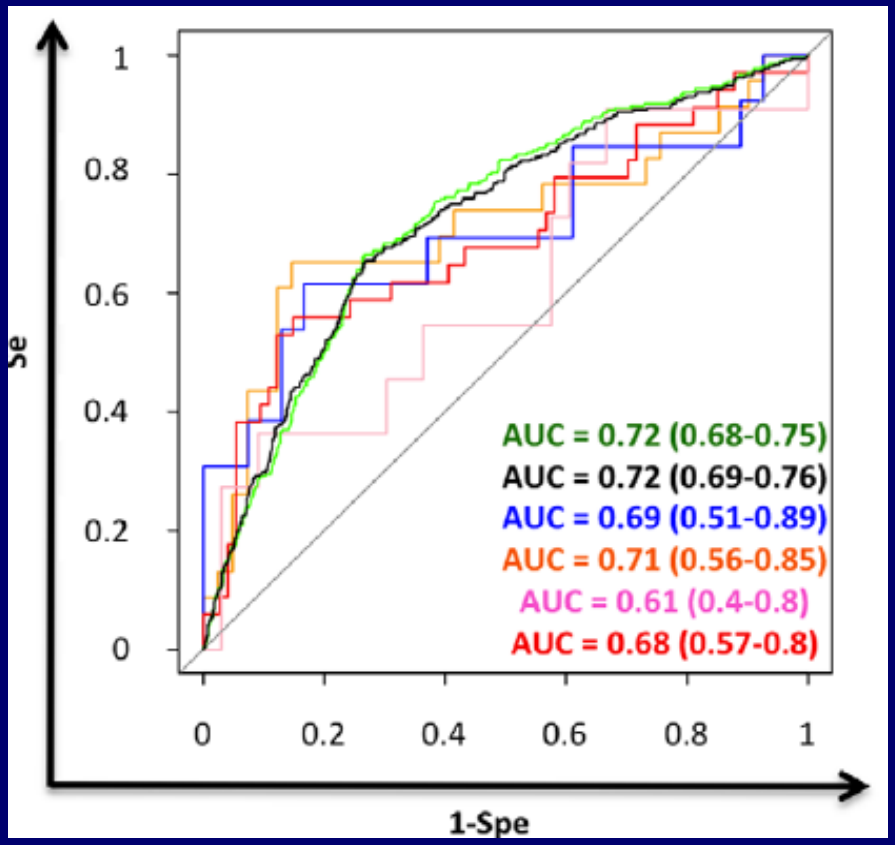


Current issues about Axillary Intervention

- Prediction of non-SLN metastasis in women with metastatic SLNs
- Completion axillary dissection in women with metastatic axillary nodes

Molecular subtype as a predictor of non-SLN metastasis in women with metastatic SLNs





Zhou W et al, PLoS 2012

Reyal F et al, PLoS 2012

Completion axillary dissection in women with metastatic axillary nodes

- Completion AD is a standard in women with positive SLNs
- AD can be omitted in women
  - with no palpable suspicious nodes
  - with tumor <3cm
  - with 3 or less positive SLNs
  - who are undergoing BCT

- Molecular subtypes ?

Q> **Surgical Treatment of breast cancer: Should it be different according to the molecular subtypes of tumor?**

A> **No.**

Conclusions

- Complete tumor removal with clear margin is crucial for local control of breast cancer:

  Nothing can compensate for poor surgery.

- Molecular subtypes determine the rates of LRR after either BCT or mastectomy.

- However, current guideline do not recommend applying different surgical strategies according to molecular subtypes of breast cancer.

Thank You!!