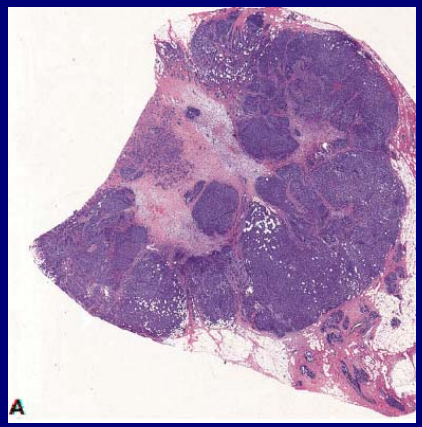
National Cancer Institute

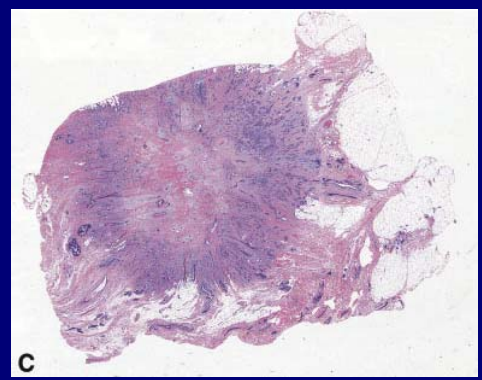
PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

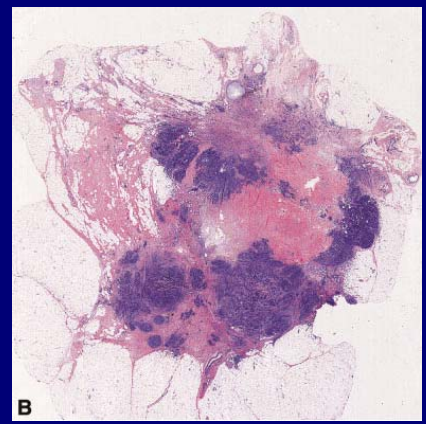
Reviewing the State of the Science and Exploring New Research Directions

Pathologic Assessment Of The Breast And Axilla After Preoperative Therapy



W. Fraser Symmans, M.D.
Associate Professor of Pathology
UT M.D. Anderson Cancer Center



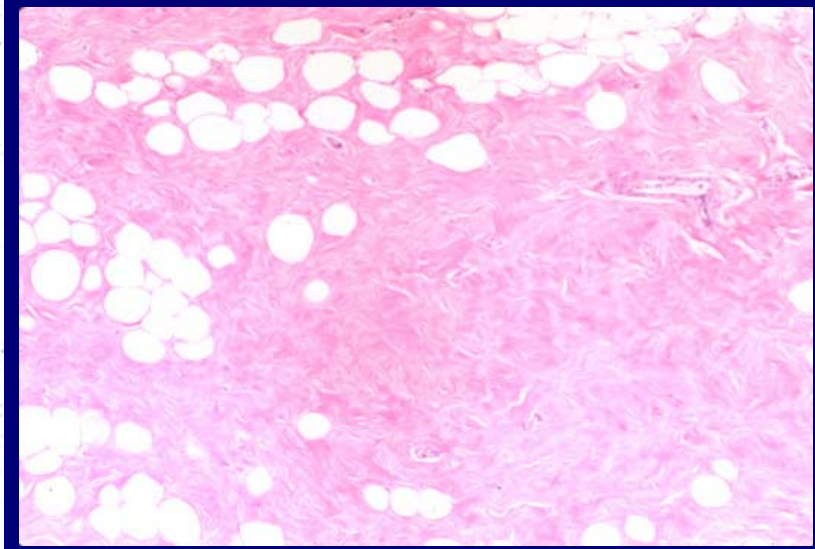


U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

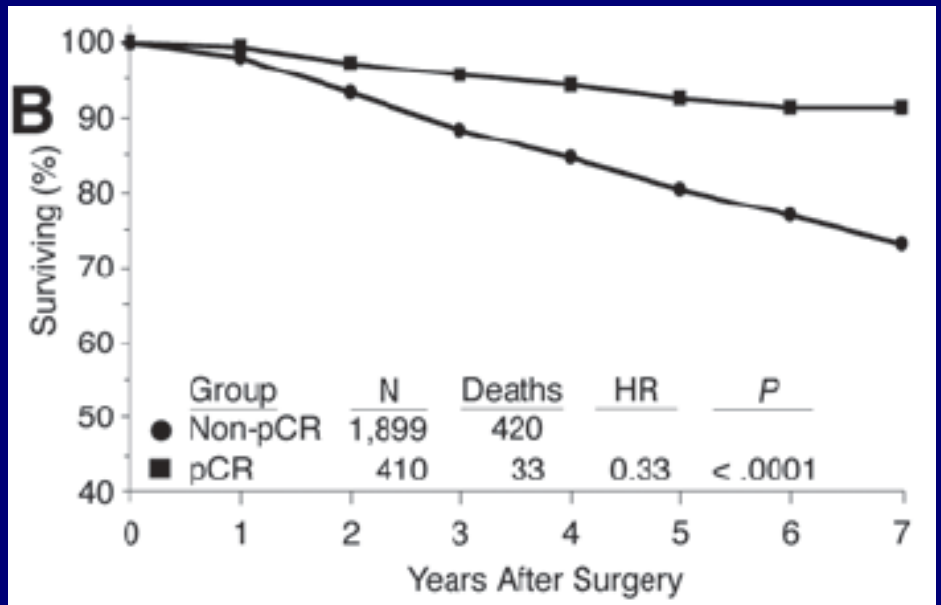
National Institutes of Health

Pathologic Complete Response (pCR)

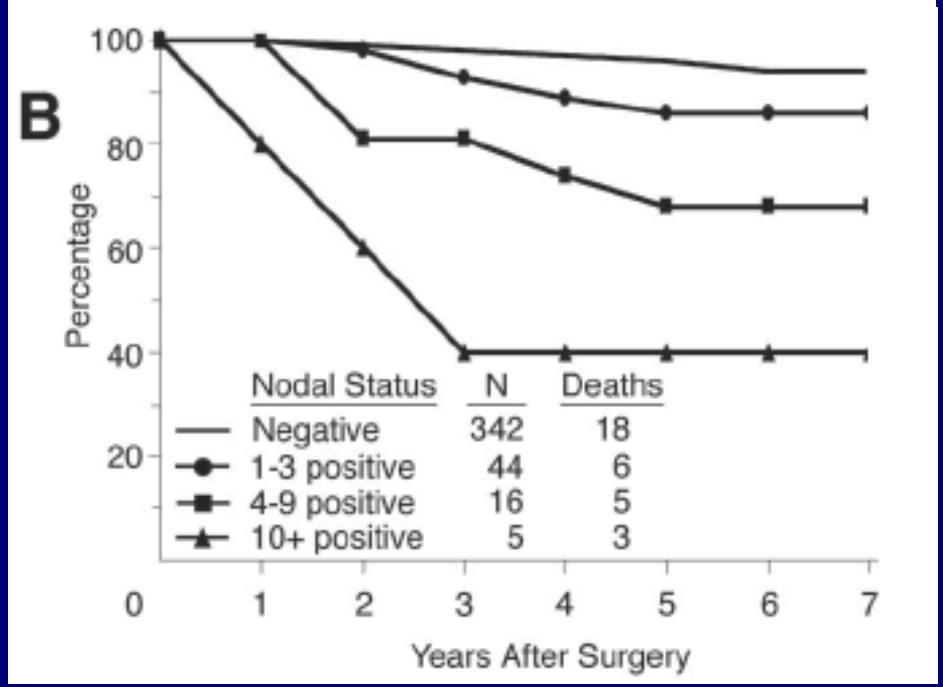
Proof of no residual invasive cancer requires:
- **Identification of the tumor bed location**
- **Adequate sampling for microscopic study**



Pathologic Complete Response: NSABP-B27



pCR in the breast

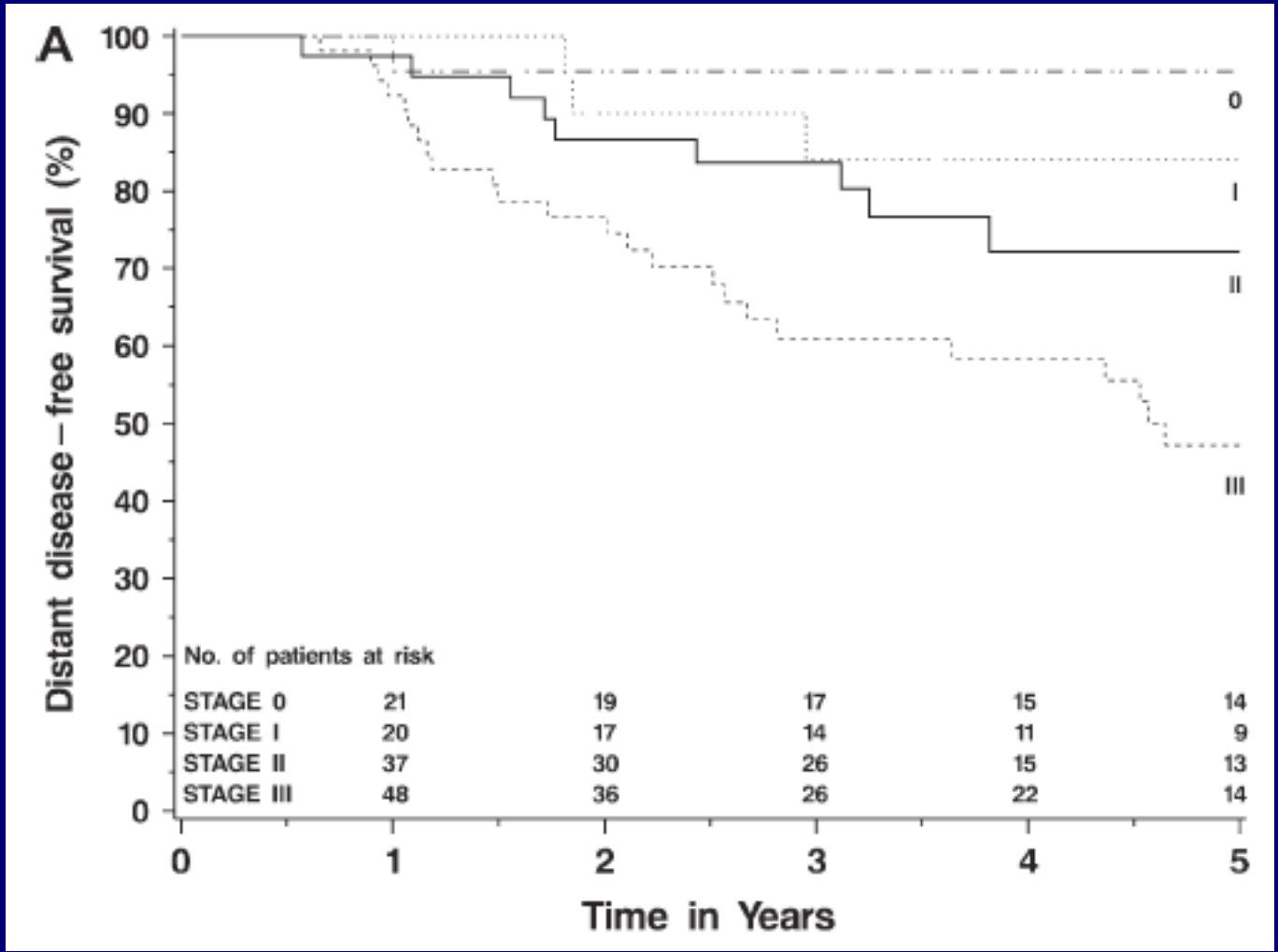


Nodal status in pCR patients

Bear et al JCO 2006 24:2019-27

Pathologic AJCC Stage After Preoperative Chemotherapy: UNC

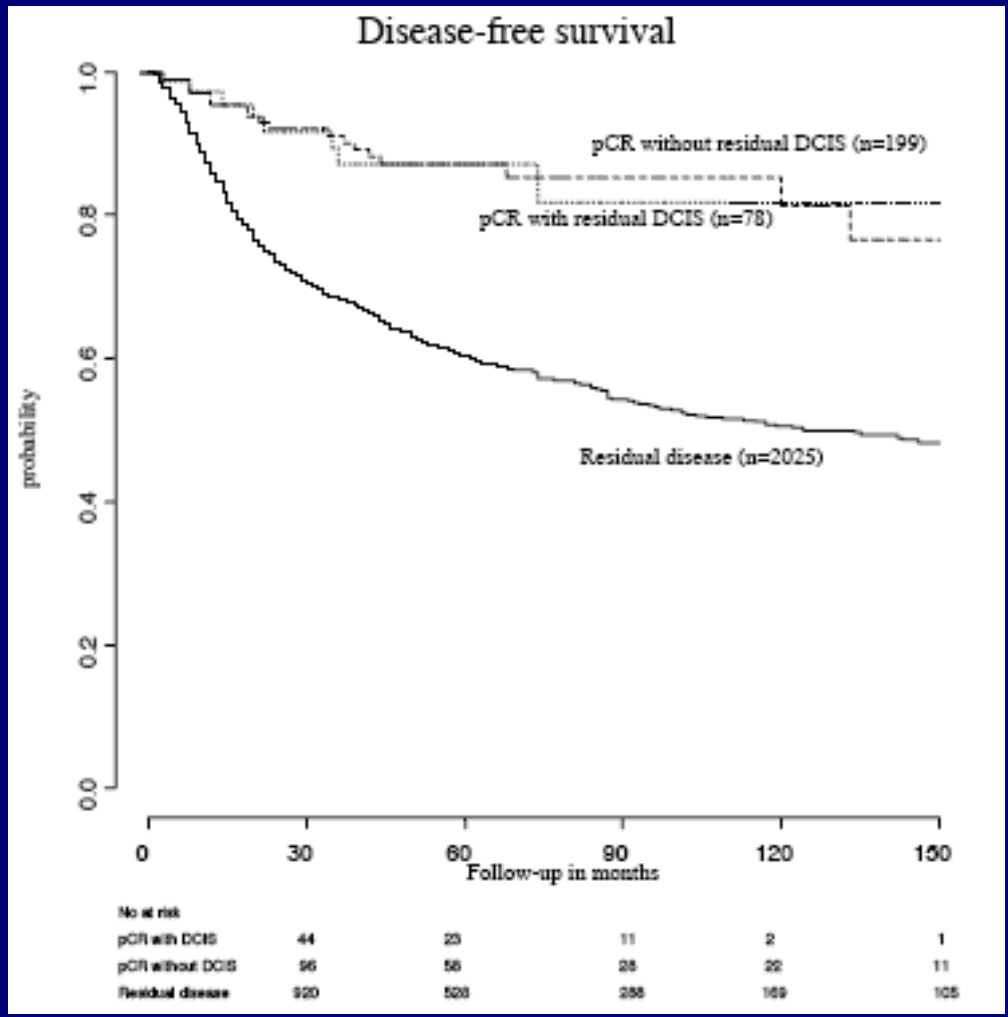
N = 132



Carey et al JNCI 2005 97:1137-42

Residual Ductal Carcinoma *in situ* Alone: MDACC

N = 2302



pCR with DCIS only in:

3% of overall MDACC experience

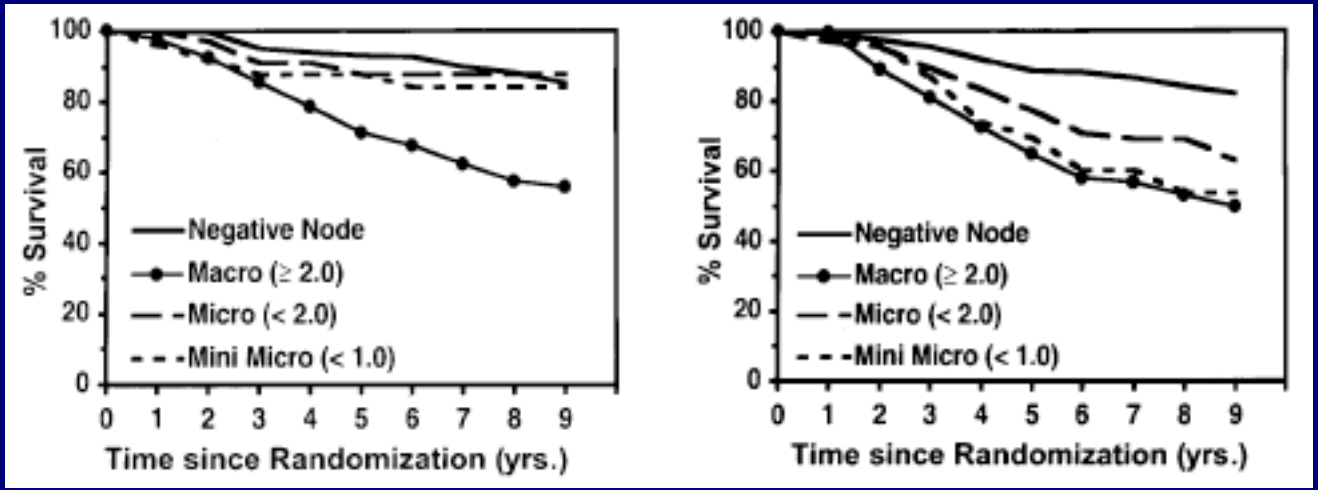
7% of recent T/FAC study

Mazouni et al JCO, in press

Nodal Micrometastasis After Preoperative Chemotherapy: NSABP-B18

Any nodal disease after neoadjuvant chemotherapy is relevant

Postoperative Chemotherapy **Preoperative Chemotherapy**



Metastasis < 2 mm in:

10% of postoperative chemotherapy patients

17% of preoperative chemotherapy patients

4% of recent MDACC T/FAC study

Fisher et al Cancer 2002 95:681-95

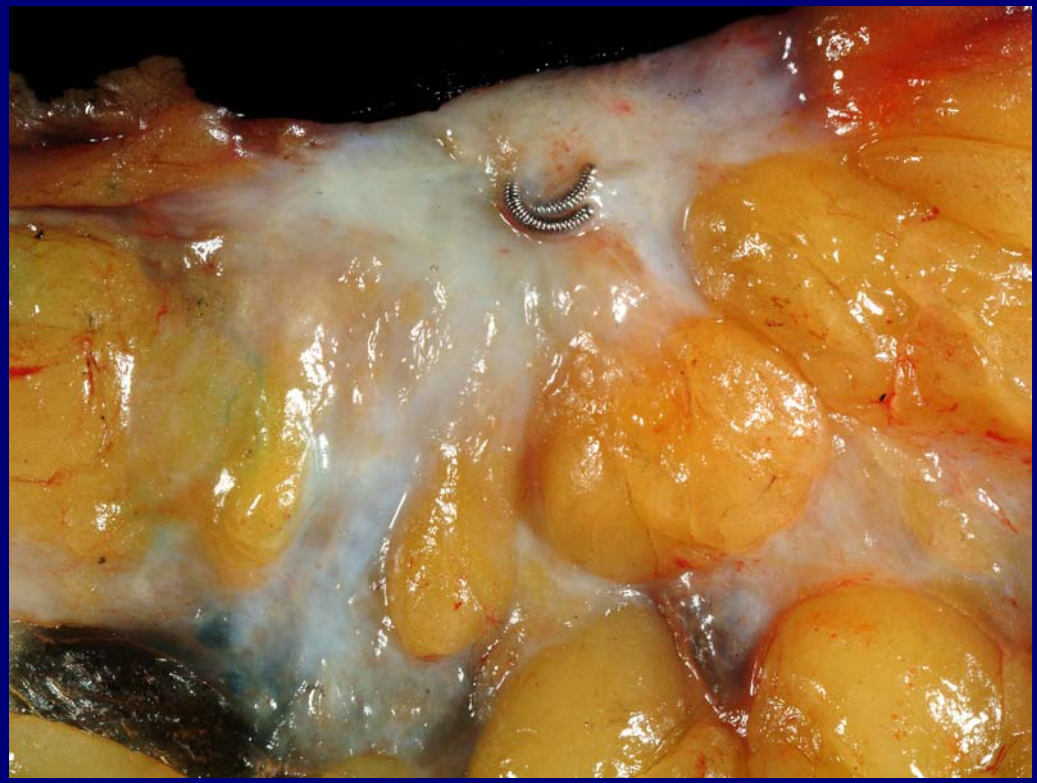
Pathologic Complete Response

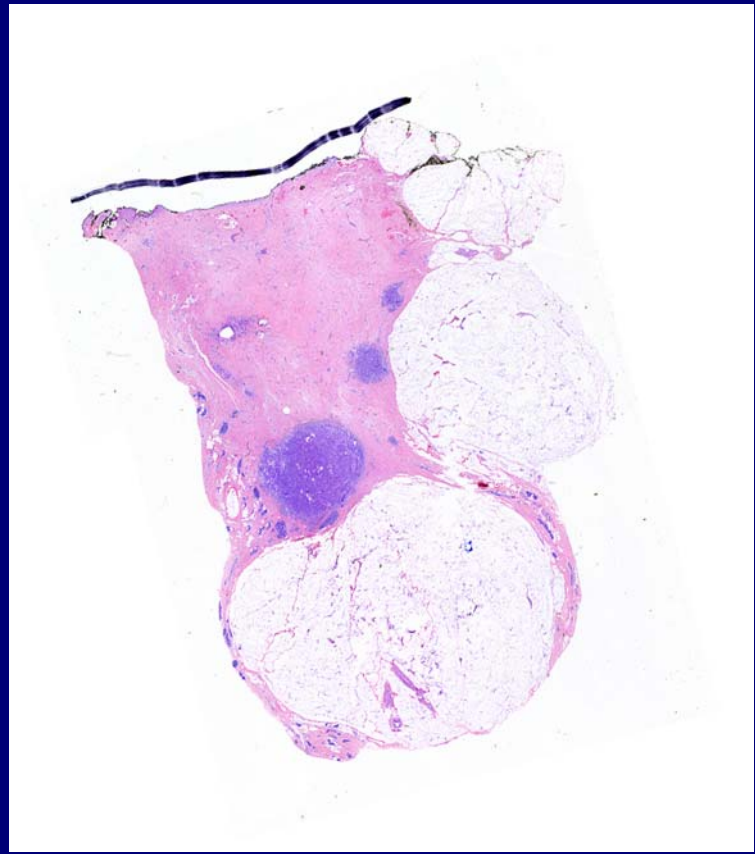
No residual invasive cancer & node-negative

Residual *in situ* disease only
- Current prognostic data are limited
- Prognosis similar to pCR (few studies)
- Relevant for local control

Residual nodal micrometastasis
- Prognosis is the same as node-positive

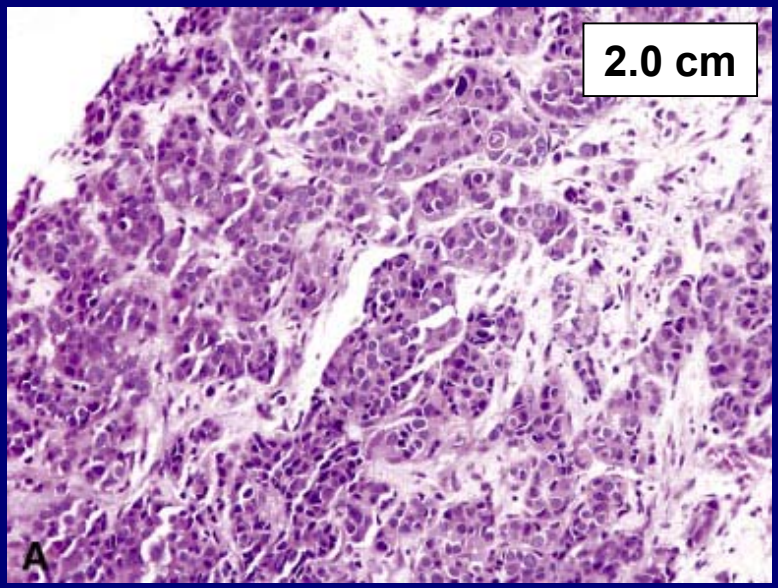
The Extent Of Residual Cancer Is Variable

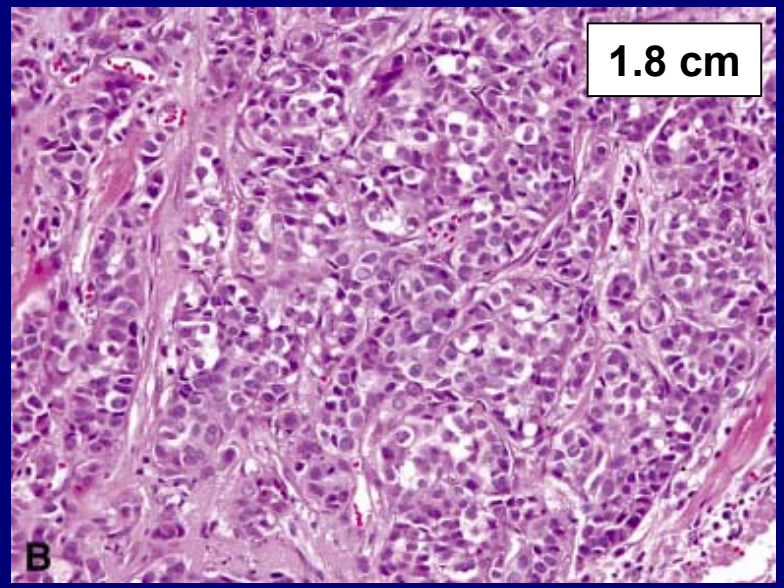


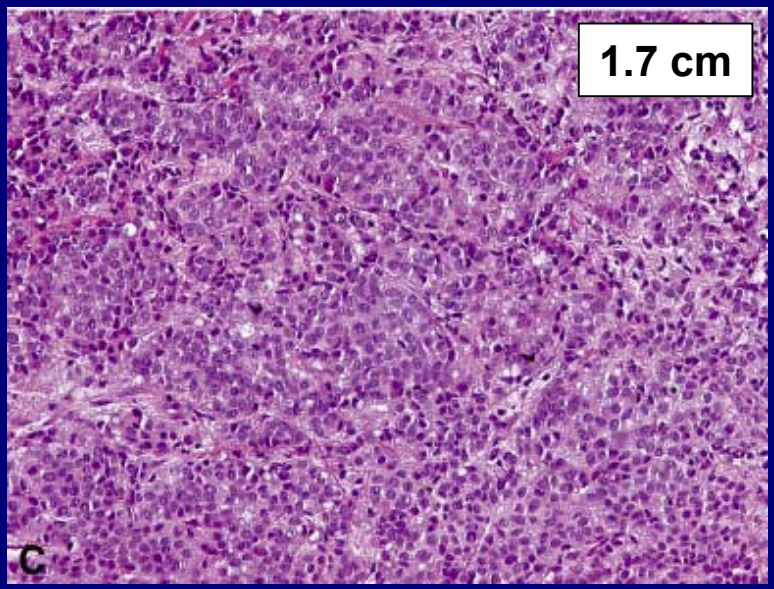


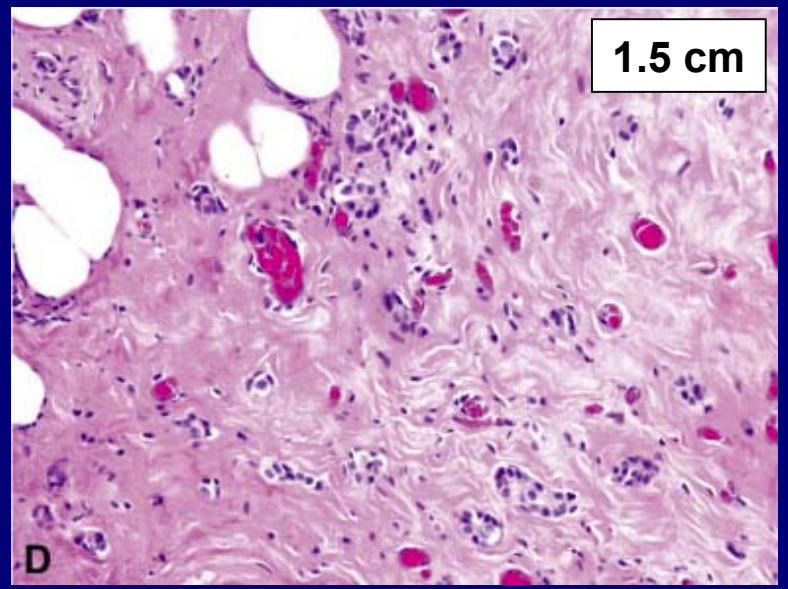
Histopathological Response Is Also Variable

Core Biopsy → Resection









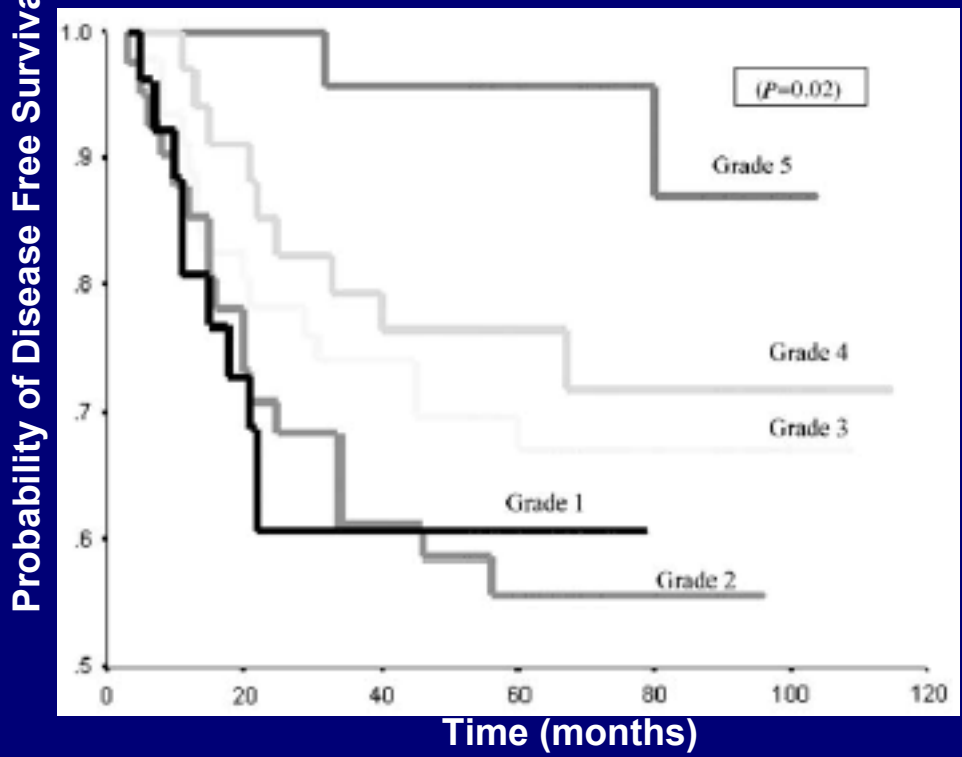
Reduction in Tumor Cellularity: "Miller and Payne"

Histopathology scoring system to assess response
Compares cancer cellularity of the core biopsy (before treatment) with the resected tumor (after treatment)

Grade 1: No reduction
Grade 2: Minor loss (≤ 30%)
Grade 3: Some loss (30% - 90%)
Grade 4: Marked loss (> 90%)
Grade 5: No residual invasive cancer

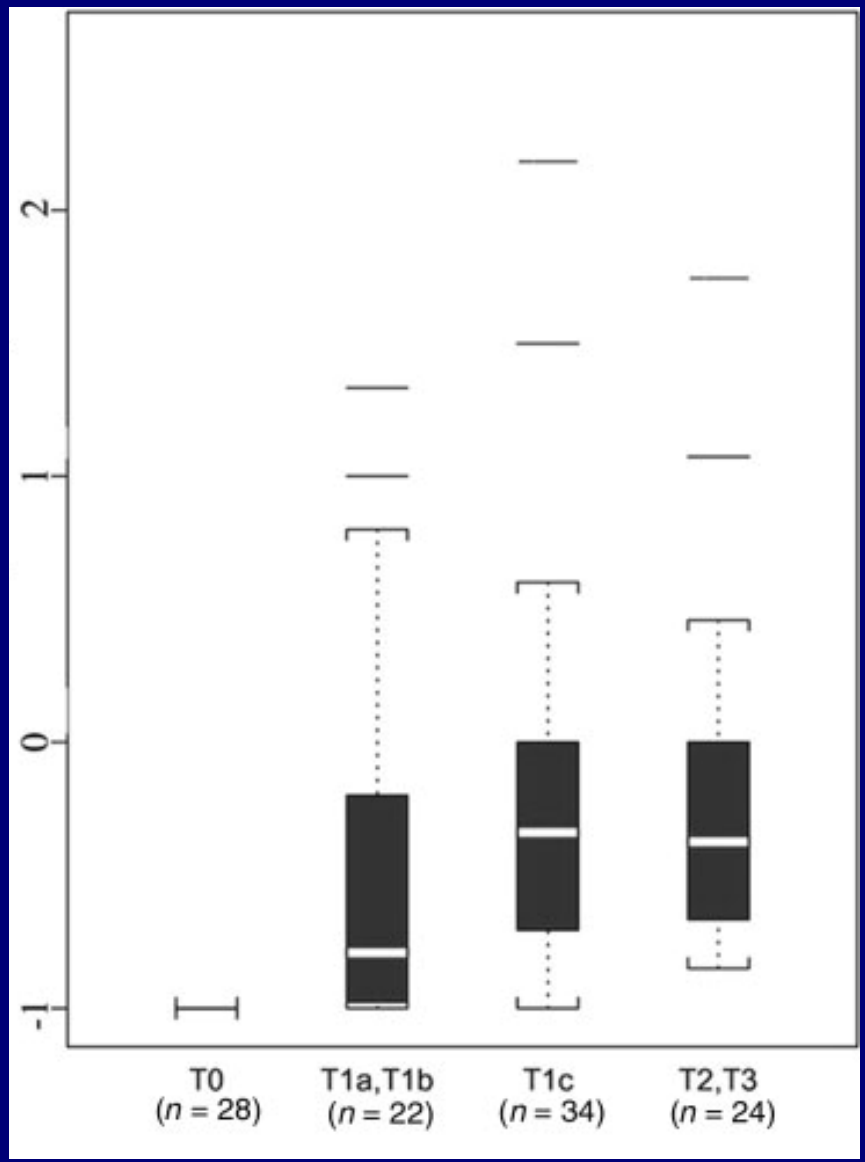
170 patients Tumor ≥ 4 cm
Rx: CVAP 4 - 6 cycles

Grade 1: 15%
Grade 2: 24%
Grade 3: 27%
Grade 4: 20%
Grade 5: 14%



Ogston et al The Breast 2003 12:320-7

Reduction In Tumor Cellularity Is Related To Residual Tumor Size



T/FAC, n = 108

The greatest cellularity reduction occurs in residual tumors ≤ 1 cm

Reduction in cellularity is variable in all T-stage groups

Rajan et al Cancer 2004 100:1365-73

Honkoop Classification

pCR	No cancer in breast or axillary nodes
Minimal Residual Disease	Only microscopic RD in breast or axillary nodes
Macroscopic Residual Disease	Macroscopic RD in breast or axillary nodes

Chevallier Classification

Grade 1	No cancer in breast or axillary nodes
Grade 2	Only *in situ* carcinoma remains, nodes are negative
Grade 3	Invasive carcinoma with stromal fibrosis
Grade 4	No or few modifications of stromal fibrosis

Sataloff Classification

Primary Tumor		Axillary Nodes		
T-A	Total or near-total therapeutic effect	N-A	N-	Evidence of therapeutic effect
T-B	> 50% therapeutic effect	N-B	N-	No evidence of therapeutic effect
T-C	< 50% therapeutic effect	N-C	N+	Evidence of therapeutic effect
T-D	No therapeutic effect	N-D	N+	No evidence of therapeutic effect

Relevant Prognostic Variables In The Post-treatment Pathologic Specimen

- Primary Tumor
  - Size
  - Cellularity
  - Invasive vs. *in situ*
  - Margins
- Axillary Lymph Nodes
  - Number of positive nodes
  - Size of metastases
  - Extranodal extension


M.D. ANDERSON #2 (ANTARES1)
DJB
6/16/2006
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VFX13-5
BREAST
55fps
GEN/11.4 MHz
21dB/DR55
MapI/VEOff
RS2/SC1
LT
BREAST
12:00
LONG
3.5cm
55fps
Fr89
SIEMENS
Pre-Rx


M.D. ANDERSON #2 (ANTARES1)
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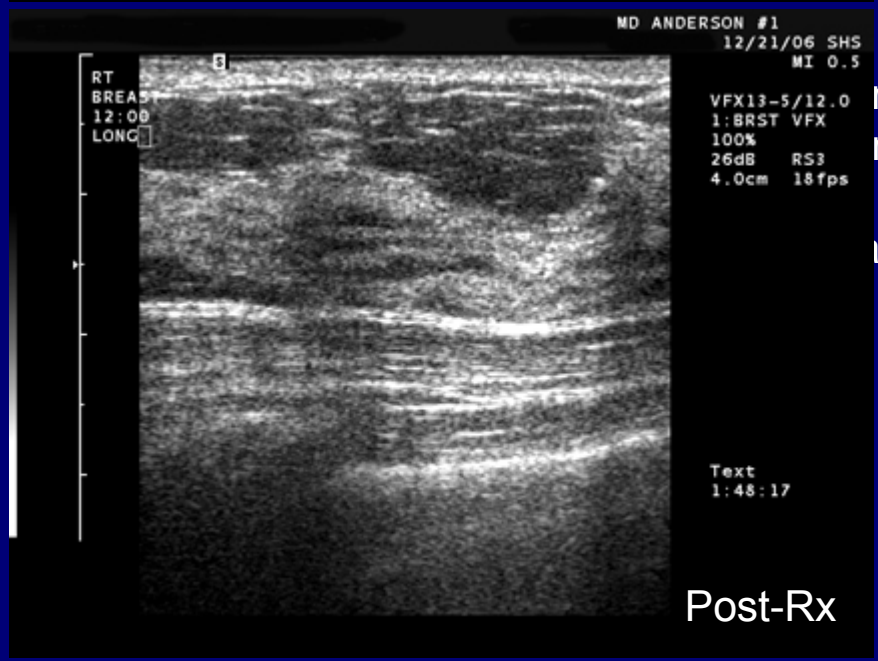
SIEMENS
Pre-Rx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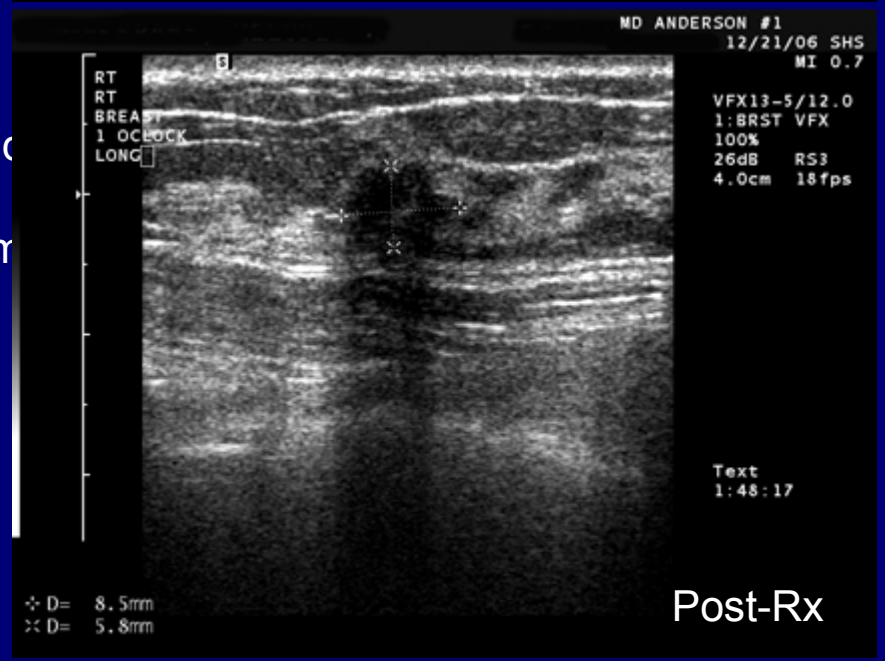
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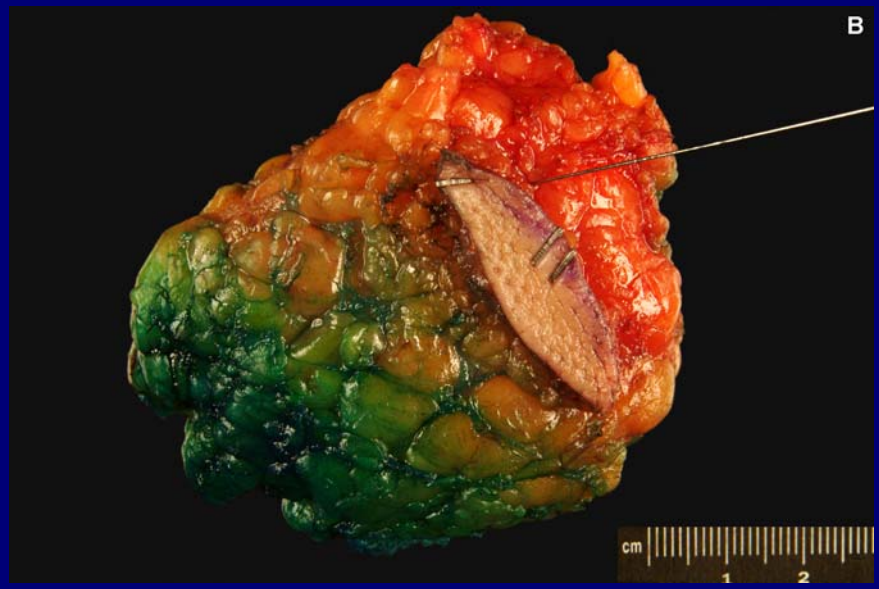
Post-Rx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cm
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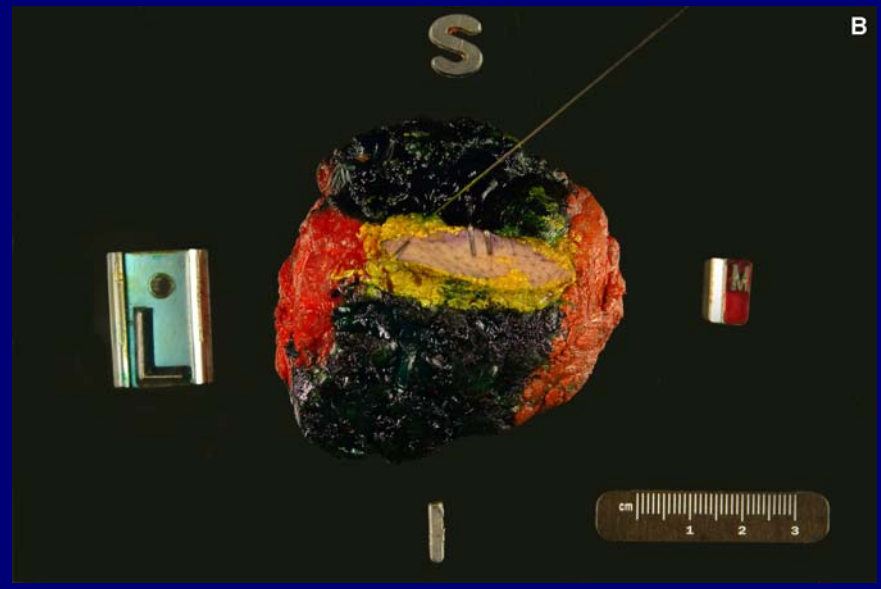
2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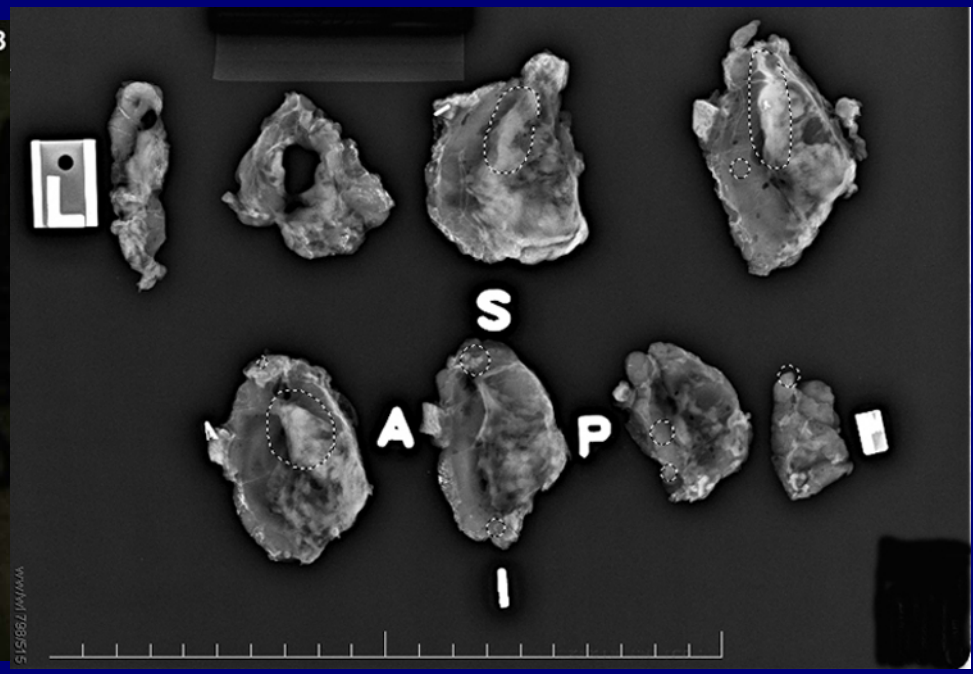
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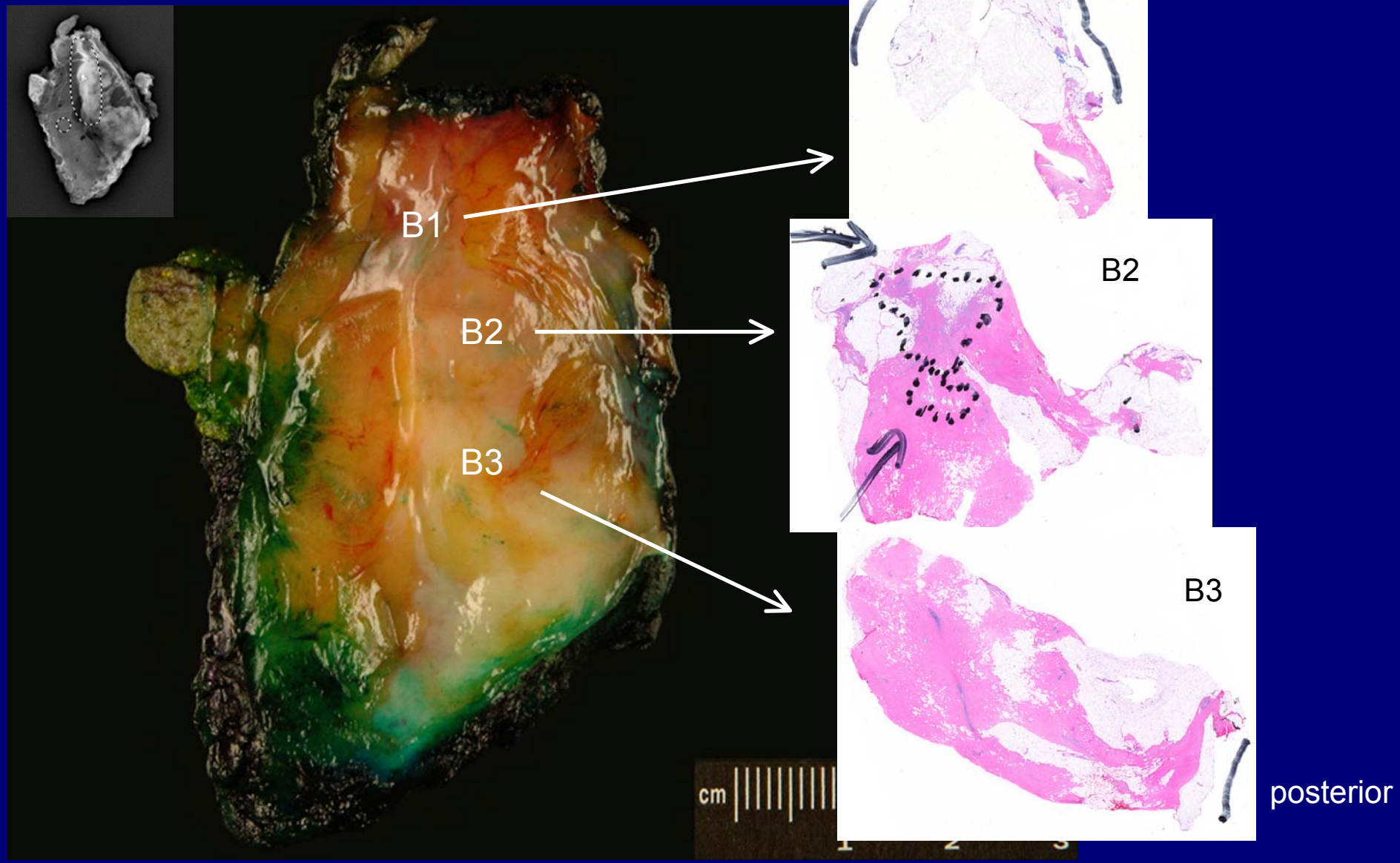
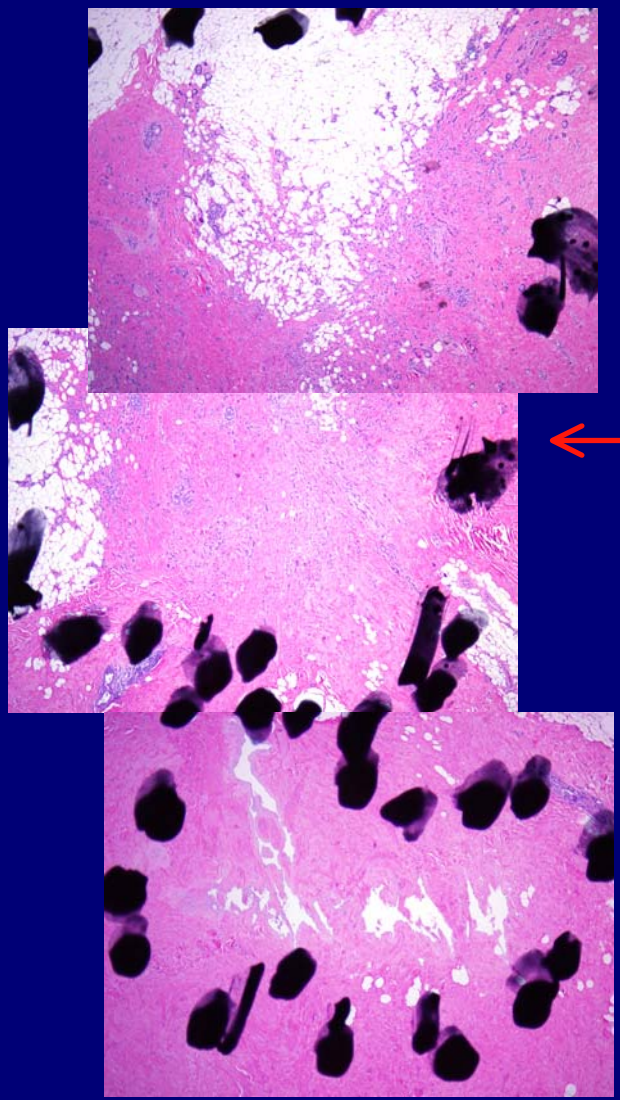
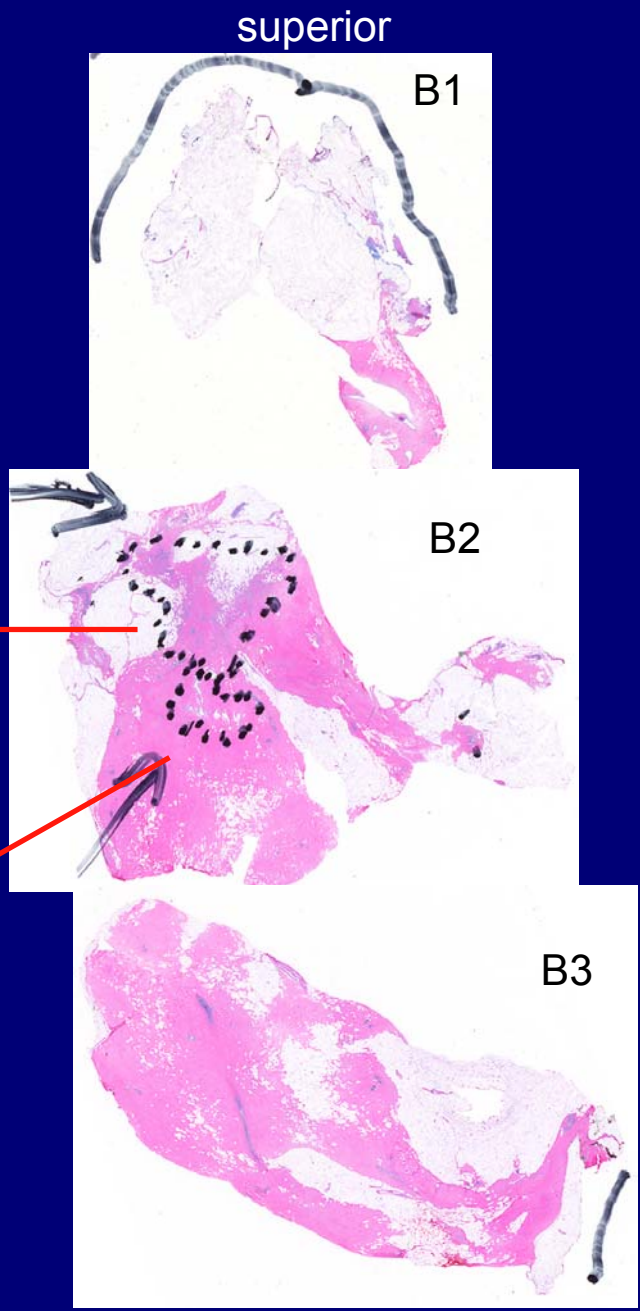

superior
B1
B2
B3
B1
B2
B3
cm
posterior


residual tumor
clip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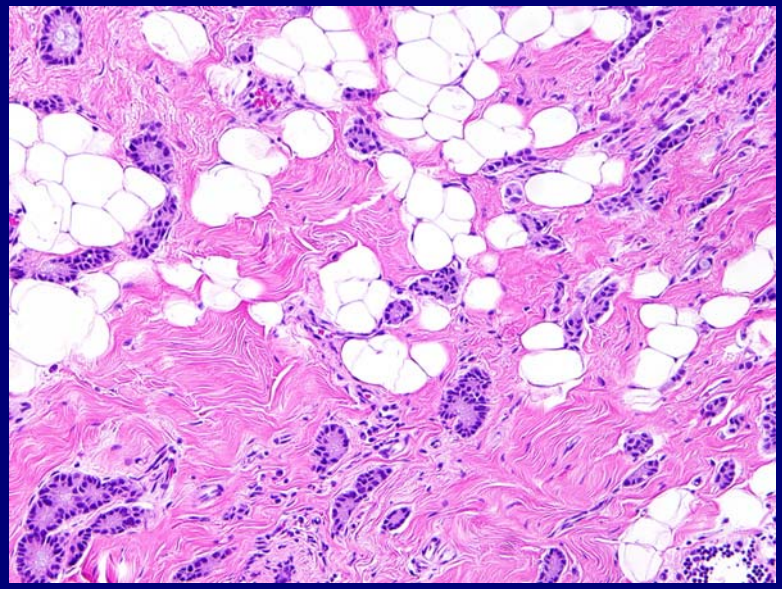
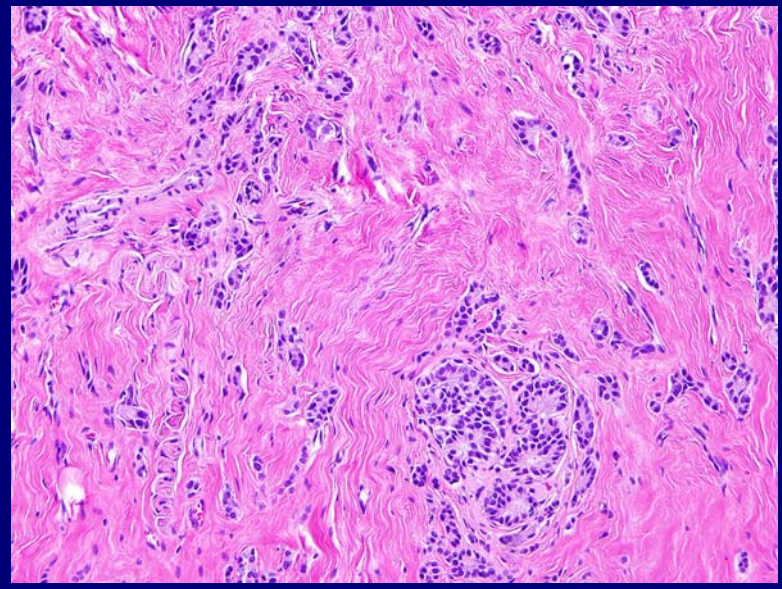
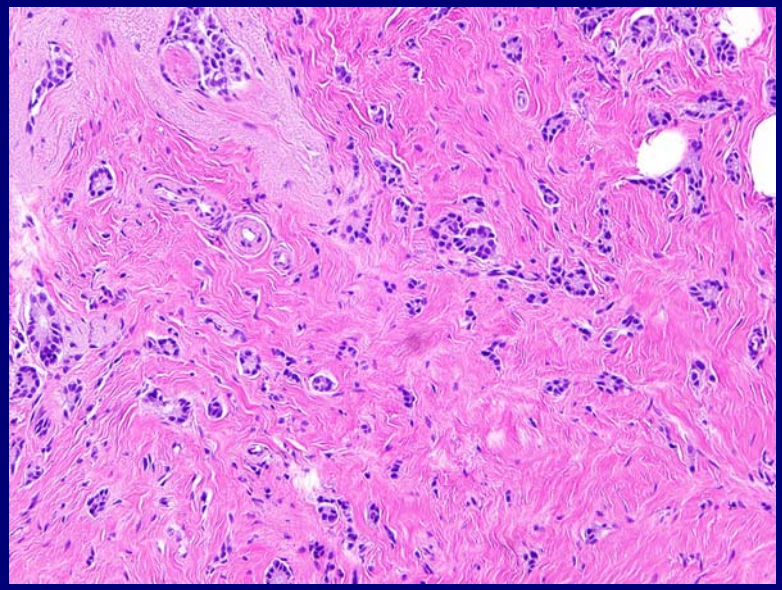
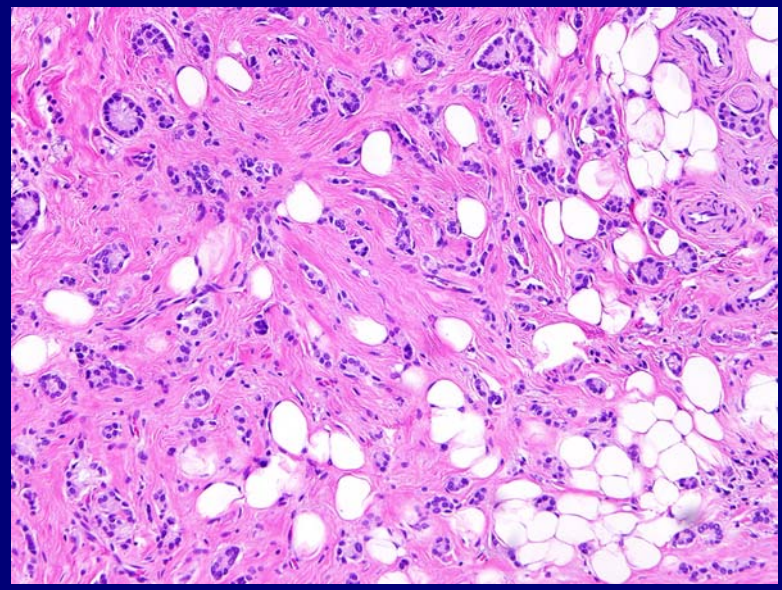
B1
B2
B3
posterior









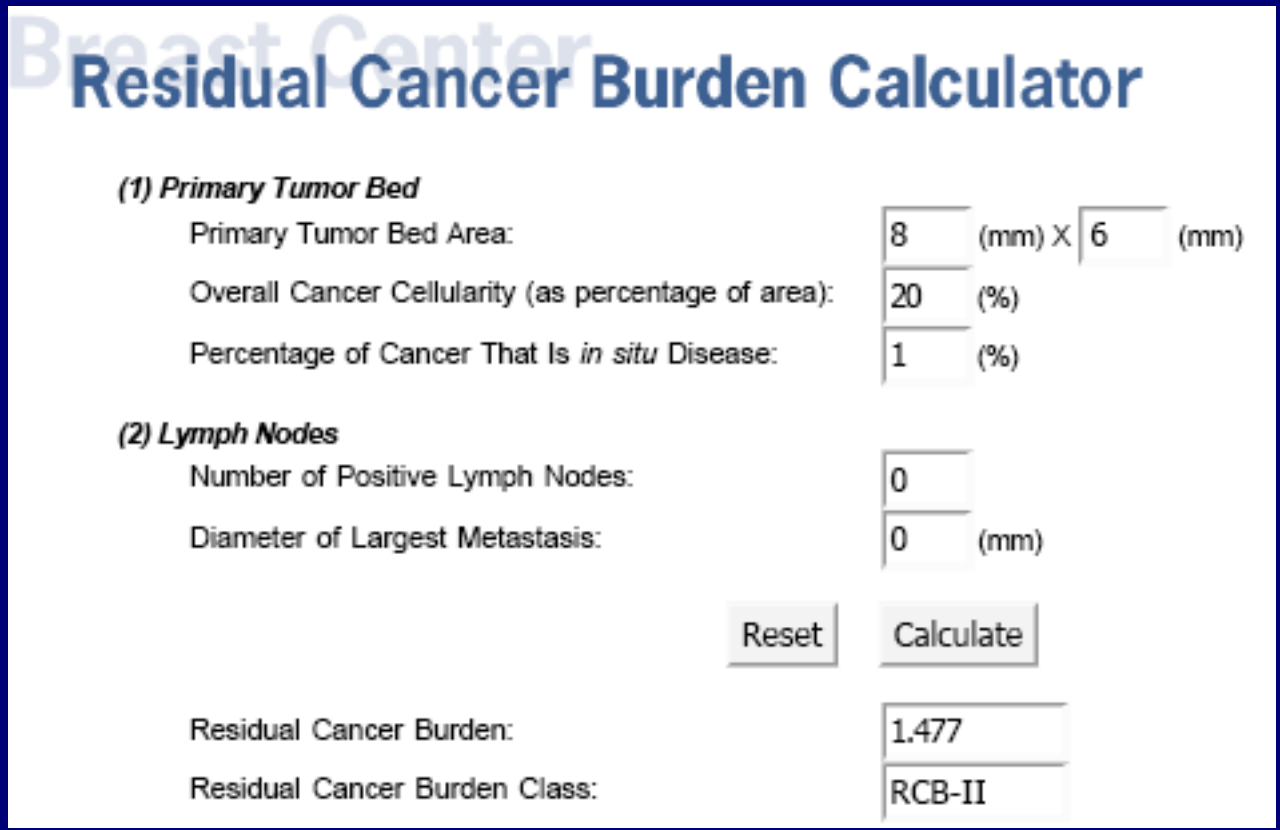
RIGHT BREAST, 1 O'CLOCK POSITION, SEGMENTAL MASTECTOMY:

RESIDUAL INVASIVE DUCTAL CARCINOMA MEASURES 0.8 X 0.6 CM AND CONTAINS APPROXIMATELY 20% CANCER CELLULARITY BY AREA, WITH 1% INTRADUCTAL COMPONENT.
SURROUNDING RESIDUAL FIBROUS TUMOR BED (2.7 X 1.0 CM) CONTAINING RARE SINGLE DUCTS WITH INTRADUCTAL CARCINOMA.
Margins of resection are free of tumor.

SENTINEL LYMPH NODE #1, RIGHT AXILLA, BIOPSY:
One lymph node, free of tumor (0/1).
Cytokeratin stain is negative.

NONSENTINEL LYMPH NODE, RIGHT AXILLA, BIOPSY:
One lymph node, free of tumor (0/1).

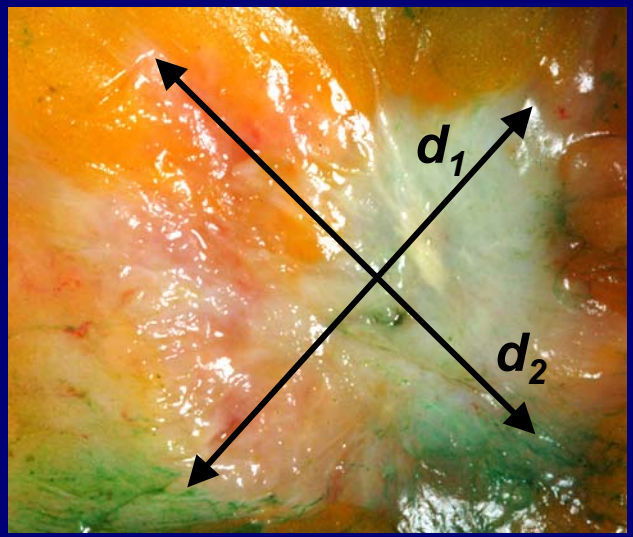
www.mdanderson.org/breastcancer_RCB

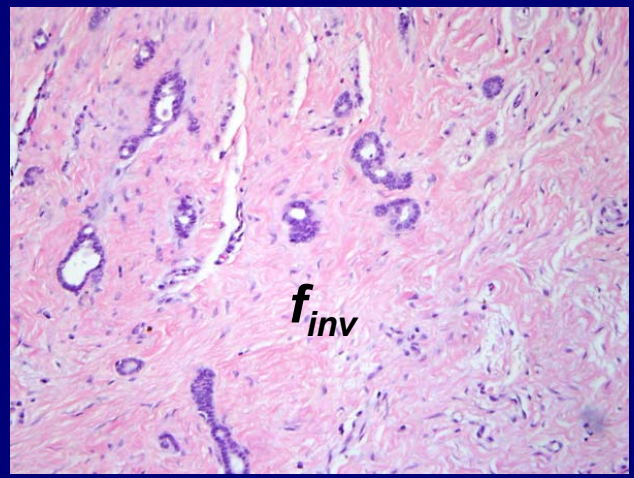


Symmans et al ASCO 2006 #536

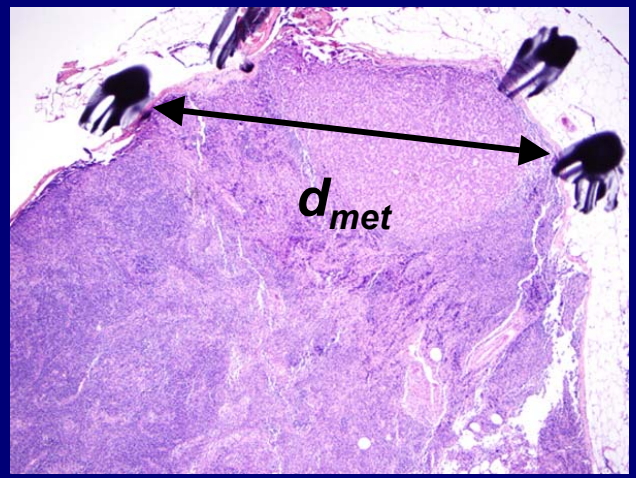
Residual Cancer Burden (RCB)

Primary Tumor Bed





Lymph Nodes



LN = Number of Positive Nodes

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

f_{inv} = % area with invasive CA

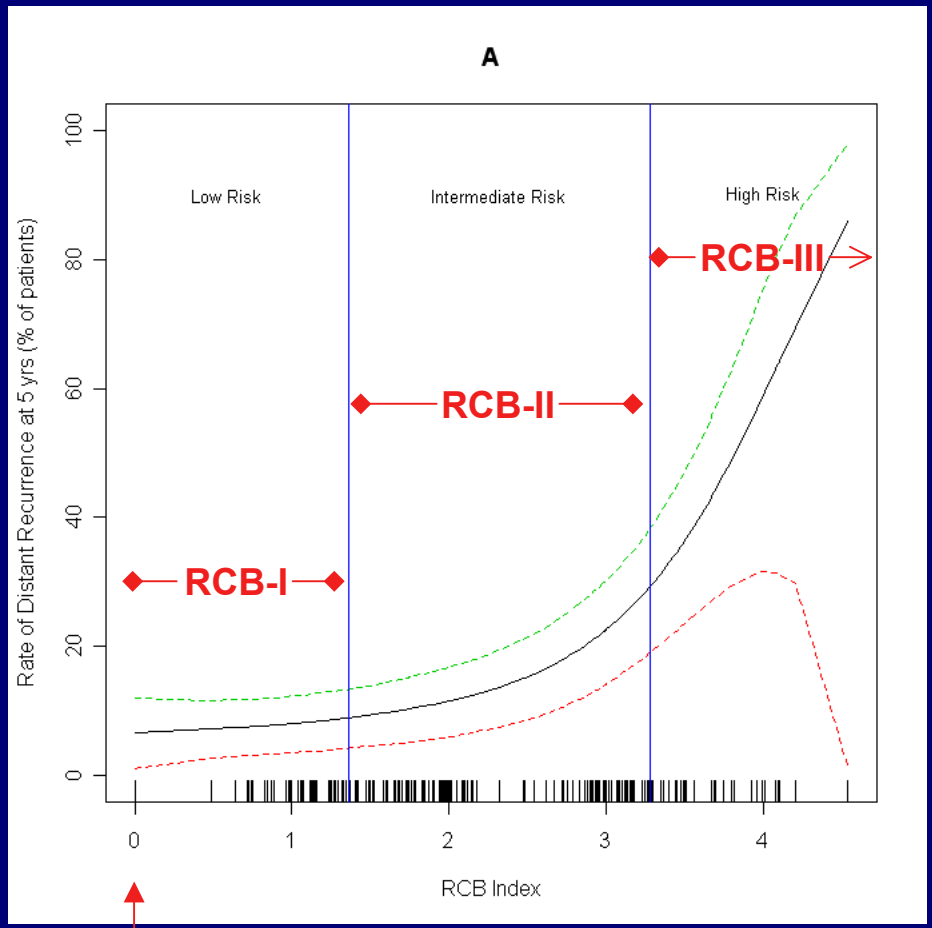
d_{met} = size largest metastasis

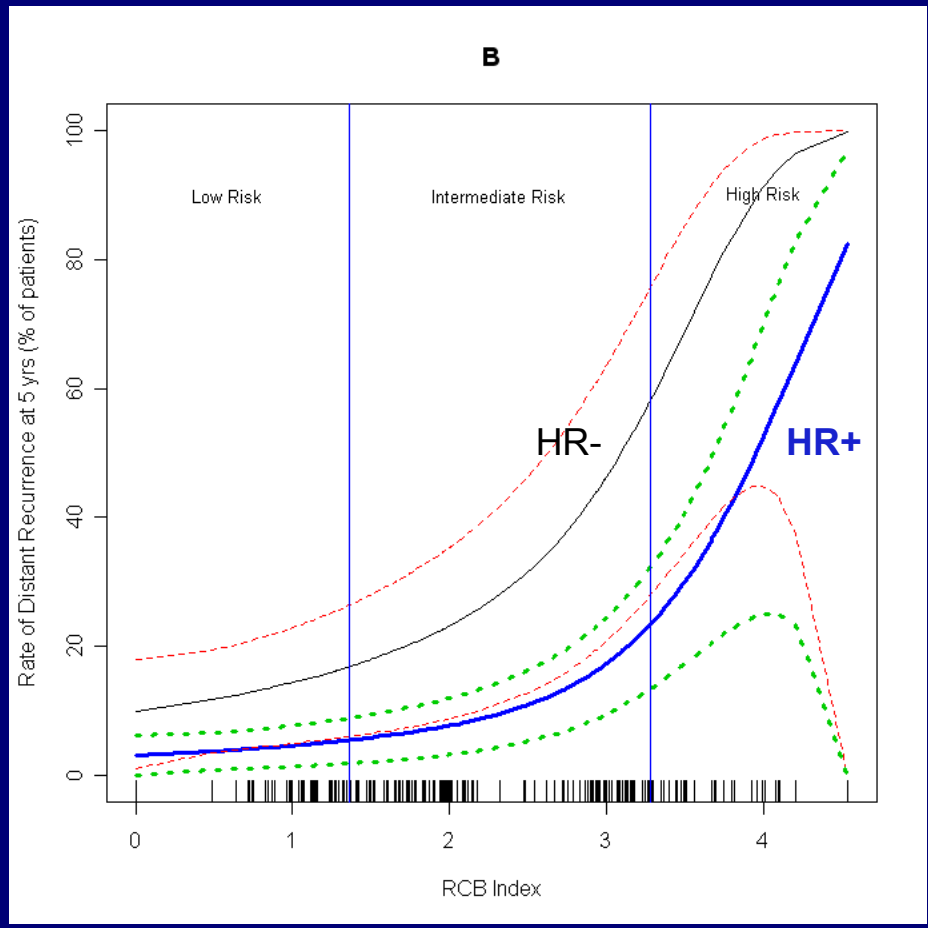
$$RCB = 1.4\,(d_{prim} \times f_{inv})^{0.17} + [4\,(d_{met} \times (1 - 0.75^{LN})]^{0.17}$$

Variable	Hazard Ratio (95% CI)	P value
Primary tumor bed size (d_{prim})	1.24 (1.04-1.48)	0.02
Fraction of invasive cancer (f_{inv})	7.37 (2.16-25.1)	0.001
Number of positive lymph nodes (*LN*)	1.11 (1.04-1.19)	0.002
Size of largest metastasis (d_{met})	1.17 (0.99-1.38)	0.06

Symmans et al ASCO 2006 #536

Residual Cancer Burden Predicts Distant Relapse After T/FAC Chemotherapy



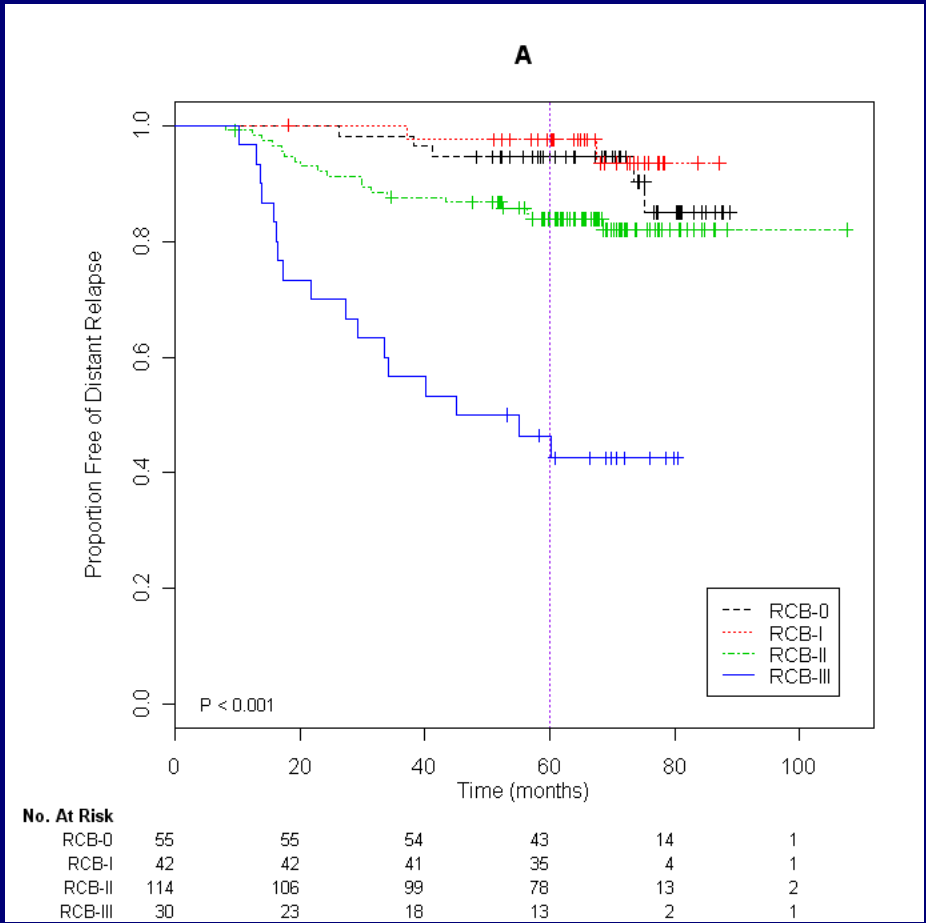


RCB-0 = pCR

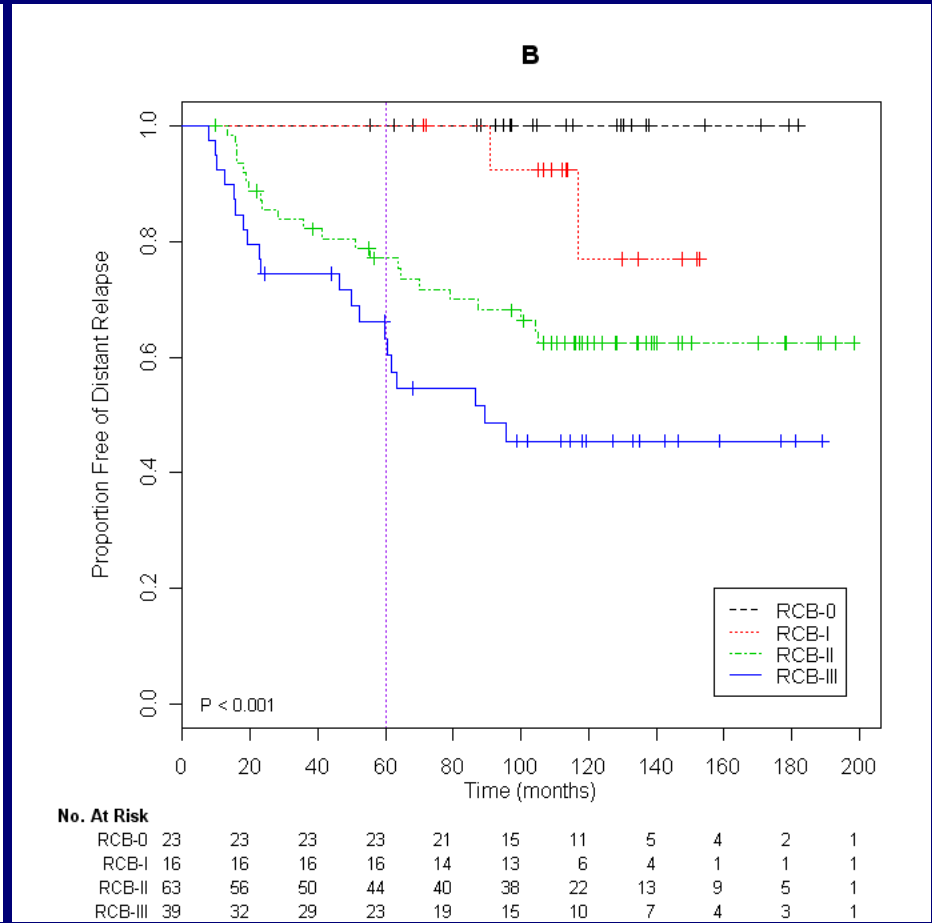
Symmans et al ASCO 2006 #536

Residual Cancer Burden (RCB) Classes Are Associated With DRFS After Chemotherapy

T/FAC (n = 241)



FAC alone (n = 141)



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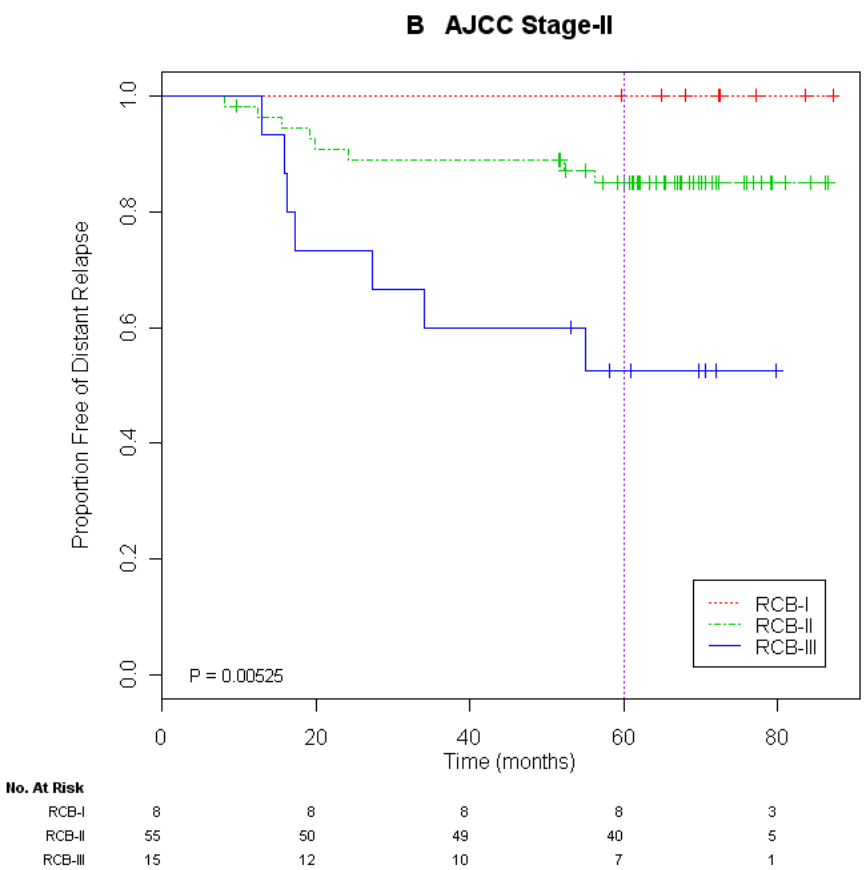
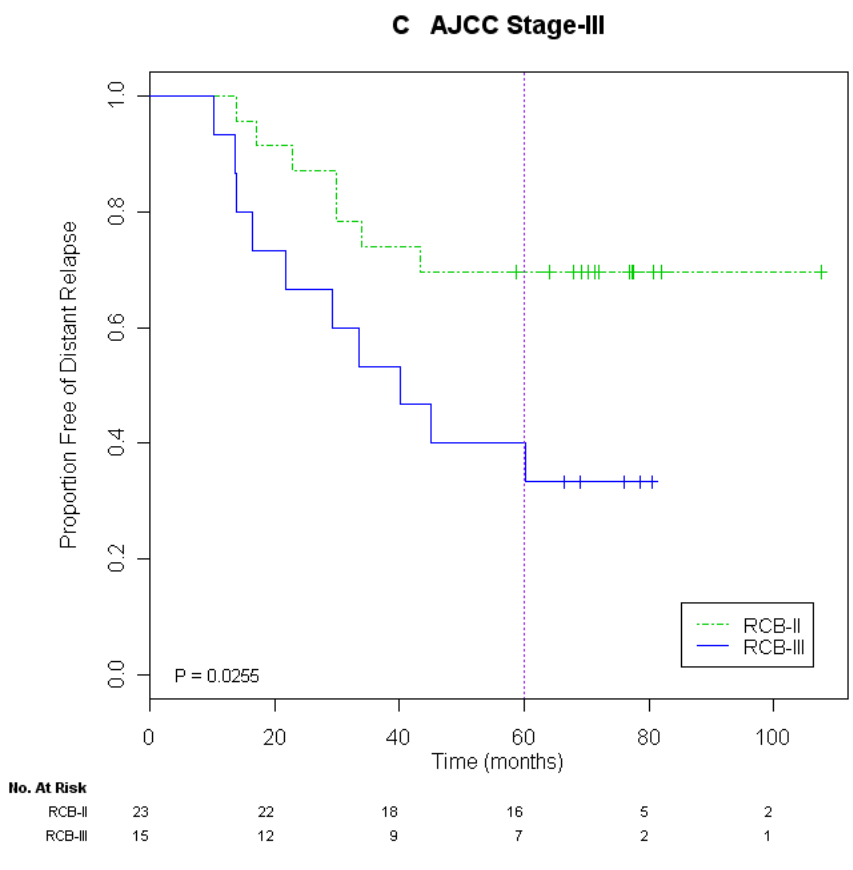
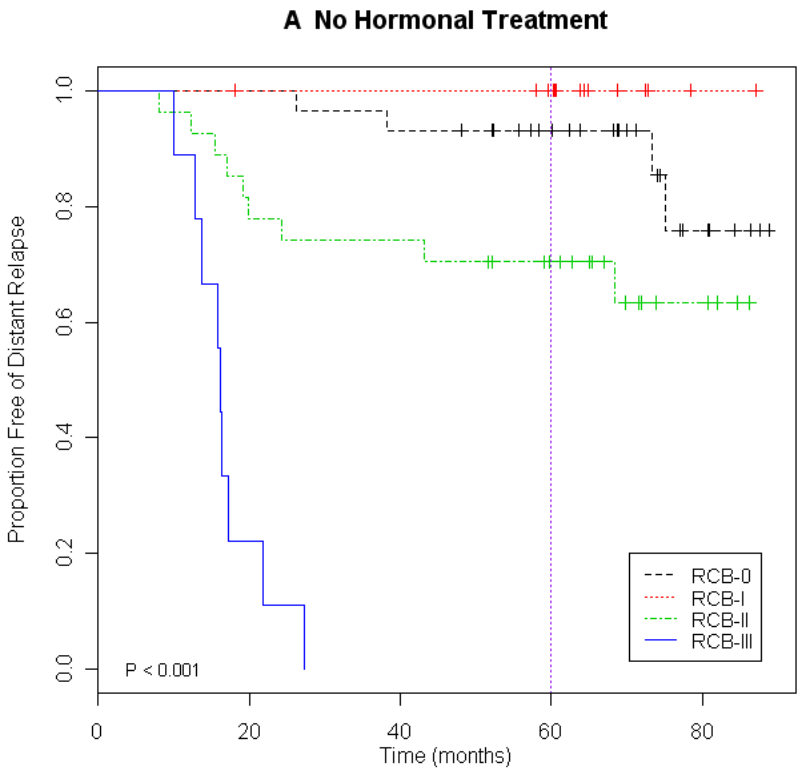
RCB Classes Stratify Residual Pathologic Stage After T/FAC Chemotherapy



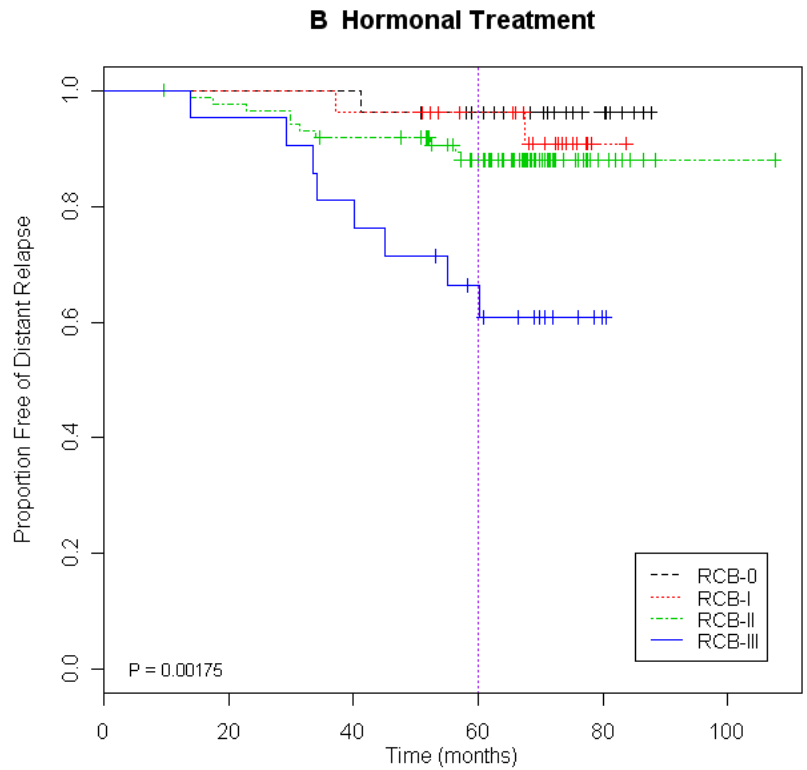


Symmans et al ASCO 2006 #536

Effect of ER Status and Adjuvant Hormonal Therapy: Residual Cancer Burden After T/FAC Chemotherapy



No. At Risk					
RCB-0	29	29	28	22	7
RCB-I	16	16	16	14	2
RCB-II	27	22	21	16	6
RCB-III	9	3	1	1	1



No. At Risk						
RCB-0	26	26	26	22	8	1
RCB-I	26	26	26	22	3	1
RCB-II	87	85	79	63	8	2
RCB-III	21	21	18	13	2	1

Symmans et al ASCO 2006 #536

Conclusions

1. The definition of pCR should be limited to yT0 & yN0
2. The extent of residual disease clearly has prognostic relevance
   - Both the primary site and regional nodal basin
   - Consistent recommendations for pathologic assessment and reporting of residual disease are needed
3. AJCC Stage, “Miller-Payne”, and Residual Cancer Burden assessments improve the classification of residual disease
   - RCB-I identifies a group with prognosis similar to pCR
   - RCB-III provides a pathologic definition of resistance
4. Accurate and reliable classification of residual disease can assist us with
   - New trial designs for preoperative treatments
   - Development of diagnostic tests to select treatment based on predicted response