Evaluation of Pathologic Response in Breast Cancer Treated with Primary Systemic Therapy

Eun Yoon Cho, MD, PhD
Department of Pathology and Translational Genomics
Samsung Medical Center
Sungkyunkwan University School of Medicine

Indications of NAC

- Management of locally advanced invasive breast ca including inflammatory BC
- 'Down-staging' of large inoperable cancers: reduced tumor size in order to avoid mastectomy
- Routine management of high risk BC: test the in vivo chemo sensitivity of the tumor cells

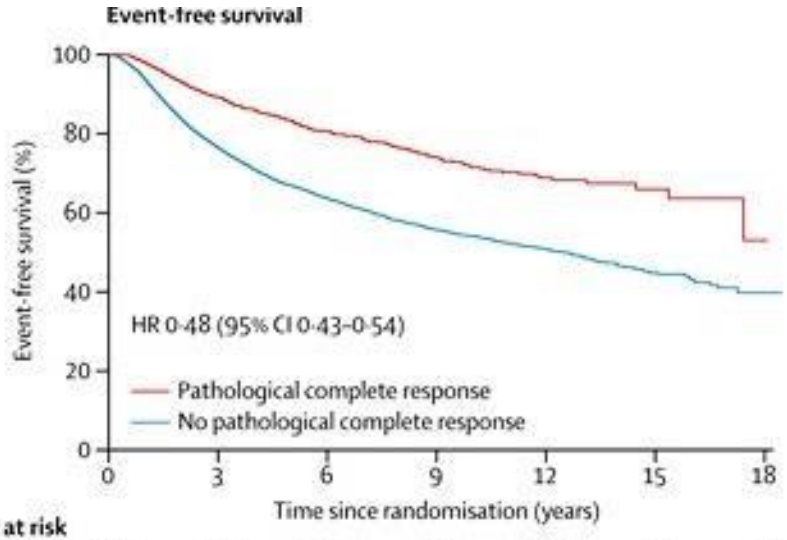
Contents

- pathologic complete response
- different patterns of tumor response in different molecular subtypes
- grading of partial response
- response in the lymph nodes
- evaluation of the axilla before and after treatment
- practical approach to sampling of the post-neoadjuvant surgical specimen
- detailed method for calculating the residual cancer burden (RCB) score

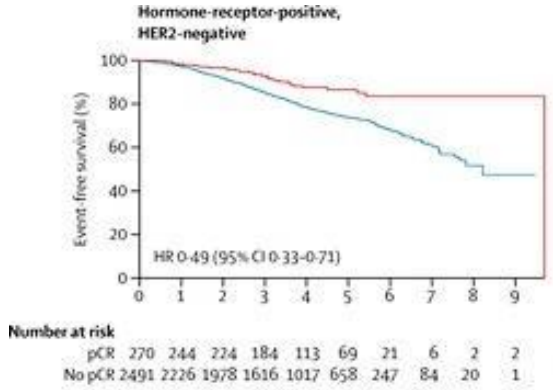
Pathologic Assessment of Specimen that received Neoadjuvant Therapy

- Pathologic complete response (pCR)
  - Absence of residual invasive carcinoma in the breast and lymph nodes at the time of surgery
  - Excellent prognostic indicator
  - validated and evaluable primary endpoint for neoadjuvant trials

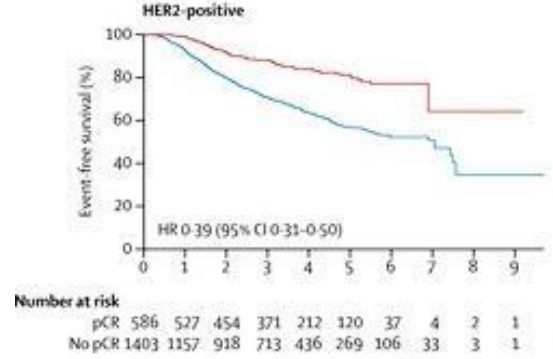
pCR and EFS



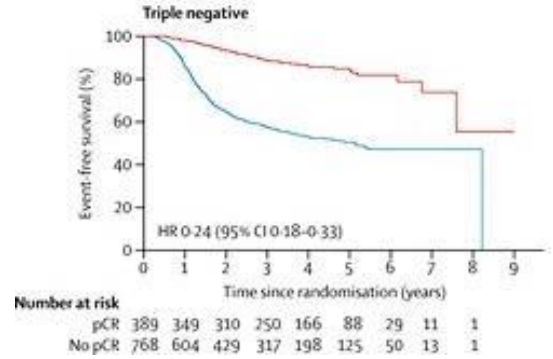
Number at risk							
Pathological complete response	2131	1513	583	337	124	35	2
No pathological complete response	9824	6169	2674	1523	525	165	1



Number at risk										
pCR	270	244	224	184	113	69	21	6	2	2
No pCR	2491	2226	1978	1616	1017	658	247	84	20	1



Number at risk										
pCR	586	527	454	371	212	120	37	4	2	1
No pCR	1403	1157	918	713	436	269	106	33	3	1



Number at risk										
pCR	389	349	310	250	166	88	29	11	1	
No pCR	768	604	429	317	198	125	50	13	1	

FDA Meta analysis (Cortazar et al, Lancet 2014)

- >11K patients from 12 NAC trials
- Median follow-up for EFS: 5.4 years

Methods to Determine Response to NAC

- Clinical examination
- Imaging methods (mammographs, US, MRI)
- Histopathologic evaluation

Clinical Response of NAC

- 60-80% patients with locally advanced breast carcinoma show measurable clinical response
- Imprecise

Methods to Determine Response to NAC

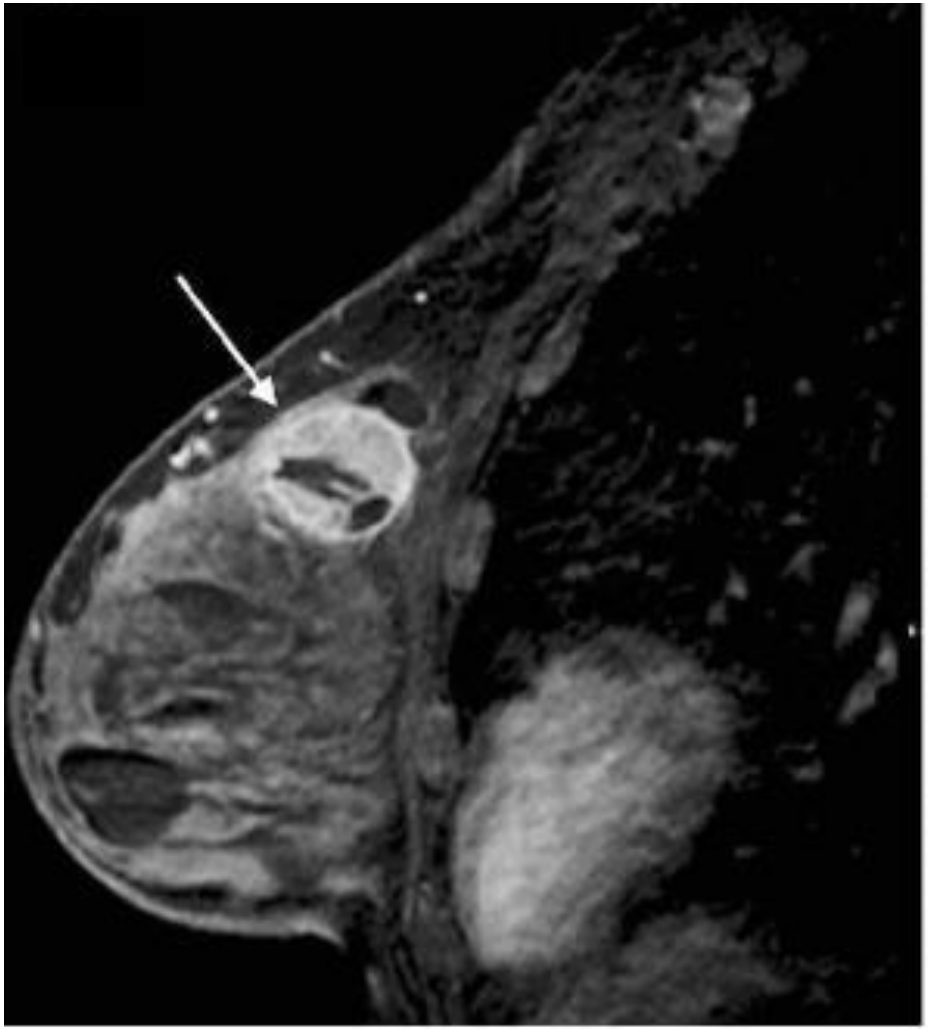
- Clinical/imaging methods
  - False negative 40-60%

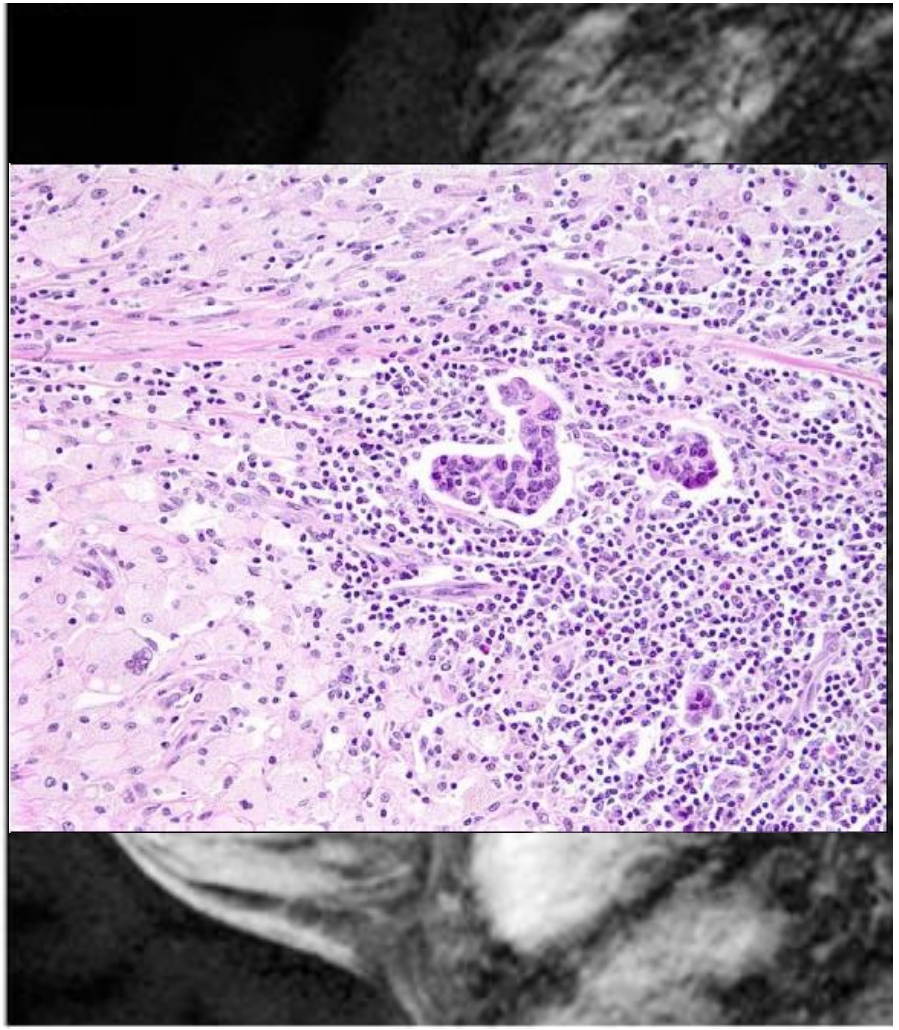
    → underestimation of disease burden (minimal residual disease with pervasive lymphovascular neoplastic embolization)
  - False positive (residual fibrosis only) 20-30%

    → overtreatment (less conservative surgical procedure)
- Histopathologic evaluation is gold standard

Pre-treatment

Post-treatment





Pre treatment Evaluation

invasive lobular carcinoma (low Ki67, ER/PR+)

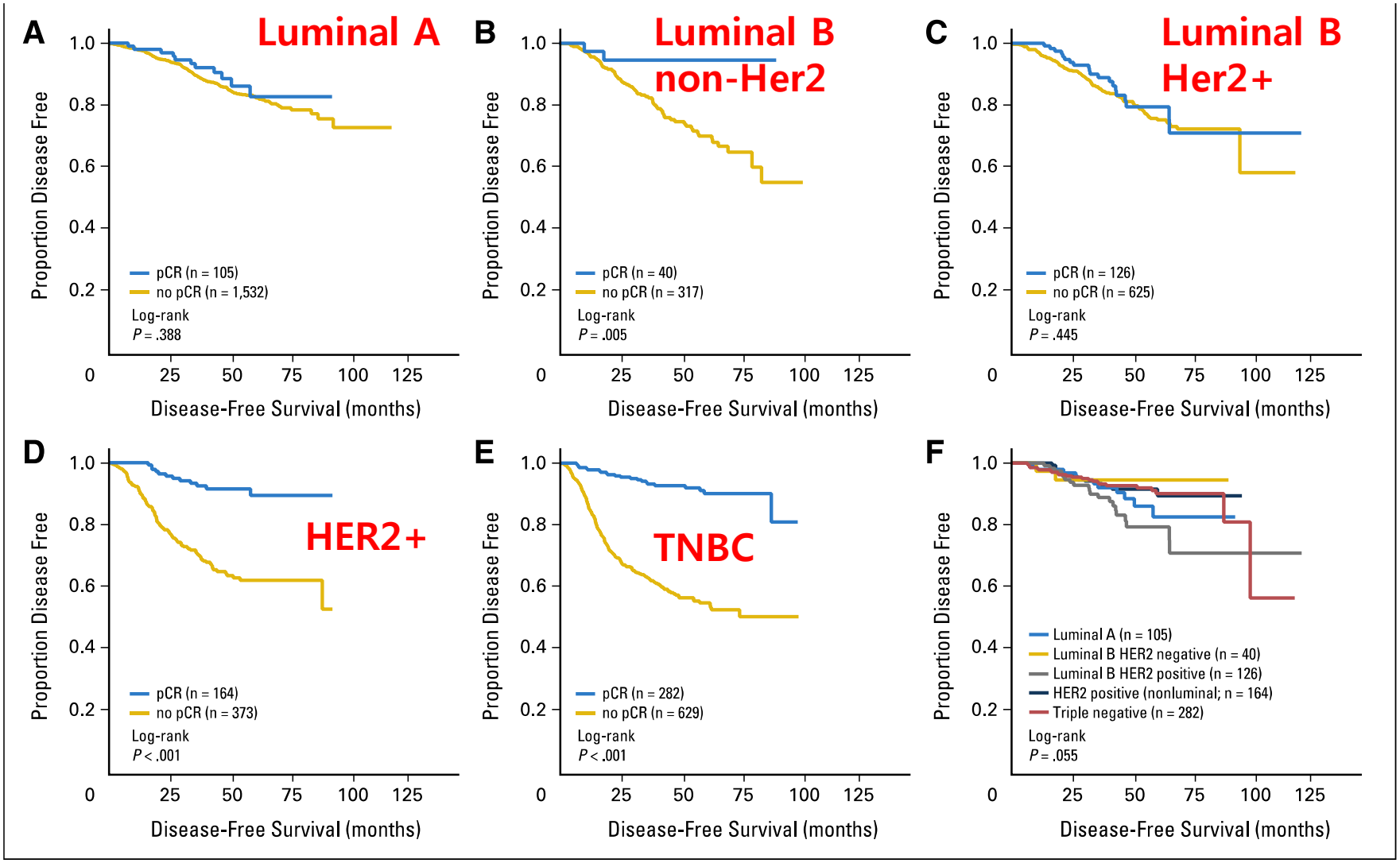
vs

high grade TNBC (high Ki67)

Pathologic Assessment of Specimen that received Neoadjuvant Therapy

- Correlation between pCR and outcomes: HER2+ & TNBC
- pCR (*Cortazar et al.* Lancet. 2014):
  - 9.6% of hormonal receptor (HR)+HER2-
  - 22.7% of HR+/HER2+
  - 39% of HR-/HER2+
  - 33.6% of TNBCs
- Residual cancer burden in the breast and nodes is associated with increased regional recurrence and decreased survival
- Accurate assessment of pCR or residual cancer burden is crucial

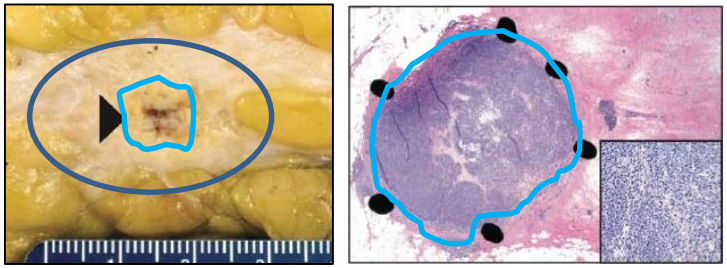
Response Rates by Subtype



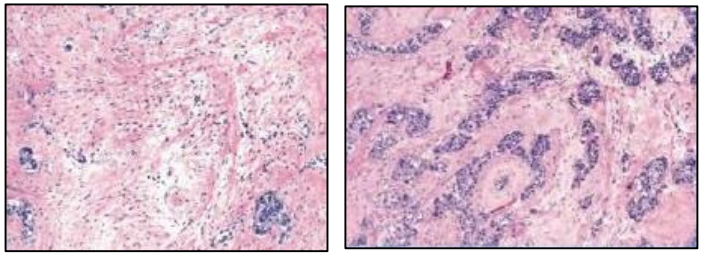
Von Minckwitz et al, JCO 2012

Patterns of Tumor Response

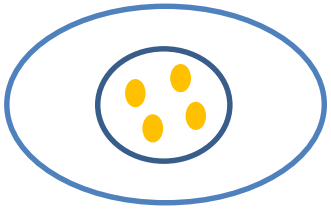
- Concentric shrinking



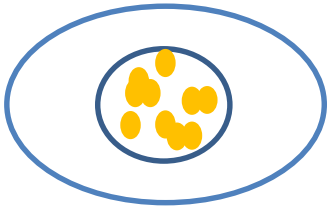
- Scattered pattern



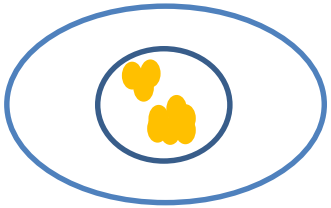
Residual Tumor Growth Pattern



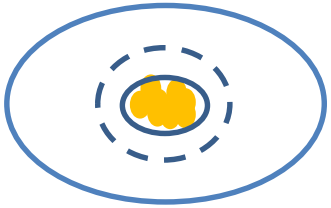
Size unchanged
Cellularity decreased



Size changed/unchanged
Cellularity decreased/heterogeneous



Size changed/unchanged
Cellularity decreased/heterogeneous
"scatter pattern"



Size decreased
Cellularity similar
"concentric shrinking"

Correlations between molecular subtypes and pathologic response patterns of residual non pCR cancer after NAC

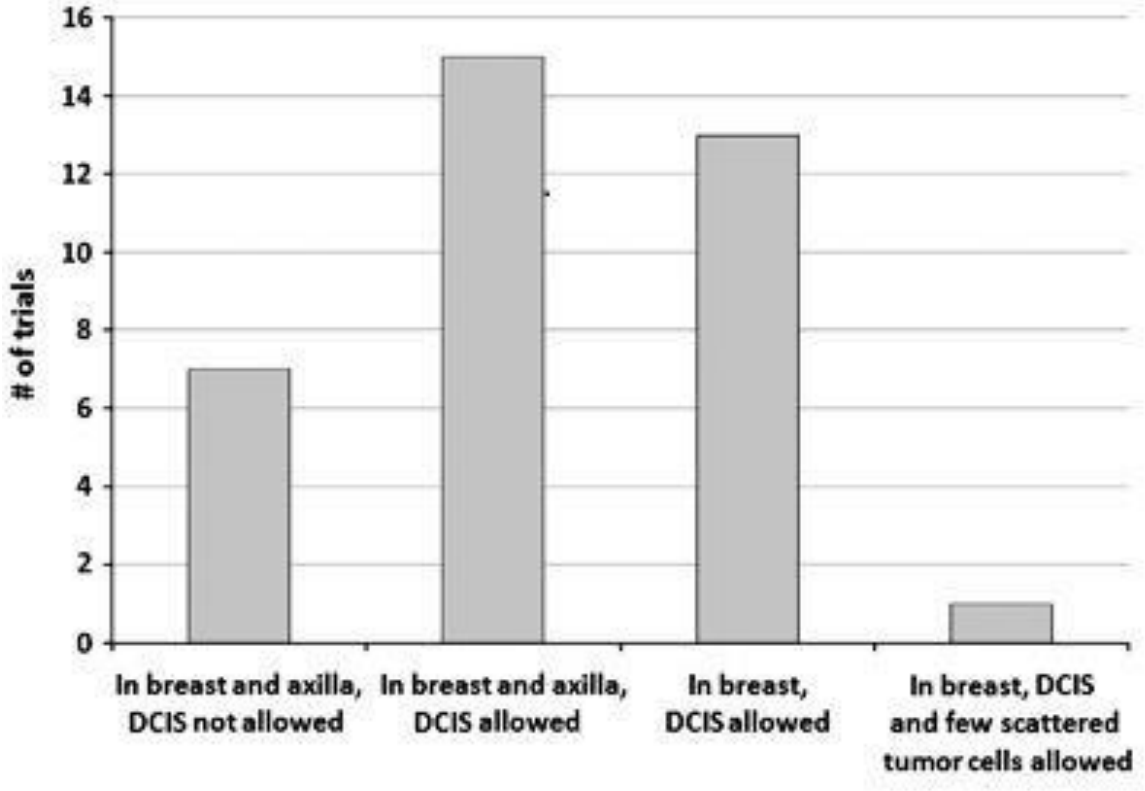
	Tumor size	Cancer cellularity	In situ component	Nuclear /histologic grade	Residual LN metastasis	TIL
HR+	No change	Decreased	Less frequent	Low/interm ediate	Frequent	Rare
HER2+	Decreased	Same	Frequent	High	Less	Frequent
TNBC	Decreased	Same	Less	High	Less	Frequent

Lee HJ et al., Ann Surg Oncol (2015)

Pathologic Response to NAC

- Less than complete response (partial response) is difficult to classify
- There are different classification systems
- Different staging systems yield different estimates of future risk

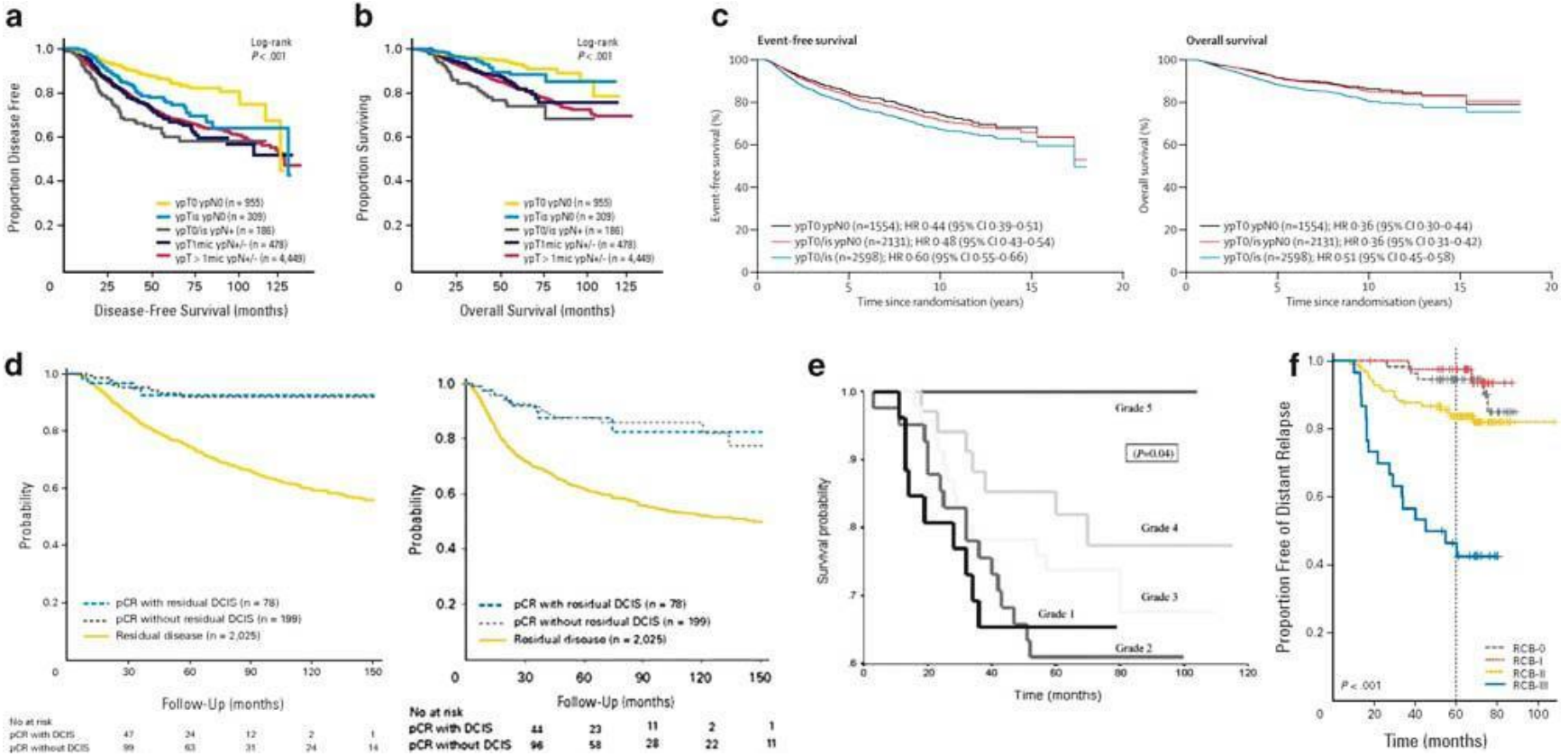
The definition of pCR



definitions of pCR in major neoadjuvant breast cancer clinical trials

Modern pathol. 2015

The definition of pCR



Survival curves showing impact of different definitions of pCR on survival: Residual disease in the LN indicates a worse prognosis, even pCR in the breast pCR±DCIS (EFF vs OS), reduction in cellularity, RDBN

Modern pathol. 2015

Residual tumor evaluation (NAC)

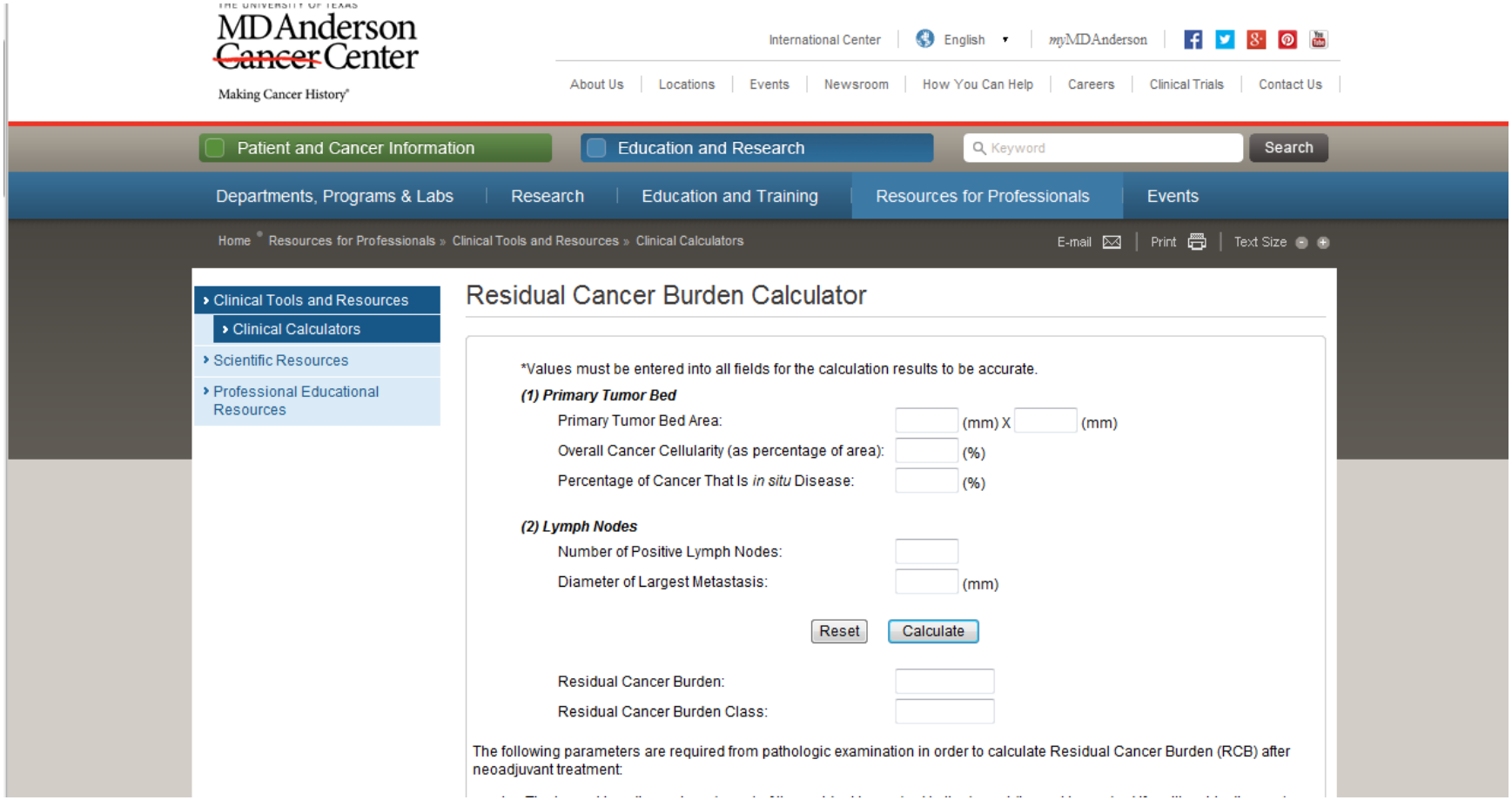
- **NSABP-B18**: simple dichotomy
- **Miller-Payne grading**: linear histologic response in breast only
- **Sataloff tumor and nodes:** breast and lymph nodes
- **Chevallier classification:** 4-step algorithm to grade response in breast and lymph nodes
- **Residual disease in breast and nodes (RDBN):** to more complex algorithms, including a formula
- **Residual cancer burden (RCB):** Web calculator
- **Residual Proliferative Cancer Burden**: combines Residual Cancer Burden with posttreatment Ki67 index
- **clinical-pathologic stage + estrogen receptor status and grade staging system (CPS+EG)**
- **AJCC**

Corben AD et al. APLM 2013

Recommendations from an international working group

- Residual Cancer Burden (RCB)
  - an online tool for the quantification of residual disease
  - simple to apply, reproducible
  - clinically validated with long-term FU data
  - the preferred method for quantifying residual disease in neoadjuvant clinical trials in breast cancer

www.mdanderson.org/breastcancer_RCB

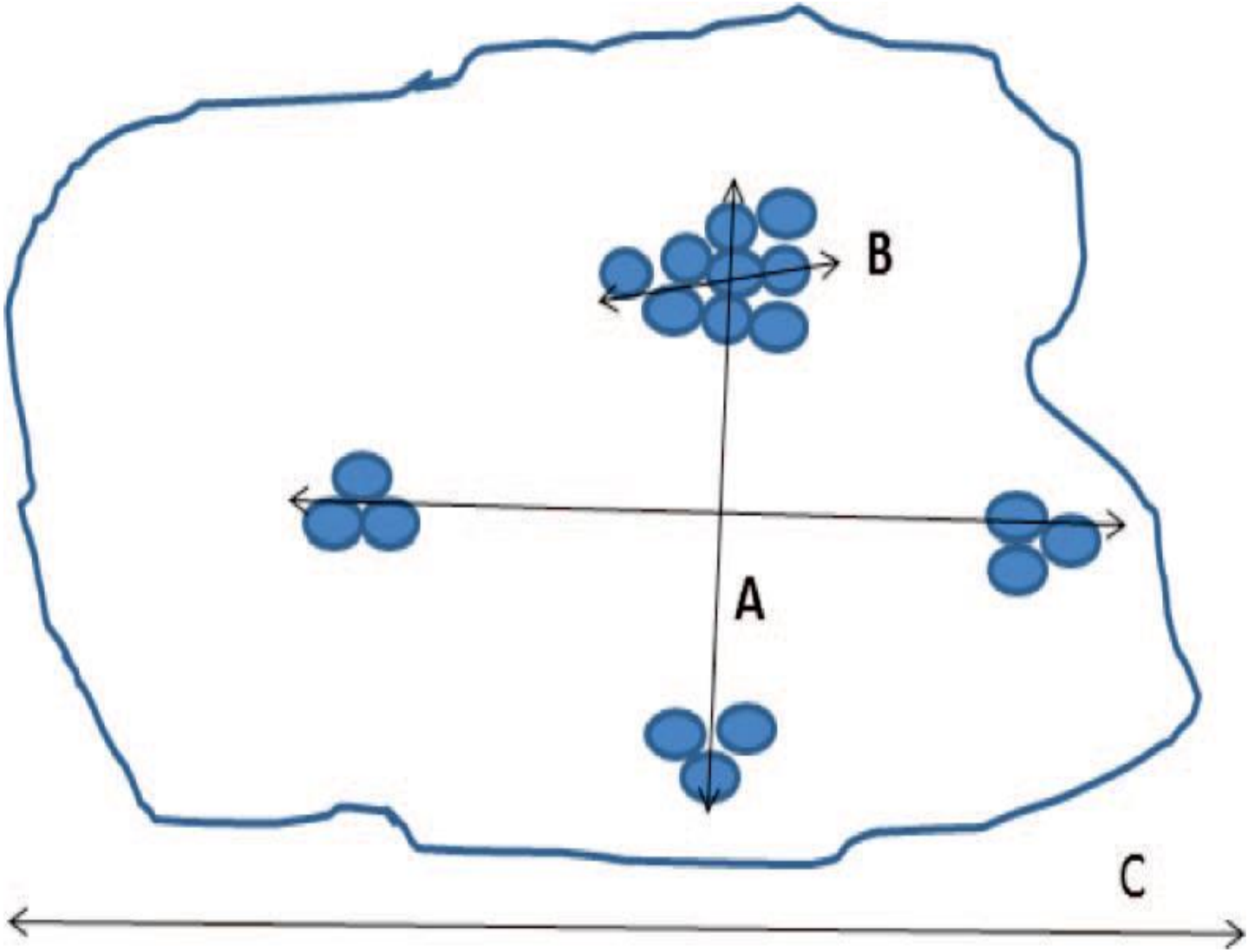


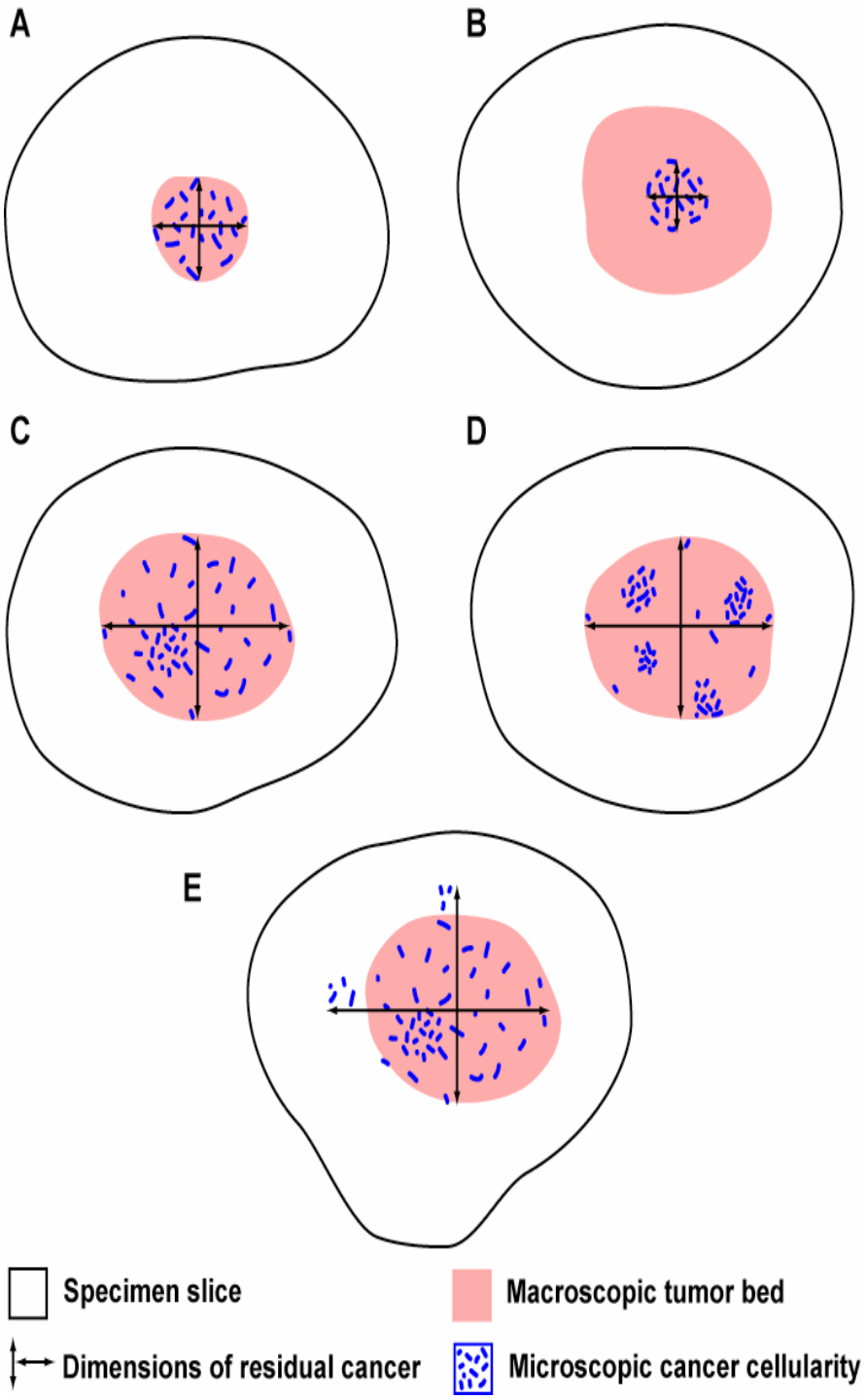
Residual Cancer Burden (RCB)

- Residual cancer burden score
  - Largest area and cellularity of residual invasive cancer of the breast
  - Number of involved lymph nodes and the largest nodal metastasis size

  - **RCB0**=pCR, **RCB I**=minimal residual disease
  - **RCB II** and **III**=moderate and extensive residual disease

What is the primary tumor bed?



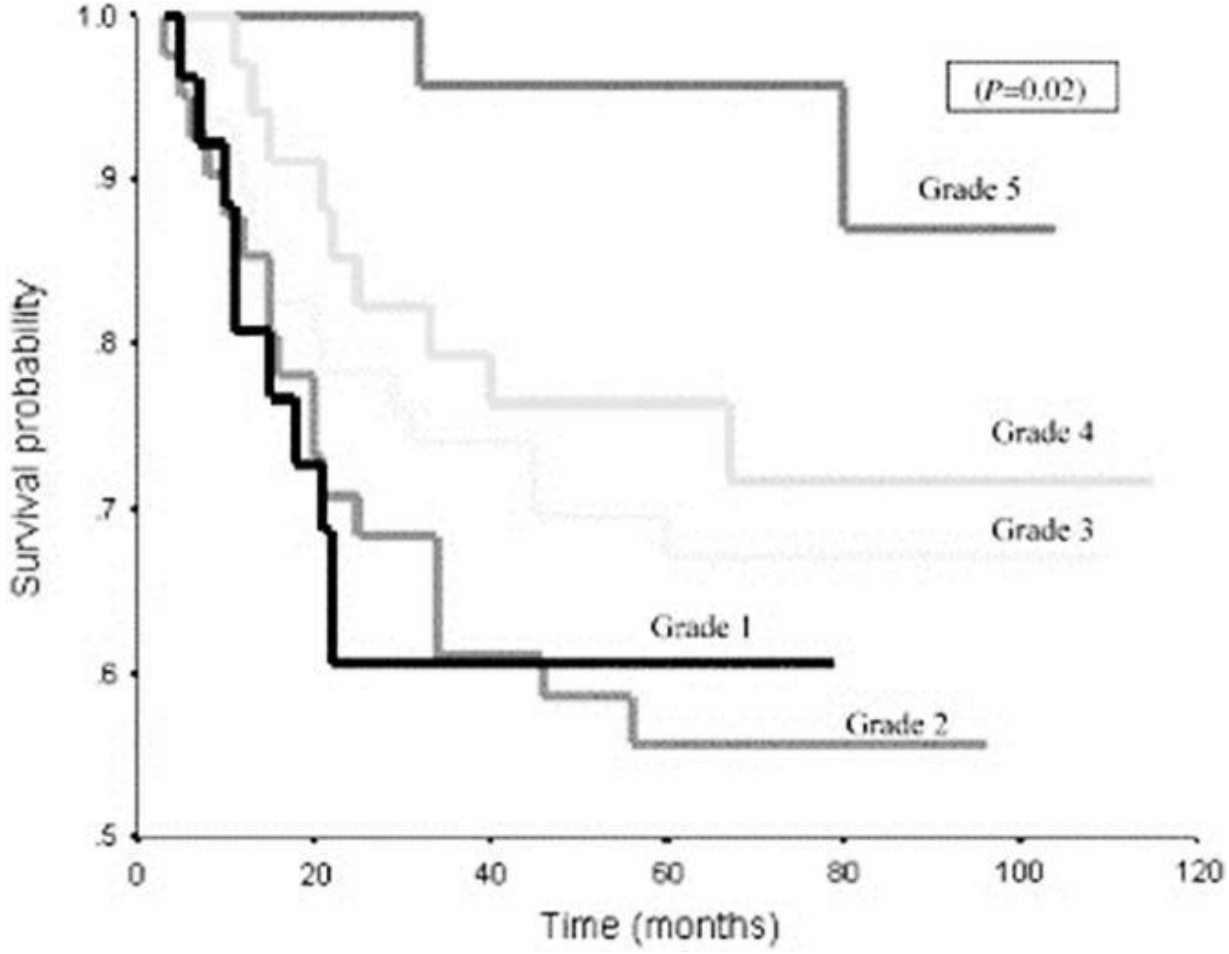

A
B
C
D
E
Specimen slice
Macroscopic tumor bed
Dimensions of residual cancer
Microscopic cancer cellularity

Pathologic assessment After NAC

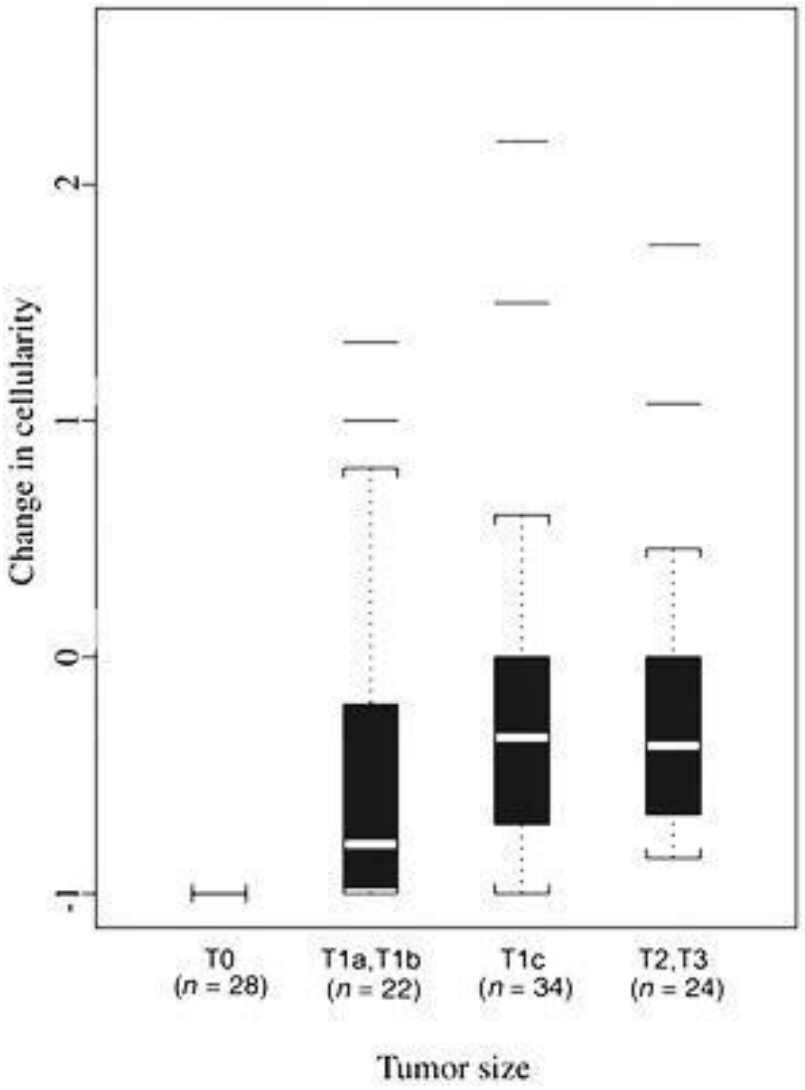
- Residual tumor size:

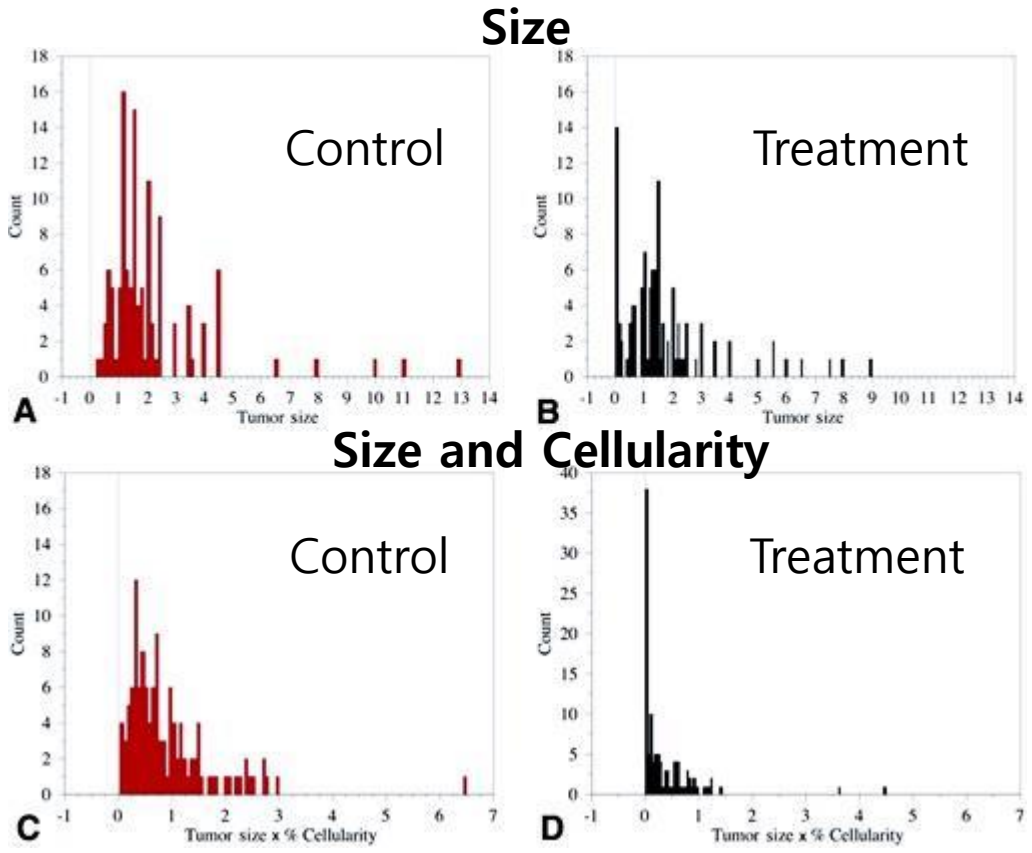
- Cellularity: comparison of cellularity with the pretreatment biopsy: Miller–Payne, Pinder, Sinn, and Sataloff system

Miller Payne System



Ogston, et al, *The breast* 2003





Variable cellularity changes in residual tumors

Rajan, et al, *Cancer* 2004

Residual Cancer Burden (RCB)

(1) Primary Tumor Bed

Primary Tumor Bed Area: _____ (mm) X _____ (mm)

Overall Cancer Cellularity (as percentage of area): _____ (%)

Percentage of Cancer That Is *in situ* Disease: _____ (%)

(2) Lymph Nodes

Number of Positive Lymph Nodes: _____

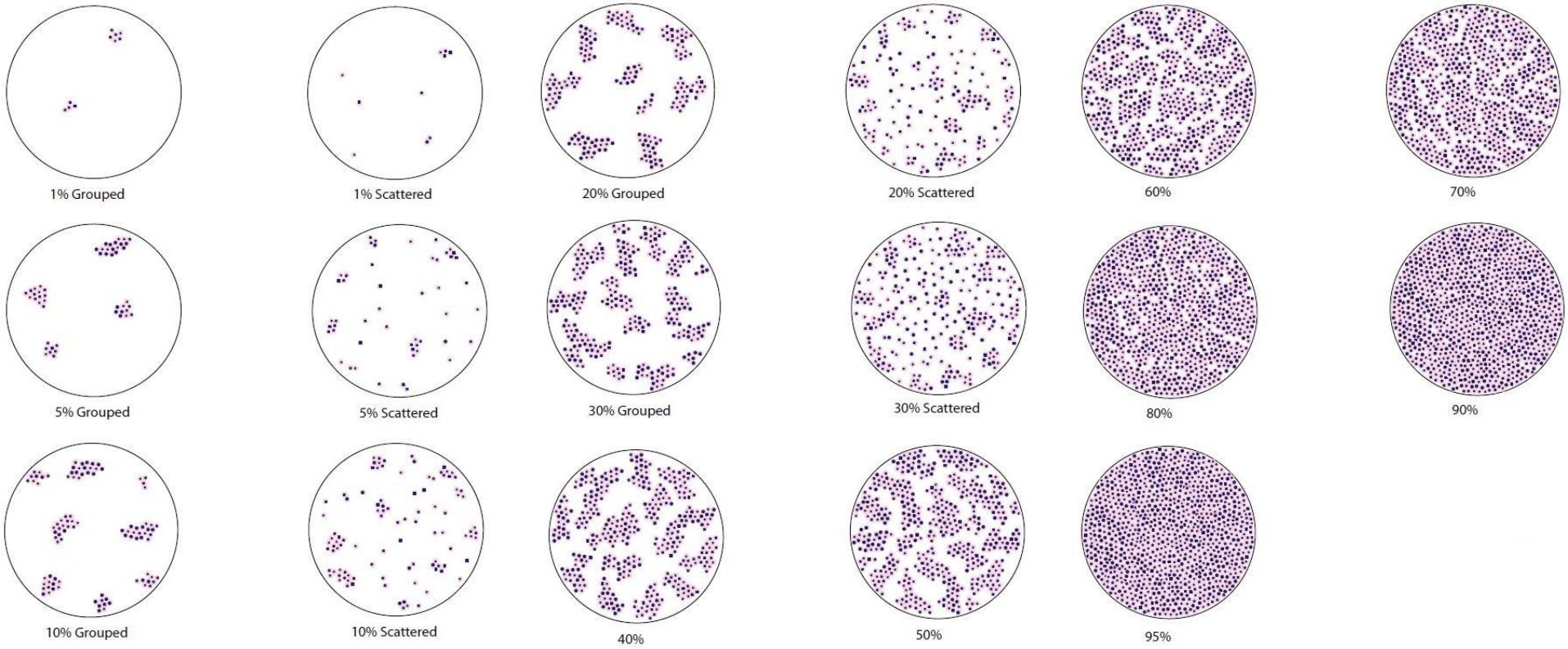
Diameter of Largest Metastasis: _____ (mm)

Reset Calculate

Residual Cancer Burden: _____

Residual Cancer Burden Class: _____

Tumor cellularity (RCB)

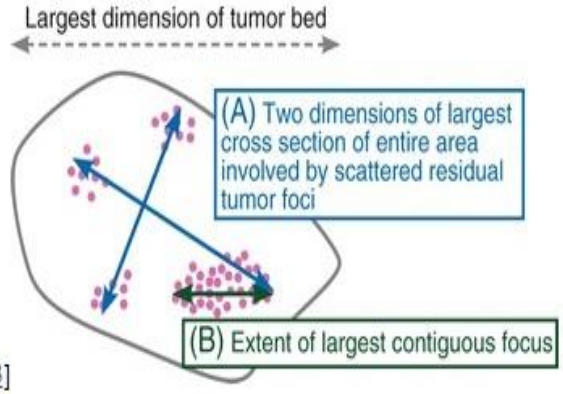


[Guide for Measuring Cancer Cellularity (pdf)]

Annals of Oncology 26: 1280–1291, 2015
doi:10.1093/annonc/mdv161
Published online 27 May 2015

Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration

V. Bossuyt[1*], E. Provenzano[2], W. F. Symmans[3], J. C. Boughey[4], C. Coles[5], G. Curigliano[6], J. M. Dixon[7], L. J. Esserman[8], G. Fastner[9], T. Kuehn[10], F. Peintinger[11,12], G. von Minckwitz[13], J. White[14], W. Yang[15], S. Badve[16], C. Denkert[17], G. MacGrogan[18], F. Penault-Llorca[19], G. Viale[20] & D. Cameron[21] of the Breast International Group-North American Breast Cancer Group (BIG-NABCG) collaboration

1. Size	(A) Two dimensions of largest cross section of entire area involved by (possibly scattered) residual invasive tumor foci (=largest distance between invasive tumor cell foci) and (B) Extent of largest contiguous focus of invasive carcinoma as recommended by AJCC 7th edition [23]  	In the opinion of the working group, the largest dimension in (A) (longest blue arrow), together with tumor cellularity, is likely a better indicator of response than measurement (B) [19, 24]. The report should clearly state how the size was determined and which dimension was used for staging, especially in cases with scattered residual disease, where there is possible interobserver variability due to differences in guidelines regarding how size should be measured. (A) is needed to calculate the Residual Cancer Burden (RCB) score.
2. Cellularity	– Qualitative statement – Largest cross section of residual tumor bed represented in blocks: … (e.g. 'G through F') – Compare with pretreatment cellularity if available (Miller–Payne or Pinder Systems)	Assessment of average cancer cellularity across the largest cross section of the residual tumor bed (that contains residual cancer) is needed to calculate the Residual Cancer Burden (RCB) score.
3. Tumor bed	– Identified or not – Presence of tumor bed at margin	
4. Lymph node metastasis	– Size of largest metastasis	The largest distance between tumor cell foci including intervening areas of fibrosis. Size of largest metastasis is needed to calculate the Residual Cancer Burden (RCB) score.
5. Treatment effect	– Presence of treatment effect in the breast – Number of lymph nodes with possible treatment effect	

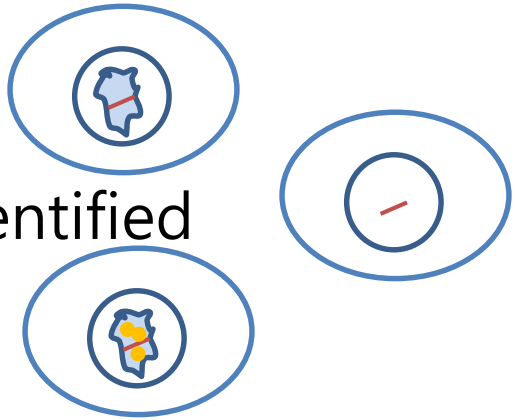
Gross Handling of Surgical Specimens After NAC

- One of the most critical steps
- the single greatest determinant for accurate definition of pCR or residual disease

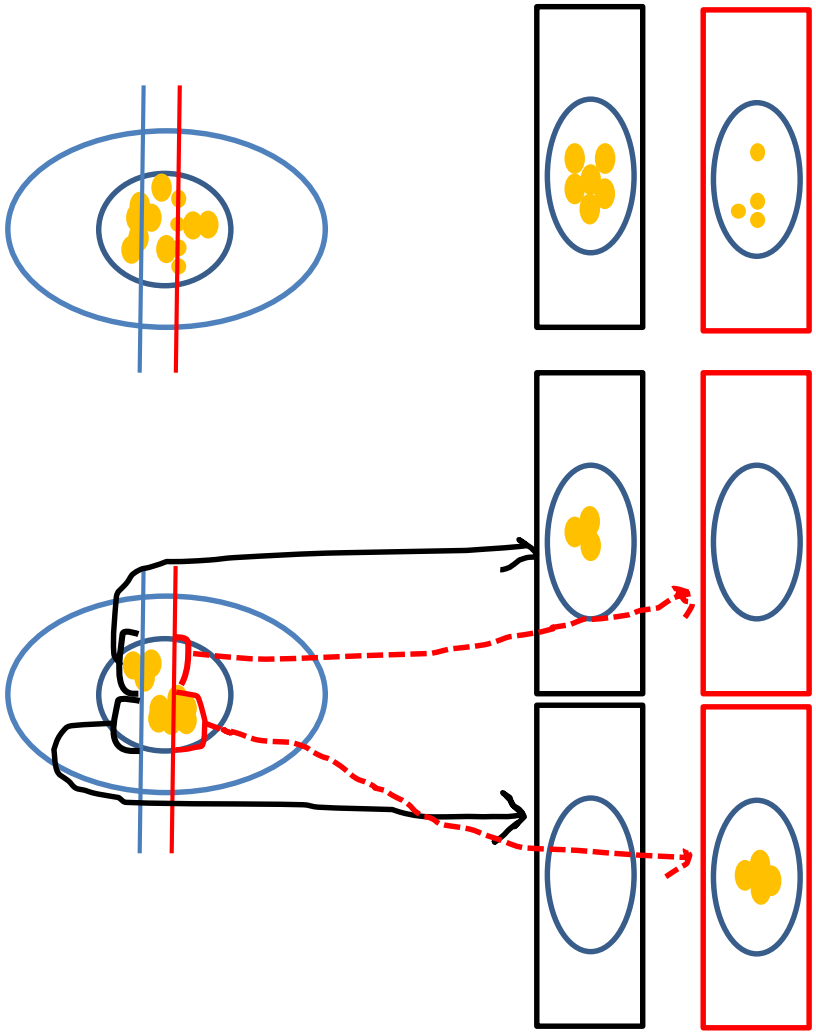
- The specimen is evaluated in the context of pretreatment clinical and imaging findings
- The tumor bed/clip must be identified

Sampling of small lumpectomy specimens

- No gross residual mass lesion
  - No residual tumor
    - Tumor bed with clip identified
    - Tumor bed indistinct, but clip identified
  - Microscopic residual disease
- Obvious gross residual tumor
  - mass sampling+α
    - Gross size confirmed
    - Microscopic residual disease beyond grossly visible tumor



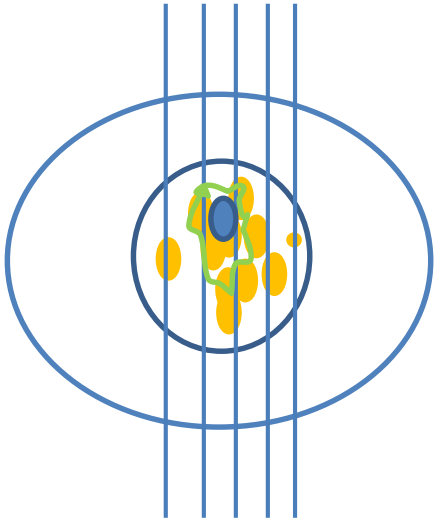
Random sampling is a problem



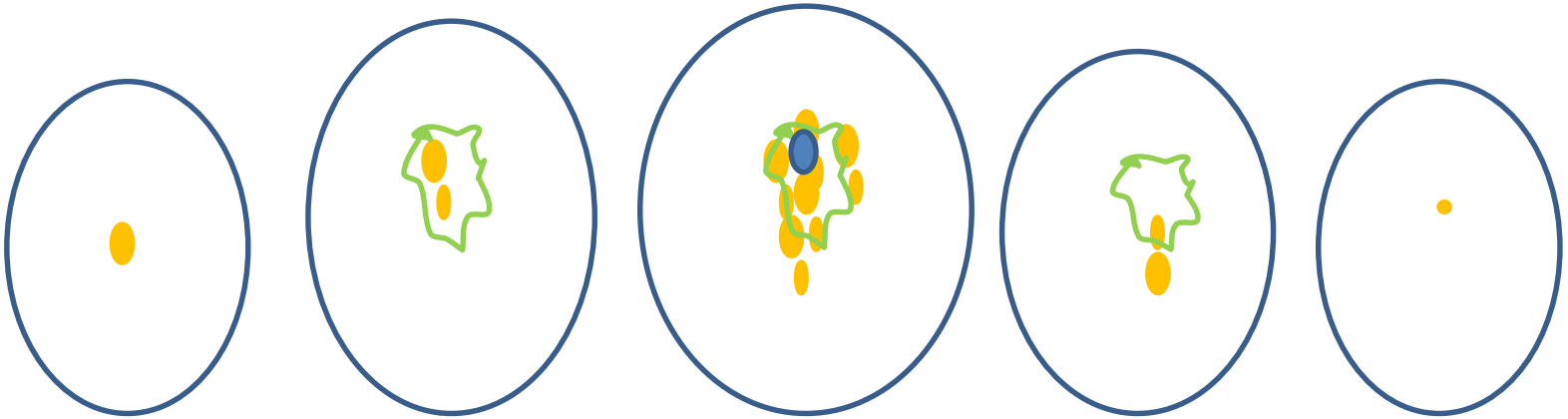
Decreased cellularity!

No residual disease!

Systemic sampling is appropriate



Mapping of the specimen
Largest cross section of tumor bed is sampled

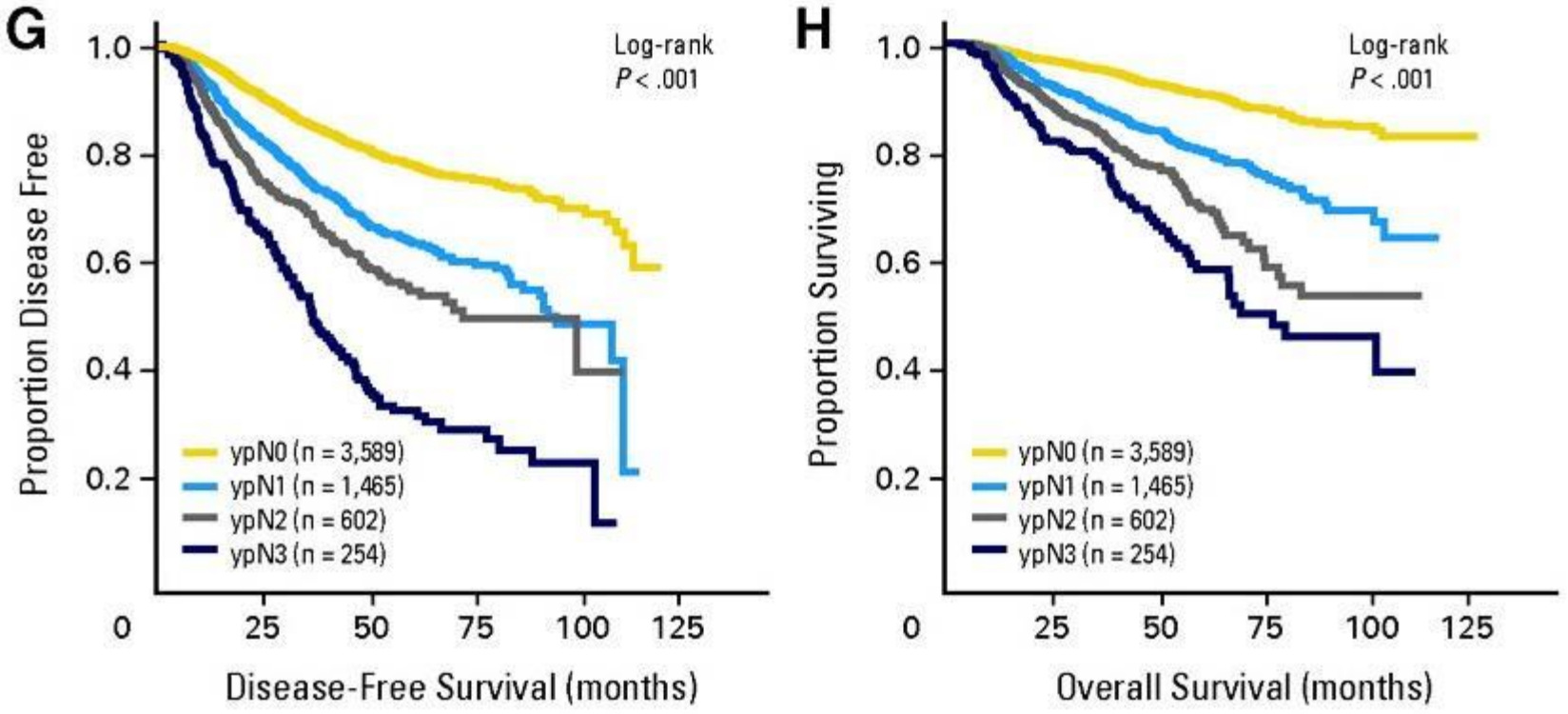


Axillary Evaluation Before NAC

- Routine axillary U/S with histological assessment of abnormal nodes by CNB or FNA
- Pre-treatment SLNB not advised unless positive result will influence decision to give chemotherapy
- Nodal response is an important prognostic factor independent of response in the breast

Evaluation of the axilla

- Nodal status after NAC is a strong predictor of outcome

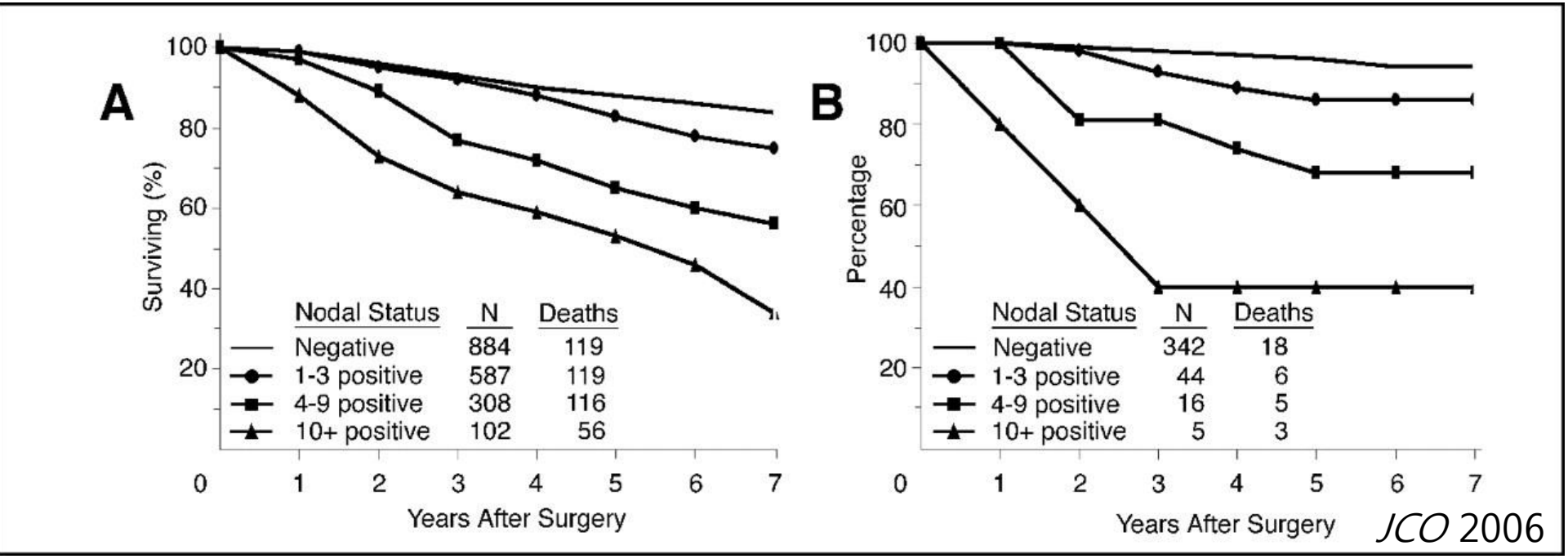


von Minckwitz, et al, *JCO* 2012

Evaluation of the axilla

- Neo-Tango result
  - 6% residual axillary disease despite pCR in the breast

Non-pCR **pCR**



JCO 2006

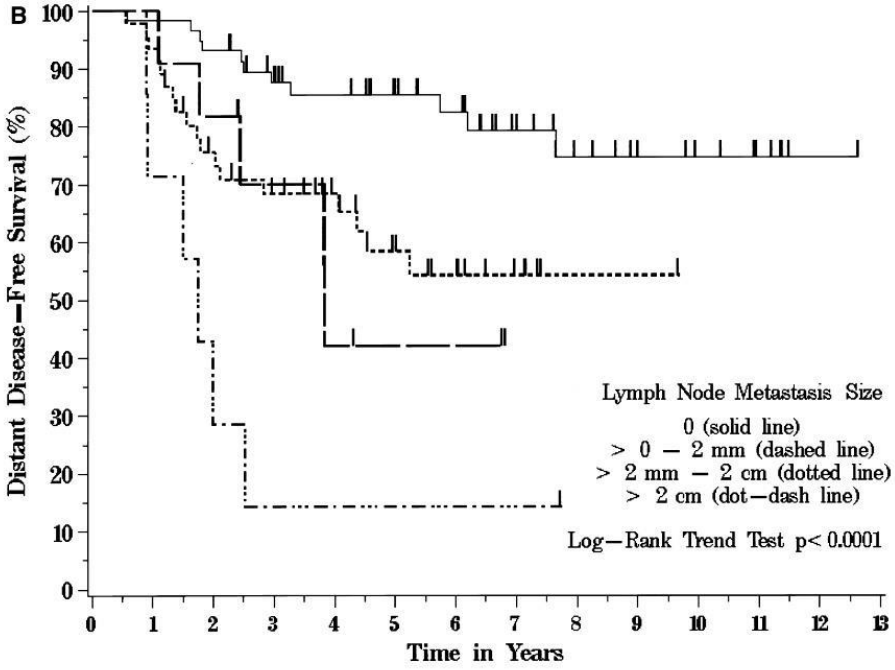
Evaluation of the axilla

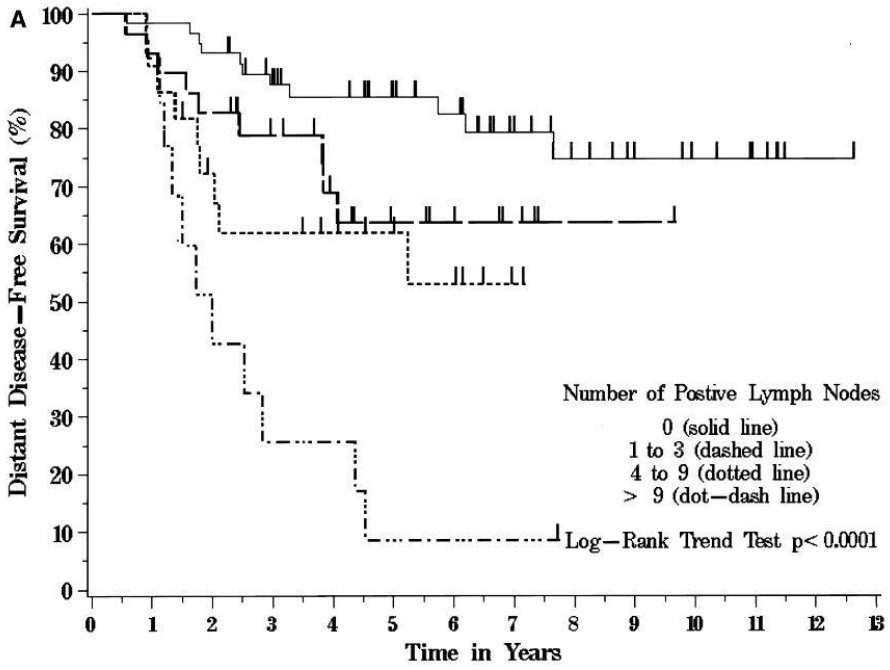
- 925 pts with proven node mets in 5 prospective NAC trials (22% axillary pCR)
- Residual primary tumor not predictive in pts with residual nodal disease.
- Residual primary tumor did not affect outcome of those with axillary pCR.
- No influence of size of metastasis: Prognosis still worse in even micromets

Hennessy, et al, *JCO* 2005

Evaluation of the axilla

- Metastasis size and number of involved lymph nodes independent predictors.
- ITC: positive node





Klauber-DeMore, et al, *Ann Surg Oncol*. 2006

Isolated Tumor Cells after NAC

- Deposit (<0.2mm) is ypTN0(i+):
  NOT regard as pCR (AJCC and WHO)

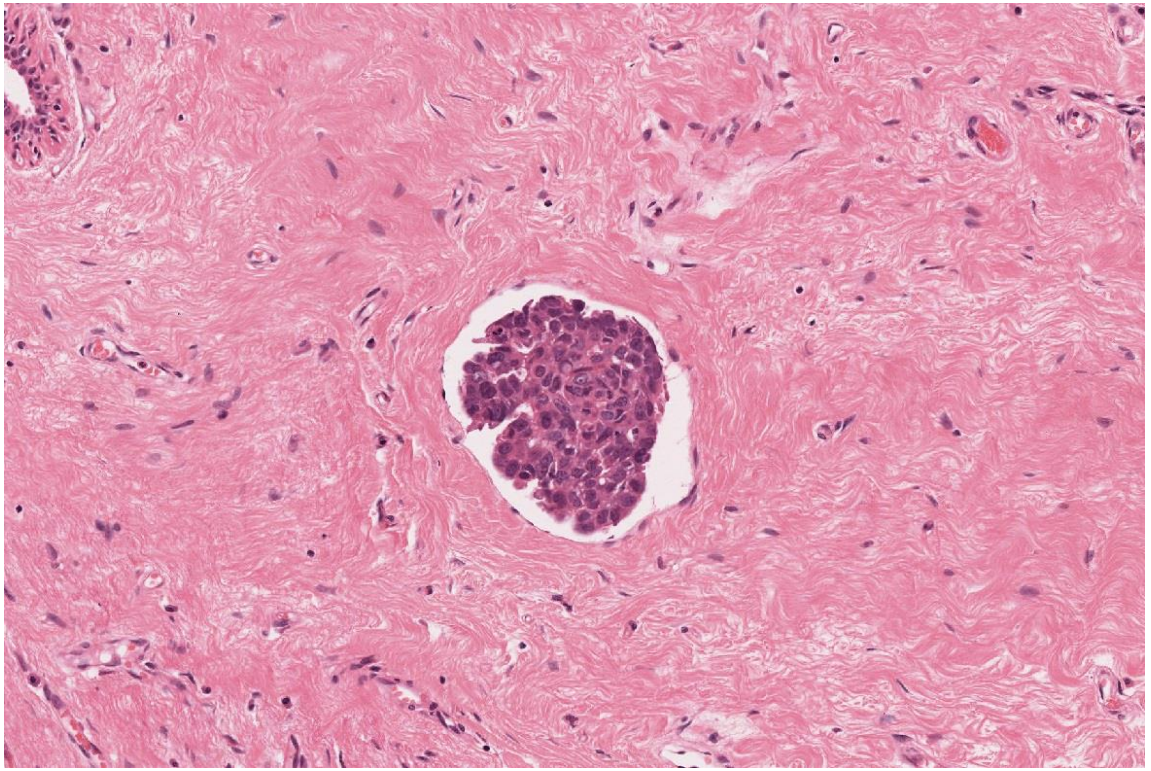
Evaluation of the axilla

- **8th AJCC**:
  - Size of largest contiguous focus of residual tumor in the node
  - Any treatment associated fibrosis should not be included

- **RCB**:
  - The largest deposit including associated treatment related fibrosis

Recommendations for the pathologic assessment of RCB

- Residual lymphovascular invasion is documented and is not classified as pCR



AJCC 8th staging after NAC

- ypT is based on largest single focus of residual invasive carcinoma
- Treatment-related fibrosis around residual tumor is NOT included in the ypT dimension (don't measure tumor bed)
- Pathologic complete response (pCR) is defined as no residual invasive cancer – ypT0 N0 or ypTis N0
- microinvasion/only LVI in breast, ITC in LN≠pCR
- Cases categorized as M1 before neoadjuvant therapy stay that way (i.e. they remain Stage IV even if there is pCR)

THANK YOU