Pathological Issues in Preoperative Therapy

Young Kyung Bae, M.D.
Department of Pathology
Yeungnam University Medical Center
Daegu, Korea

Content

- Pre-treatment diagnosis and assessment of predictive markers
- Factors associated with pathological complete response (pCR)
- Post-treatment histological assessment and grading of the therapy response
- Evaluation of lymph nodes

Preoperative (neoadjuvant) therapy

- Increases breast conservation rates by surgical downstaging
- Pathologic response correlates with patients survival

	Neoadjuvnat therapy (preoperative)	Adjuvant therapy (postoperative)
Purpose	↓ Tumor burden	↓ Disseminated tumor cells Stem cells
Endpoint	Pathological complete response (pCR)	Increase survival

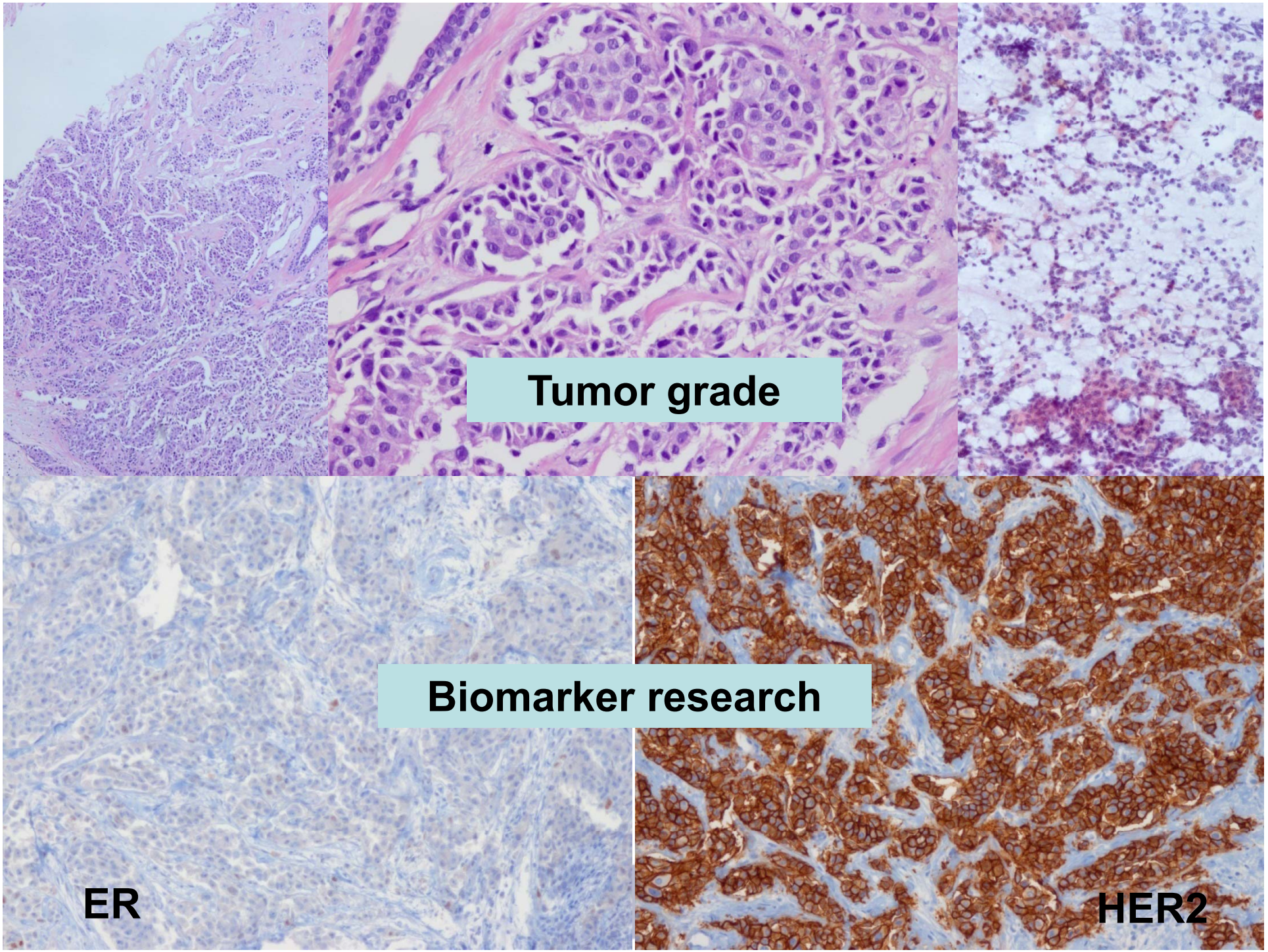
Pathologic complete response (pCR)

- The criteria for pCR are still controversial!
  - **No residual invasive cancer within both the breast and lymph nodes**

- About 60% of patients with no grossly detectable residual tumor after preoperative chemotherapy have persistent carcinoma histologically

Histological diagnosis

- A **core needle biopsy (CNB)** of the primary tumor is preferred to fine needle aspiration
  - Type, histological grade, presence of lymphovascular invasion, ER, PR, HER2…
- Fine needle aspiration can be used to confirm ALN metastasis


Tumor grade
Biomarker research
ER
HER2

ER, PR and HER2 on CNB

Concordance rate between CNB and excision				
	N	ER	PR	HER2
Park et al. (2009)	104	99%	97.1%	86.5%
Wood et al. (2007)	100	95.8%	90.3%	86.6%
Mann et al. (2005)	100	86%	83%	80%
Jacobs et al. (1998)	56	100%	NA	100%

ER, PR and HER2 on CNB

- **Pre-treatment CNB**
  - ✓ Test for ER, PR
  - ✓ Test for HER2 (retest by ISH if any membranous staining is seen on immunohistochemistry)

Pathologic features and response to neoadjuvant chemotherapy

Response	Features
Good	Ductal High grade ER- HER2+ High proliferation
Poor	Multicentric Low grade ER+ Low proliferation

Molecular subtypes and pCR

Molecular classification	No	pCR (%)	
Luminal A/B subtype	30	7	
Normal breast like	10	0	
HER2+	20	45	
Basal subtype	22	45	$p<0.001$

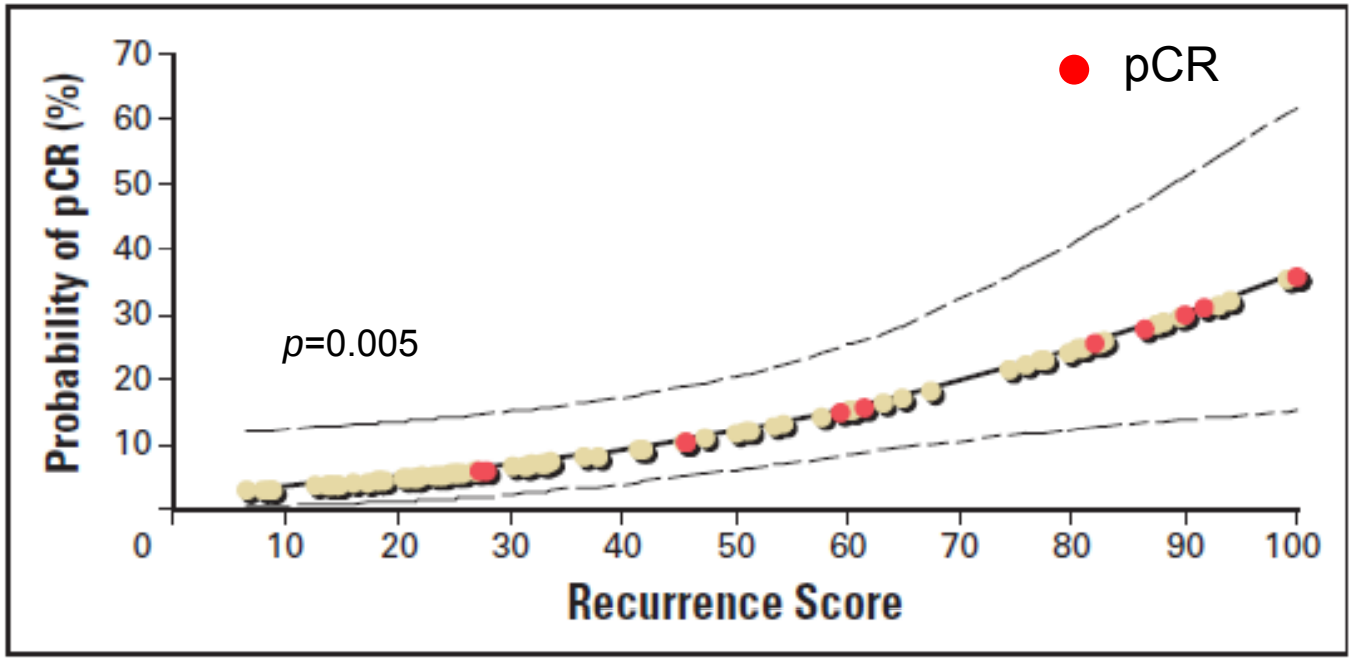
Clin Cancer Res 2005;11:5678-85

Triple negative status and pCR

		pCR(%)		
Regimens	**No**	**TNBC**	**Non-TNBC**	***p***
FAC/FEC/AC	308	20	5	0.001
TFAC/TFEC	588	28	17	0.072
Single agent taxane	58	12	2	0.82
Other	164	14	7	0.33
Total	**1118**	**22**	**11**	**0.034**

J Clin Oncol 2008;26:1275-81

Recurrence score and pCR



Gianni et al. JCO 2005;23:7265-77

Breast cancer molecular profiles and tumor response to neoadjuvant doxorubicin and paclitaxel: The I-SPY TRIAL (CALGB 150007/150012, ACRIN 6657)

IHC	Distribution (n=190)	pCR (n=190)	*p*
HR+HER2–	48%	10%	
HR+HER2+	12%	32%	
HR–HER2+	12%	50%	
HR–HER2–	28%	33%	
Gene profile Intrinsic subtypes	**Distribution (n=149)**	**pCR (n=144)**	***p***
Luminal A	29%	2%	
Luminal B	19%	15%	
HER2-enriched	15%	52%	
Basal	32%	34%	
Normal-like	5%	43%	< 0.0001

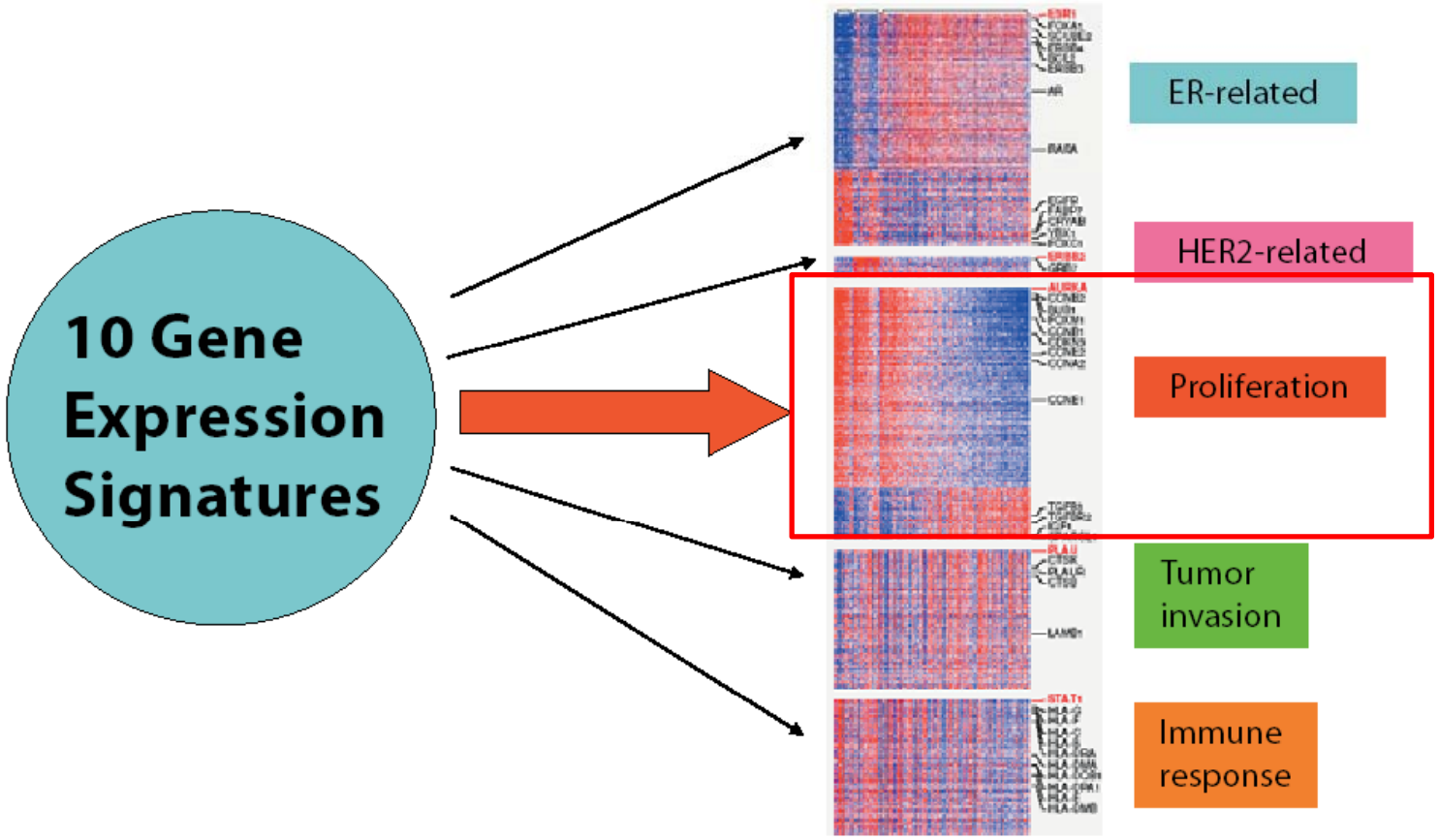
Esserman et al. 2009 ASCO abstract #LBA515

The I-SPY TRIAL, continued

Gene profile	Distribution (n=149)	pCR (n=144)	*p*
ROR-S			
Low	26%	5%	
Moderate	38%	22%	
High	37%	40%	8.8×10^{-4}
NKI 70			
Good signature	9%	0%	
Poor signature	91%	27%	0.038
Wound Healing			
Quiescent	23%	6%	
Activated	77%	30%	0.0049
p53 Mutation Gene Signature			
Wild type	50%	11%	
Mutation	50%	38%	3.7×10^{-4}

Esserman et al. 2009 ASCO abstract #LBA515

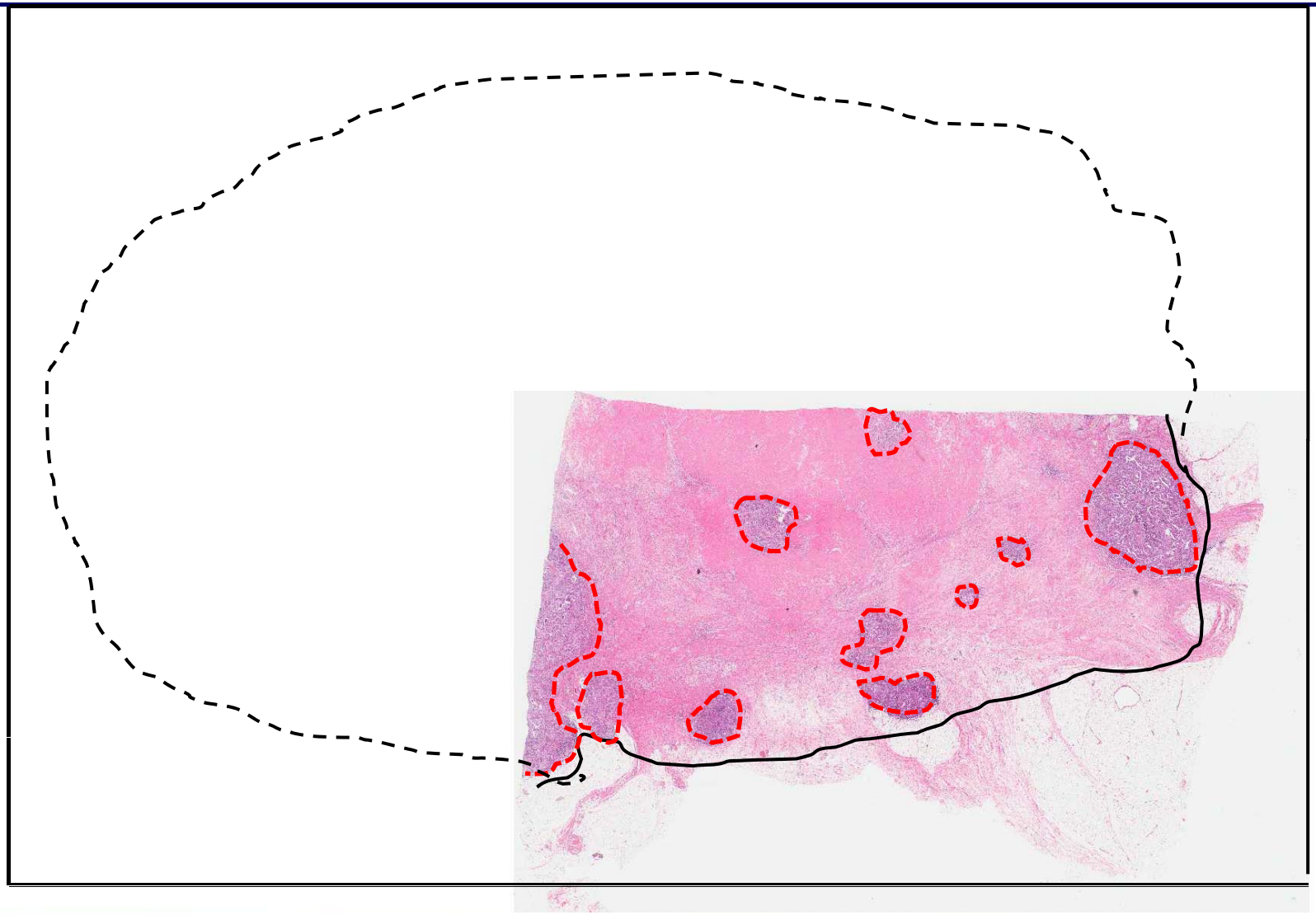
Proliferation-related genes are important in prognosis of breast cancer



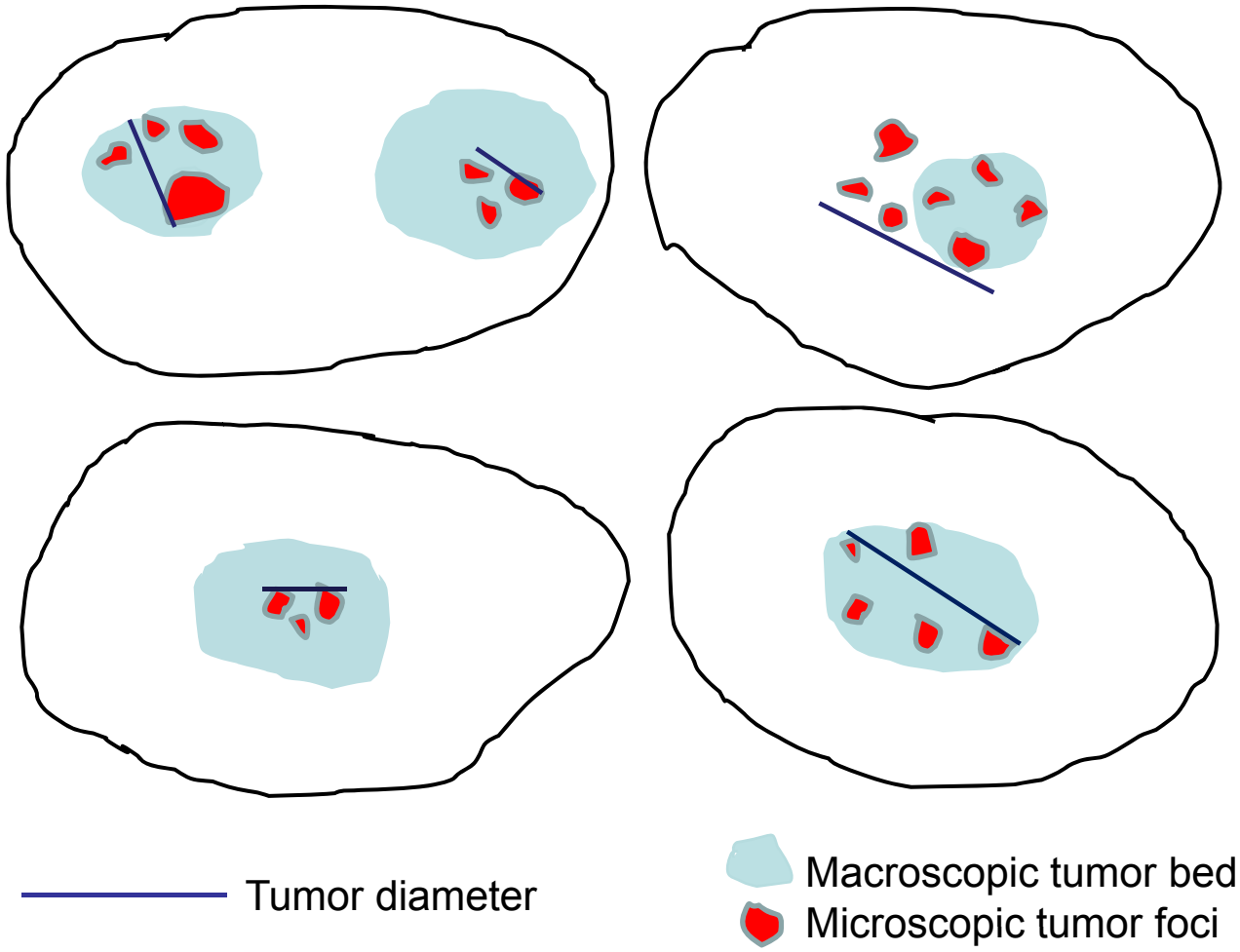
Pathobiology 2008;75:104-111

Histological assessment of therapy response

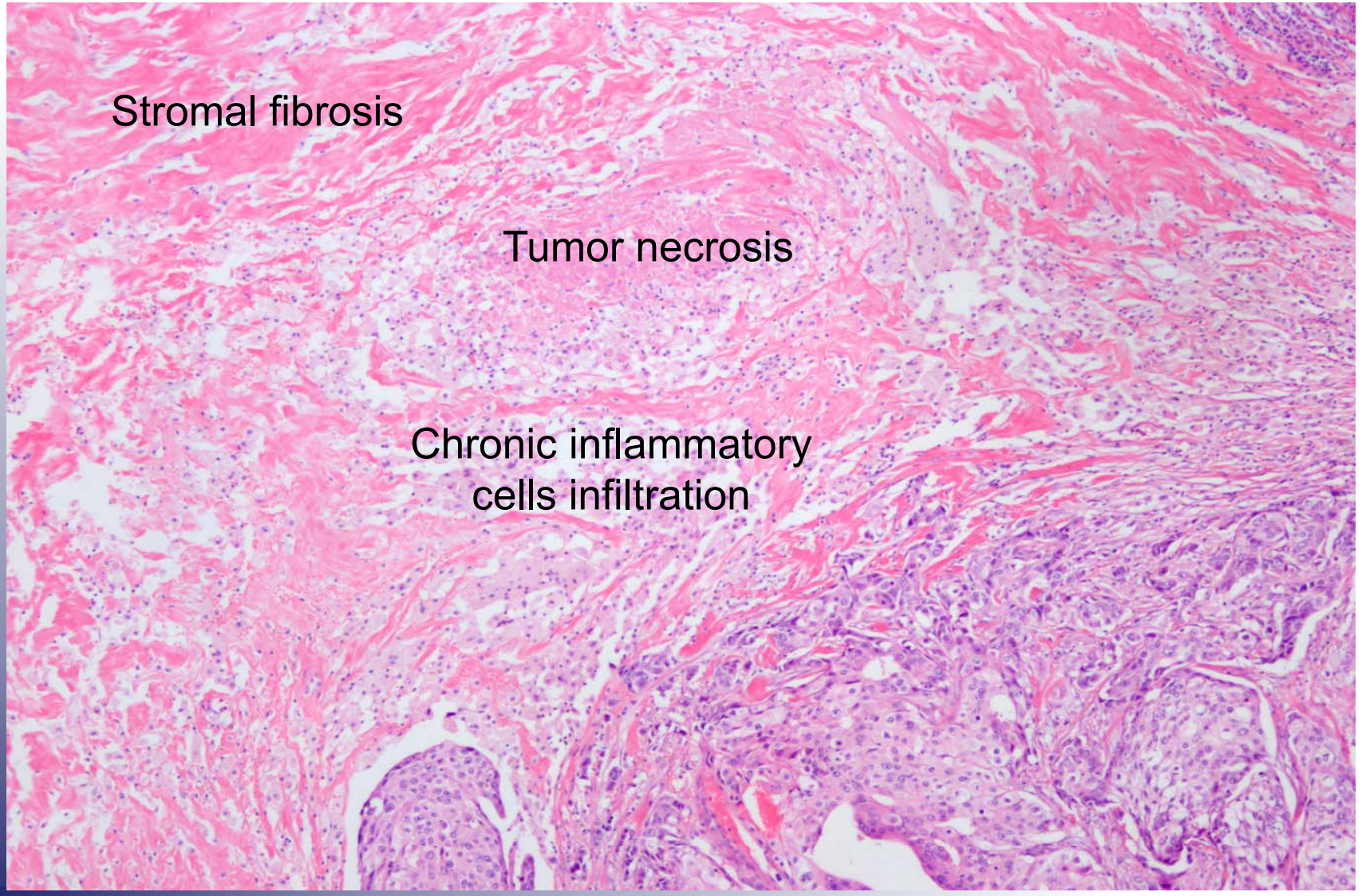
- Correlate with clinical and radiologic findings
- Sample widely to confirm pCR

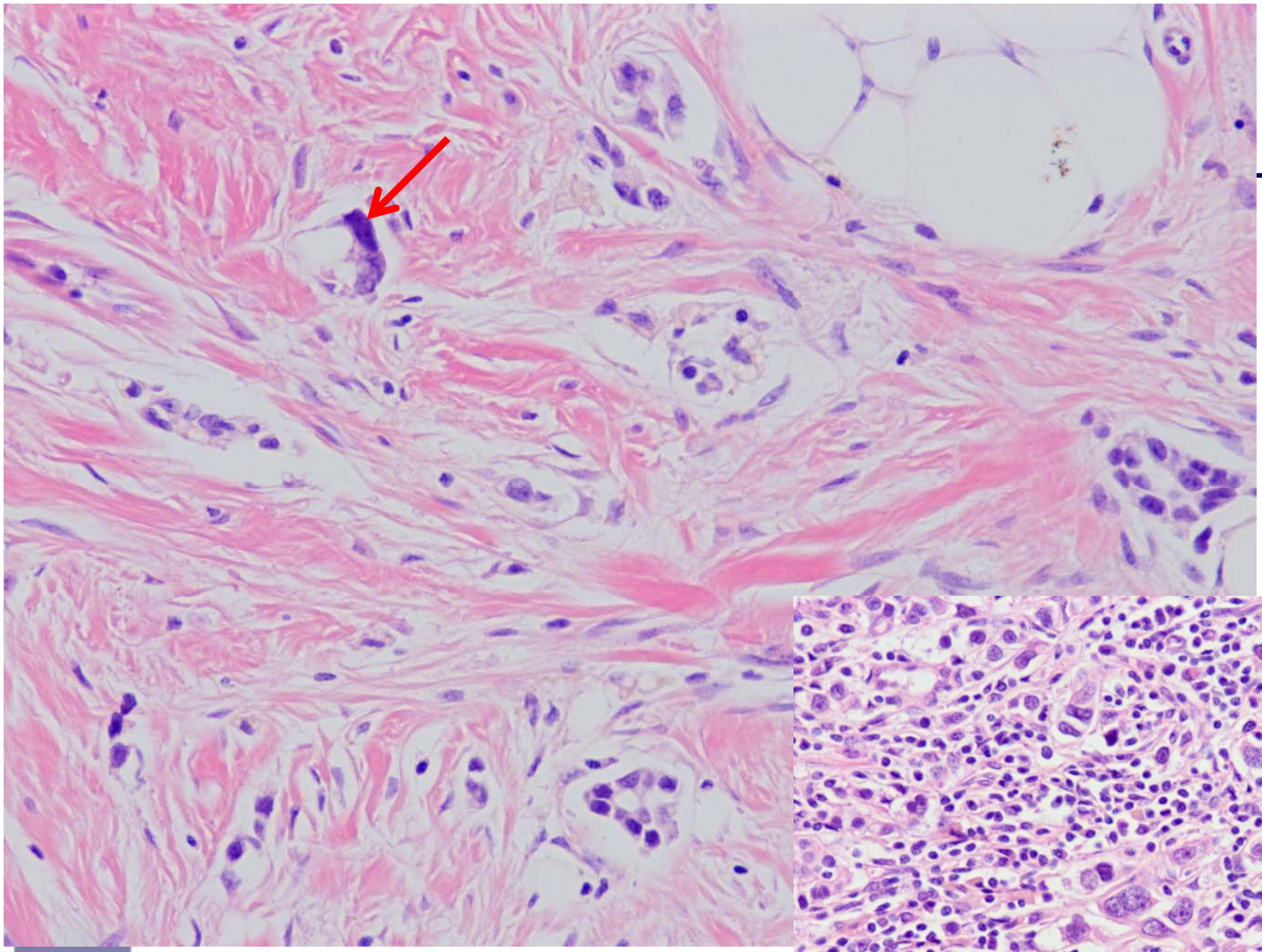


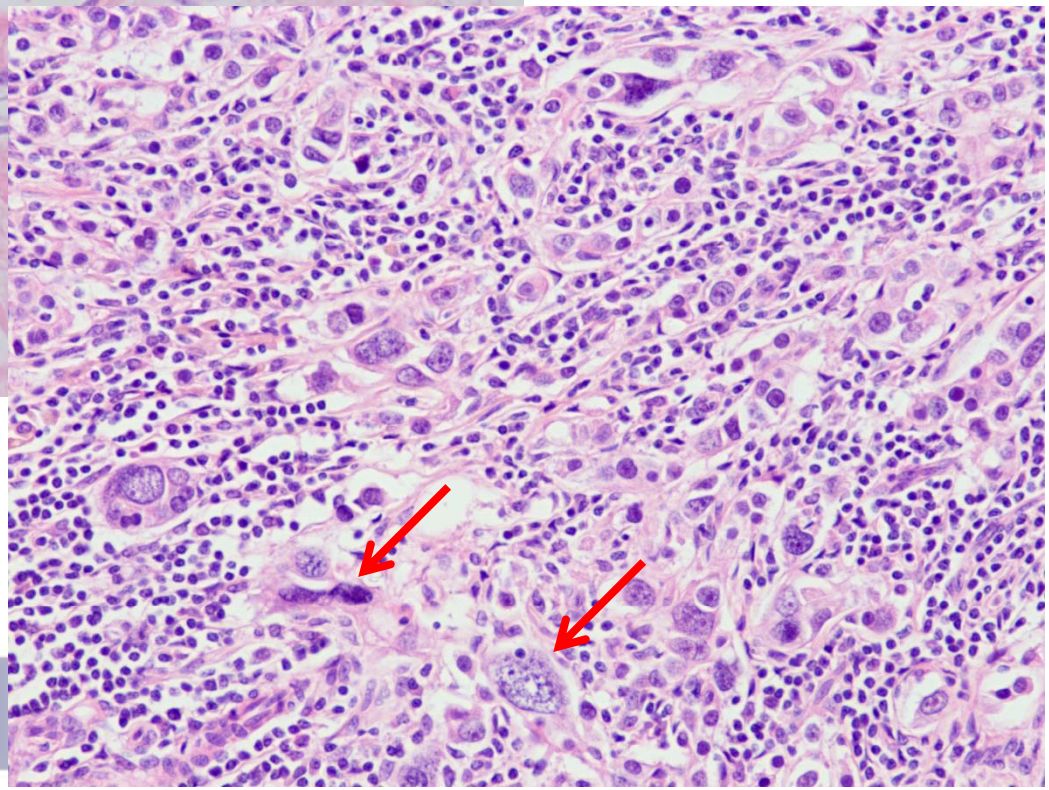
Tumor size


Tumor diameter
Macroscopic tumor bed
Microscopic tumor foci

Therapy effects on tumor cells





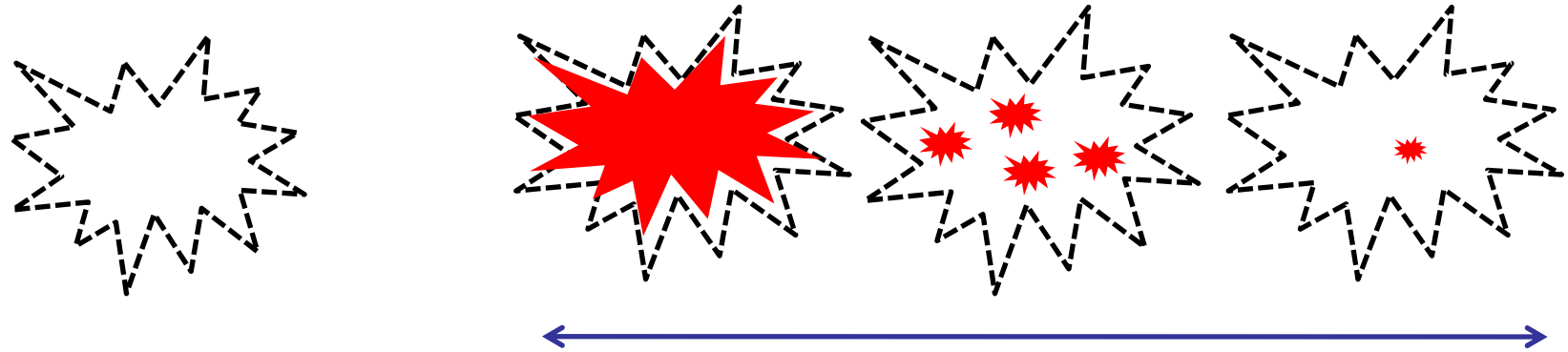


Therapy effects on immunohistochemical markers

- No significant differences in ER, PR, and HER2 expression before and after neoadjuvant treatment
- Hormone receptor status changed in 5% of neoadjuvant chemotherapy groups due to tissue sampling
- Proliferation rates (Ki67 index and mitotic count) may be increased, decreased or remain unchanged
- A tendency to have increased immunoreactivity for p53

Virchows Arch 2005;446:489-96
Am J Surg 2003;186:348-50
Anticancer Res 1996;16:3105-10

Grading of histological response



Pathologic complete response (pCR)

Residual disease (RD)

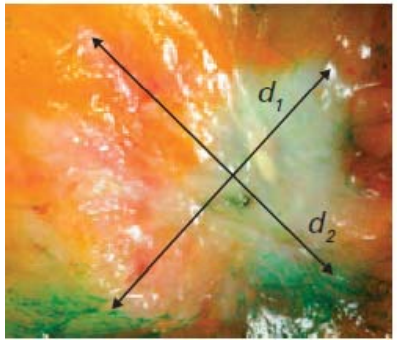
Residual tumor after chemotherapy

Original tumor before chemotherapy

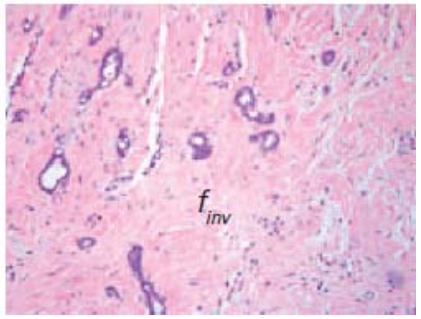
Residual cancer burden (RCB)

$$RCB = 1.4\,(f_{inv}d_{prim})^{0.17} + [4(1-0.75^{LN})d_{met}]^{0.17}$$

Primary tumor burden (size and cellularity)= f_{inv} x d_{prim}

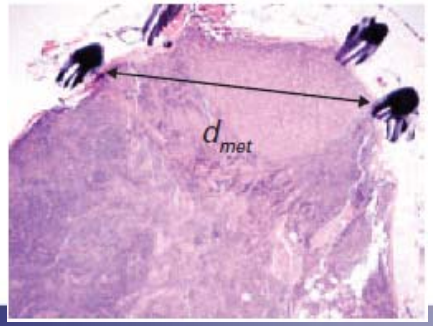


$d_{prim} = \sqrt{d_1 d_2}$



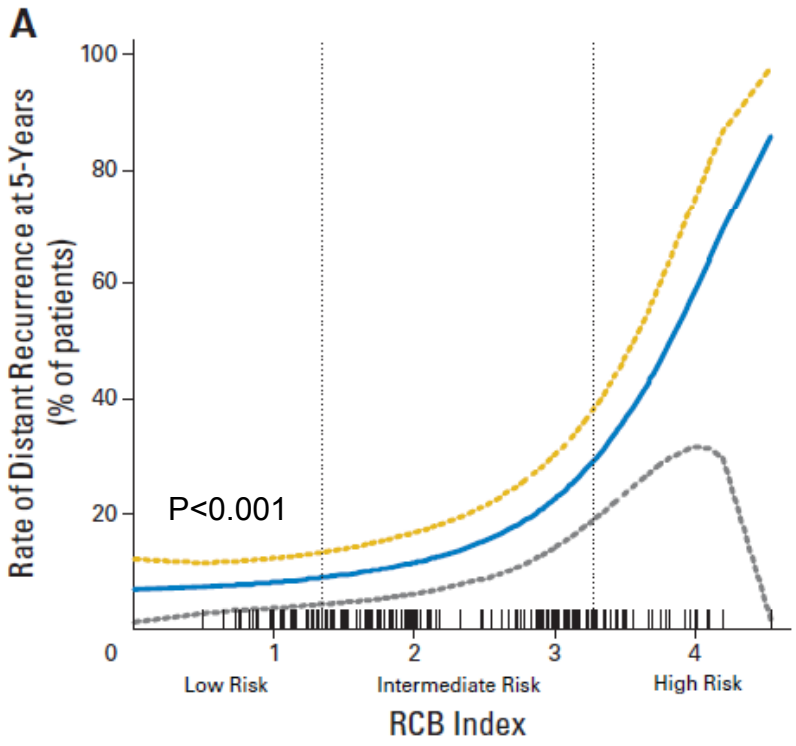
f_{inv} = (1 – (%CIS/100)) x (%CA/100)

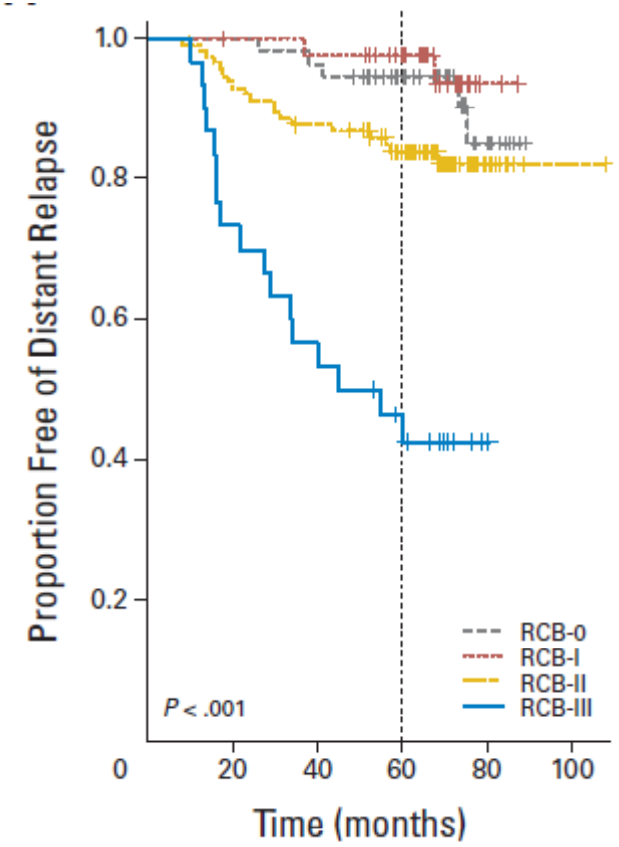
Axillary nodal burden (number and size)= $4(1\text{-}0.75^{LN})\ d_{met}$



J Clin Oncol 2007;254414-22

Residual cancer burden (RCB)





RCB 0 pCR, no invasive tumor
RCB Ⅰ minimal RD
RCB Ⅱ moderate RD
RCB Ⅲ extensive RD

English | Español | Türkçe | عربي

About Us | Locations | Events | Careers | Publications | How You Can Help | Contact Us | Go to myMDAnderson

Patient and Cancer Information | Education and Research | Keyword | Search

Departments, Programs & Labs | Research | Education and Training | Resources for Professionals | Events

Home » Education and Research » Resources for Professionals » Clinical Tools and Resources

E-mail | Print | Text Size

- Clinical Tools and Resources
  - Clinical Calculators
- Scientific Resources

Medical Calculator

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed

Primary Tumor Bed Area:	10 (mm) X 8	(mm)
Overall Cancer Cellularity (as percentage of area):	50	(%)
Percentage of Cancer That Is *in situ* Disease:	10	(%)

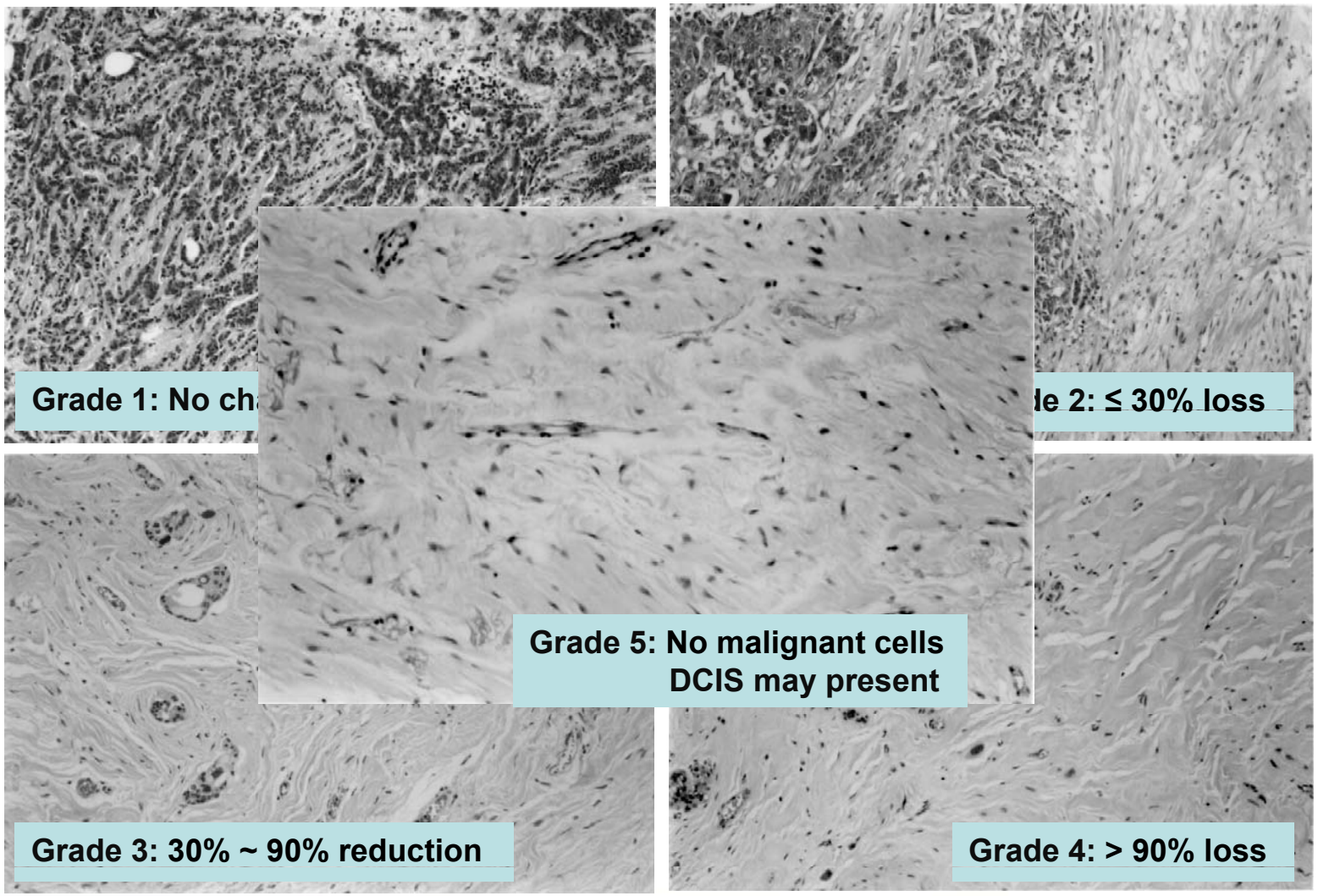
(2) Lymph Nodes

Number of Positive Lymph Nodes:	0	
Diameter of Largest Metastasis:	0	(mm)

Reset | Calculate

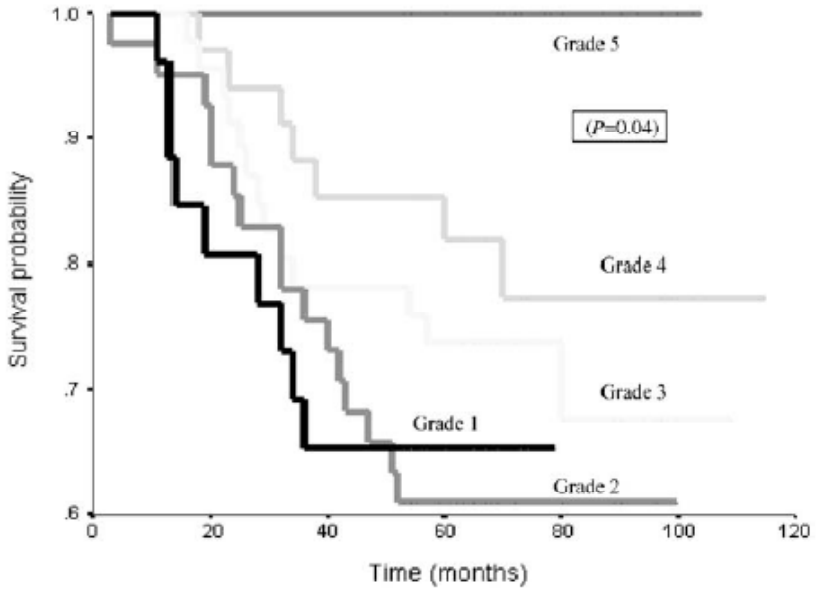
Residual Cancer Burden:	1.774
Residual Cancer Burden Class:	RCB-II

Miller-Payne cellularity assessment

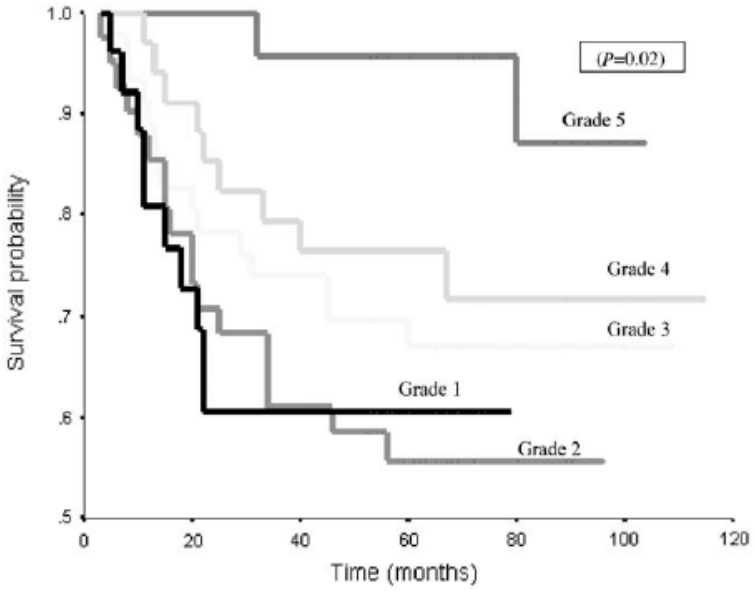


Ogston et al. Breast 2003;12:320-7

Miller-Payne cellularity assessment



OS



DFS

Ogston et al. Breast 2003;12:320-7

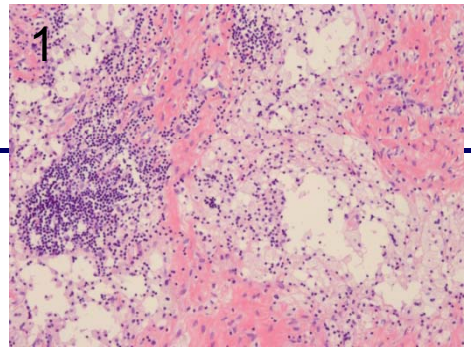
Breast Cancer (2008) 15:5–7
DOI 10.1007/s12282-007-0016-x

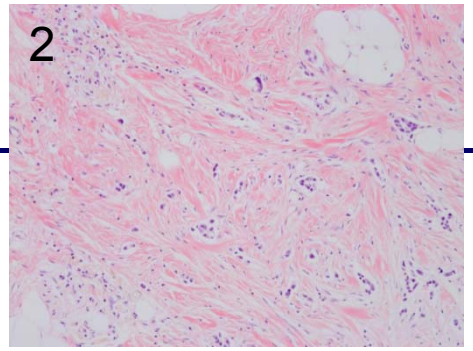
SPECIAL ARTICLE

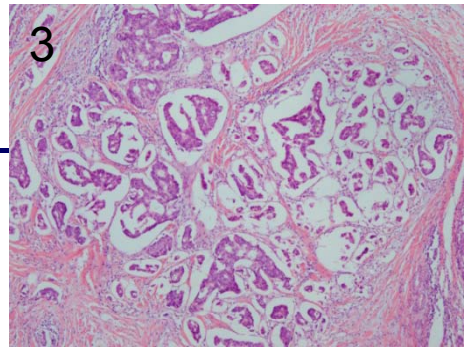
Histopathological criteria for assessment of therapeutic response in breast cancer (2007 version)

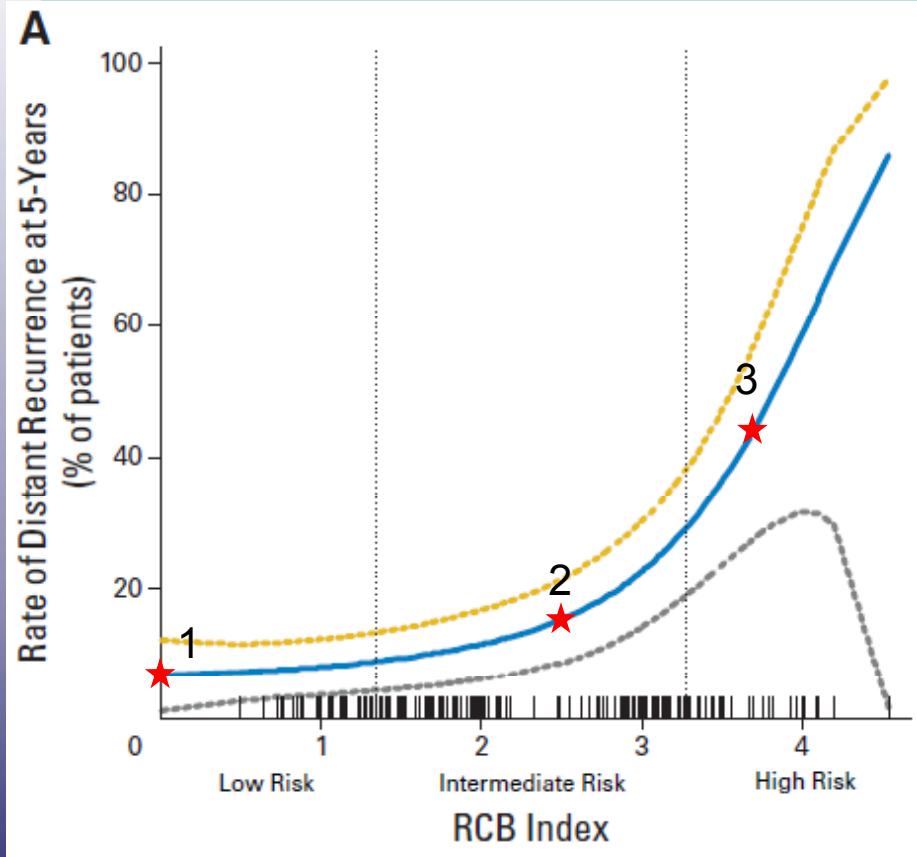
Masafumi Kurosumi · Sadako Akashi-Tanaka · Futoshi Akiyama · Yoshifumi Komoike · Hirofumi Mukai · Seigo Nakamura · Hitoshi Tsuda · (Committee for Production of Histopathological Criteria for Assessment of Therapeutic Response of the Japanese Breast Cancer Society)

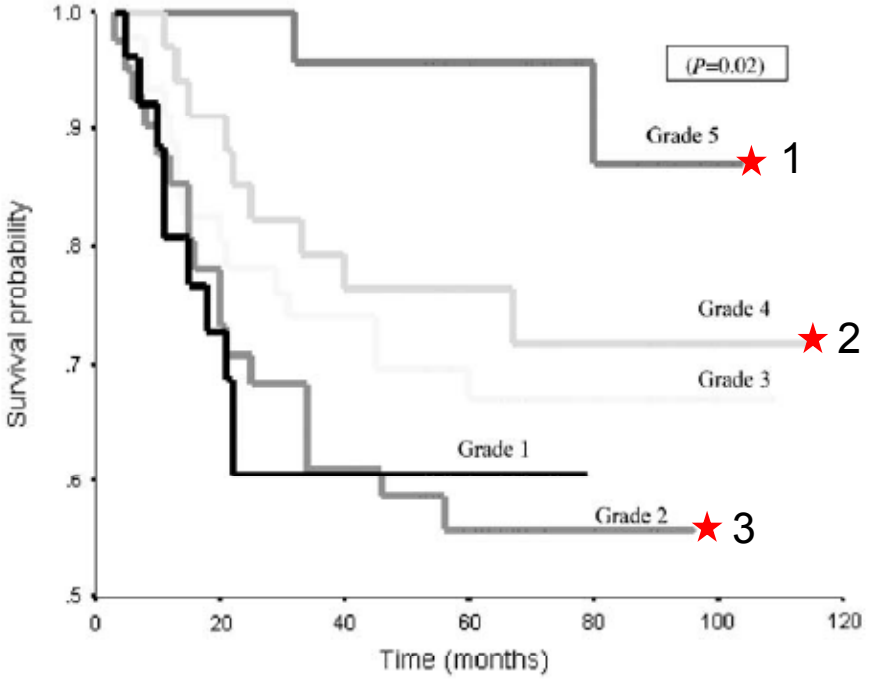
Grade 0 No response
Grade 1 Slight response
(1a) Mild response: marked changes in <1/3 of cancer cells
(1b) Moderate response: marked changes in 1/3~2/3
Grade 2 Marked response
(2a) marked changes in >2/3
(2b) only a few remaining cancer cells
Grade 3 Complete response
disappearance of all tumor cells











DFS

Miller/Payne cellularity

Importance of histological grading of therapy response

- The amount of residual invasive cancer after preoperative therapy is an important prognostic predictor!!!

Evaluation of sentinel lymph node

- Timing : before or after preoperative therapy

  - Pre-treatment SLN biopsy:

    Accurate assessment of initial nodal stage

  - Post-treatment SLN biopsy:

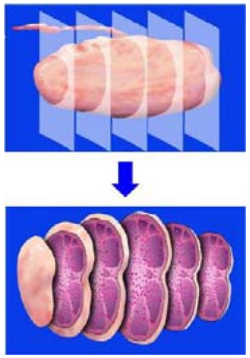
    Assessment of therapy response (pCR, RCB)

    No need for two-step operation

Lymph node handling

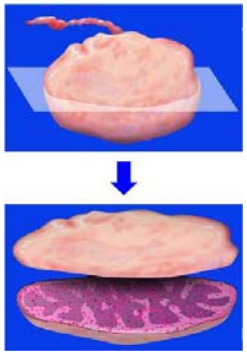
- **Sentinel LNs**

2 mm interval

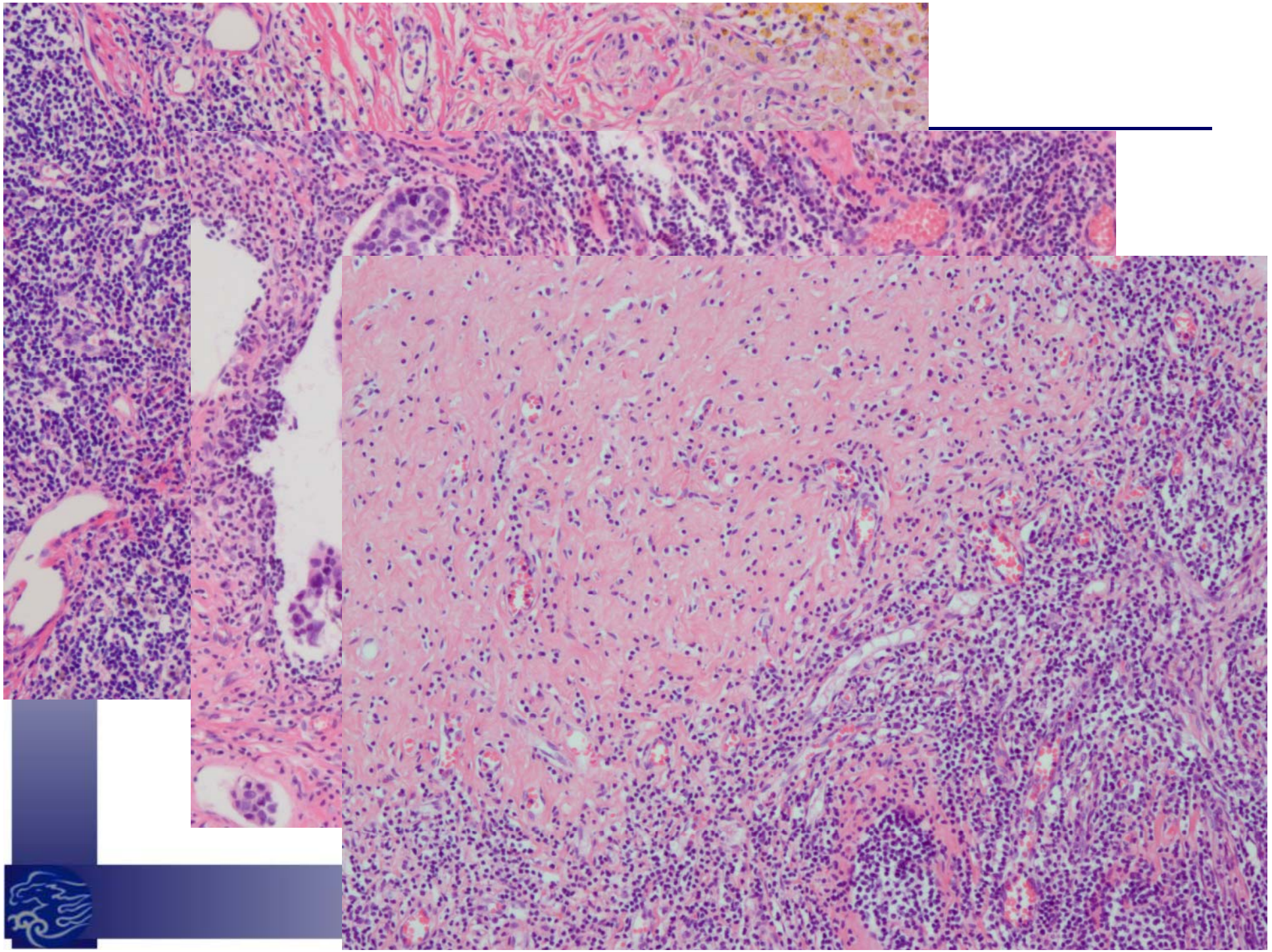


Cytokeratin immunostaining if the LN has minimal residual carcinoma

- **Non-sentinel LNs**



A single representative H&E section without cytokeratin immunostaining



Nodal status and clinical outcome

- Conversion to node-negative status after treatment
  - ER-negative tumor
  - pCR in the primary tumor
- The number of or the extent of involved lymph nodes is related to survival regardless of pCR or RD in the breast

Bear et al. J Clin Oncol 2006;24:2019-27
Kuerer et al. Ann Surg 1999;230:72-8

Summary

- Pre-treatment core needle biopsy provides full range of prognostic and predictive information
- Pathologic response in the breast and lymph nodes after preoperative therapy is an important prognostic factor
- A comprehensive and validated grading system of pathologic response is necessary to predict disease recurrence after preoperative therapy
- Pathologists take a role in the multidisciplinary approach to develop a new marker predicting response and resistance to therapy