Quantifying Post-Neoadjuvant Therapy Residual Disease and its Impact on Relapse Risk

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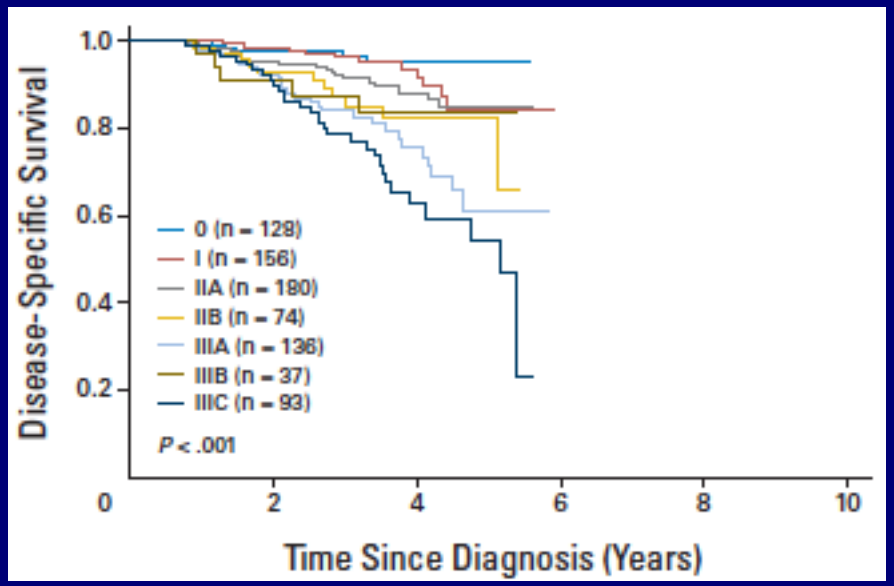
Disclosure

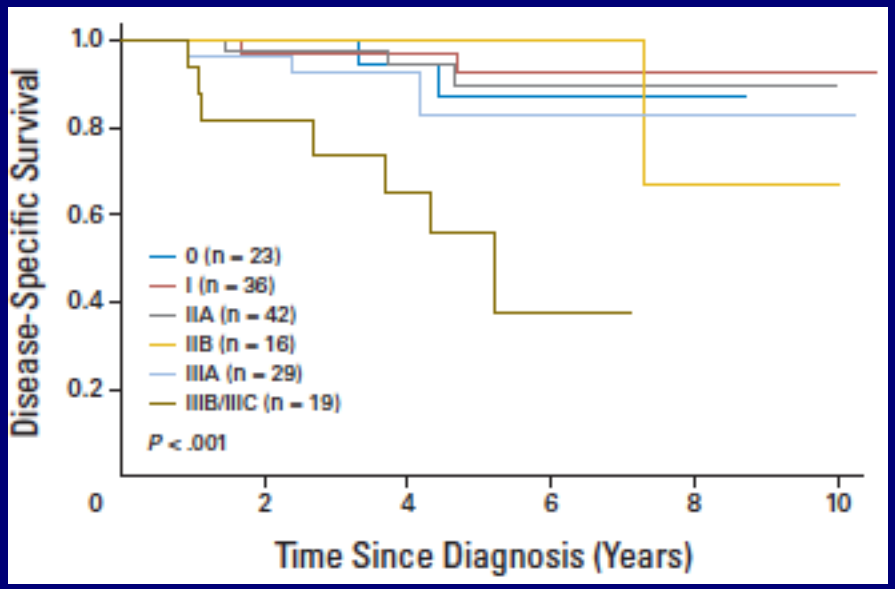
Nuvera Biosciences, Inc.
co-founder, intellectual property

Pathologic Stage (yp) After Neoadjuvant Chemotherapy

Internal Validation Cohort (MDACC)



External Validation Cohort (U Mich)

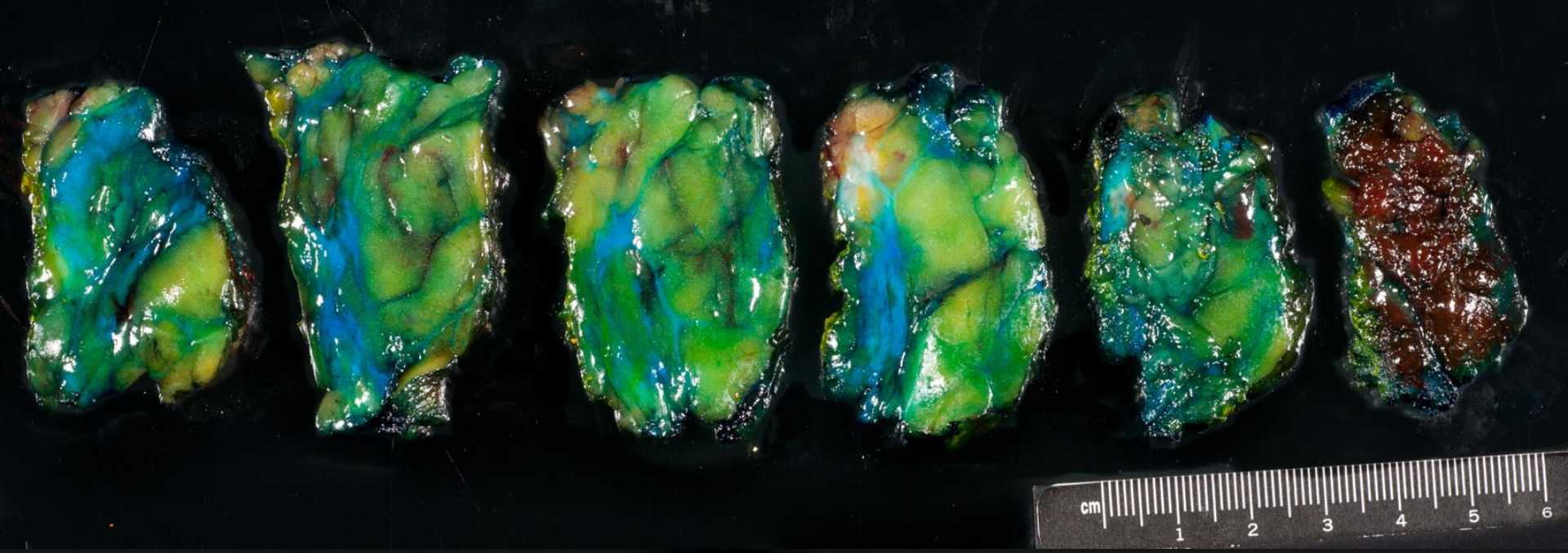


Based on 6th edition of AJCC Staging System (2003)

Mittendorf et al JCO 2011;29:1956-62

AJCC Stage of Tumor and Neoadjuvant Treatment 7th edition, 2010

- Introduced the following specific recommendations:
- Clinical T Stage should be based on the clinical or imaging measurement that is thought to be most accurate
- Postneoadjuvant therapy T Stage should be based on clinical or imaging (ycT) or pathologic findings (ypT)
- Estimate the size of tumors that are unapparent by clinical modalities or gross pathologic examination by carefully mapping the relative positions of the tissue sections and determining which contain tumor
- Pathologic (posttreatment) size should be estimated based on the best combination of gross and microscopic histological findings


cm
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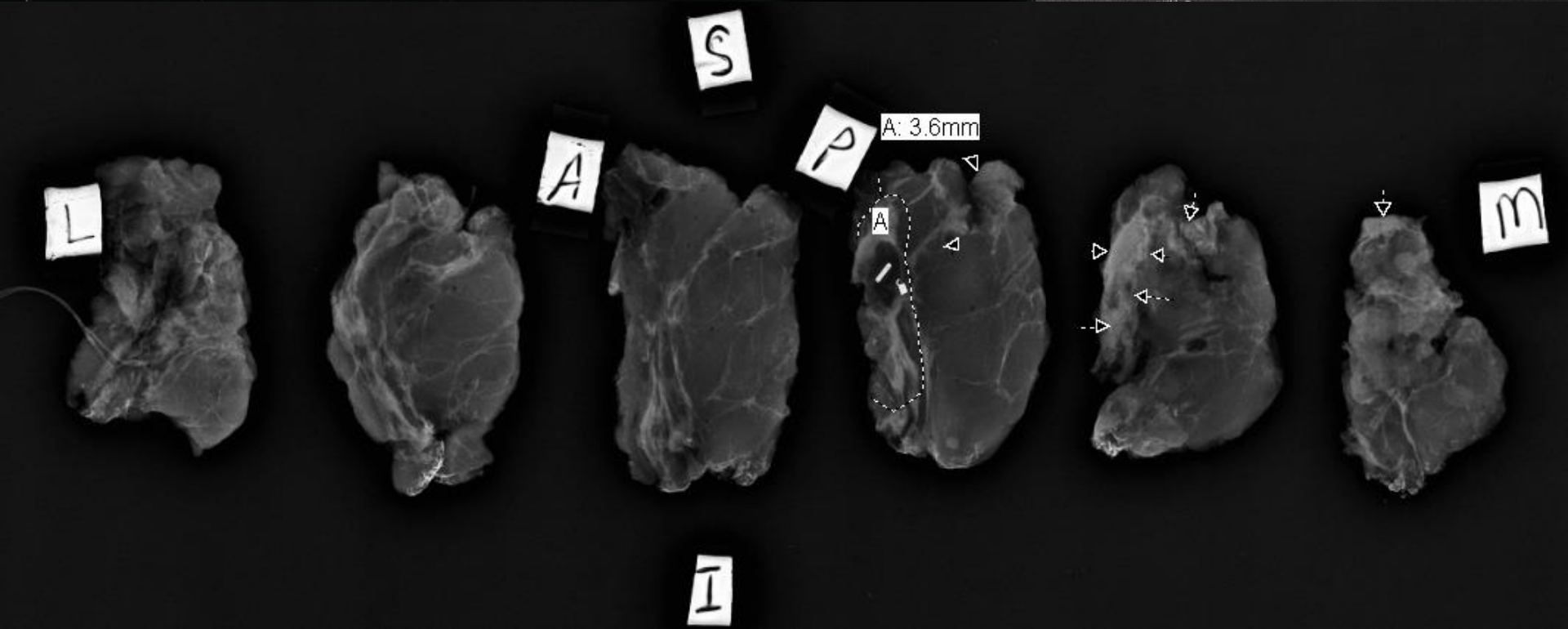
2
3
4
5
6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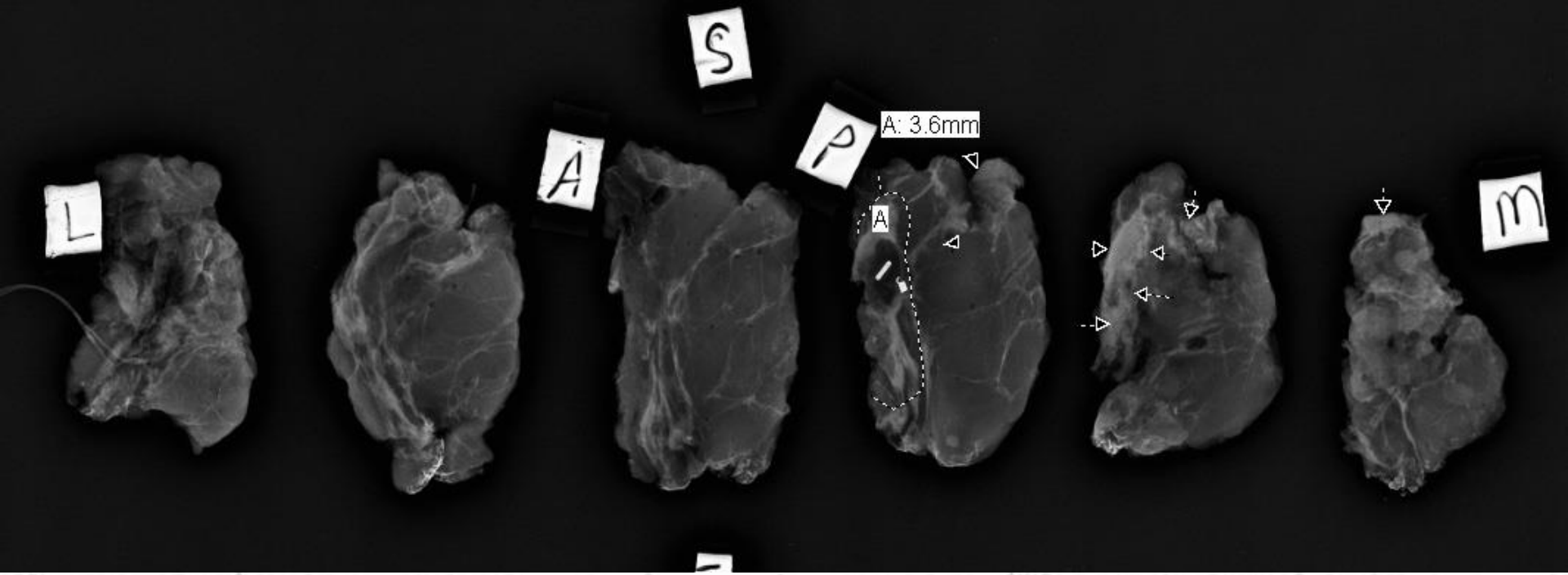
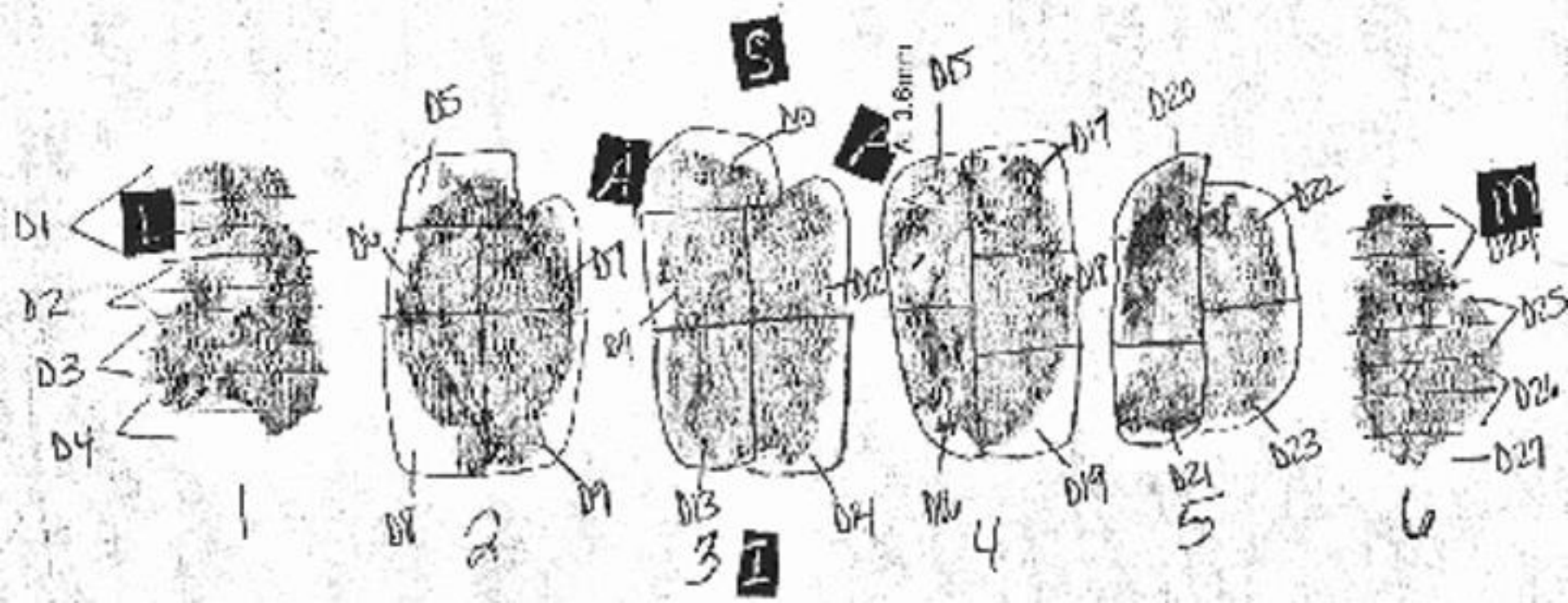
A
P
I
L
M
A: 3.6mm
A


S
A
P
A: 3.6mm
L
M


S
A
P
A: 3.6mm
L
M
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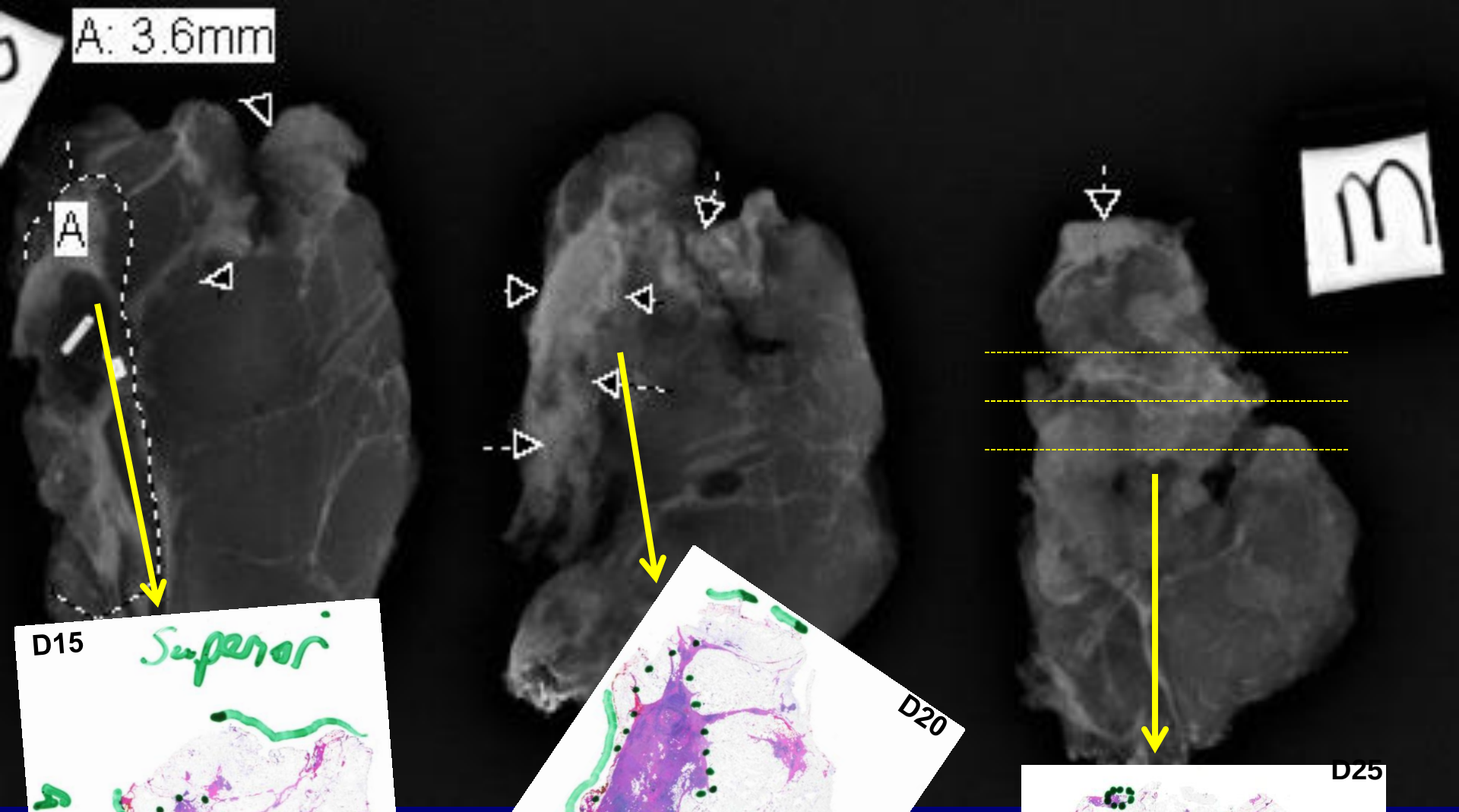
A: 3.6mm
A
B
D15
Superior
Anterior
D20
D25

AJCC Stage of Tumor and Neoadjuvant Treatment 7th edition, 2010

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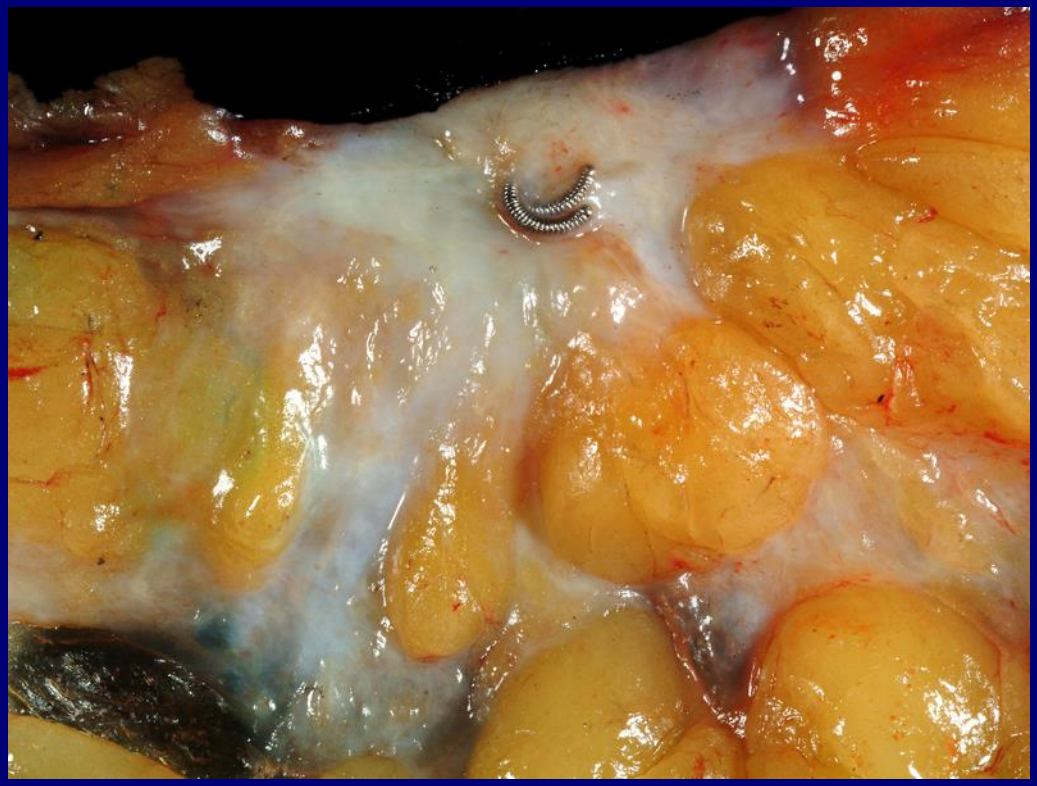
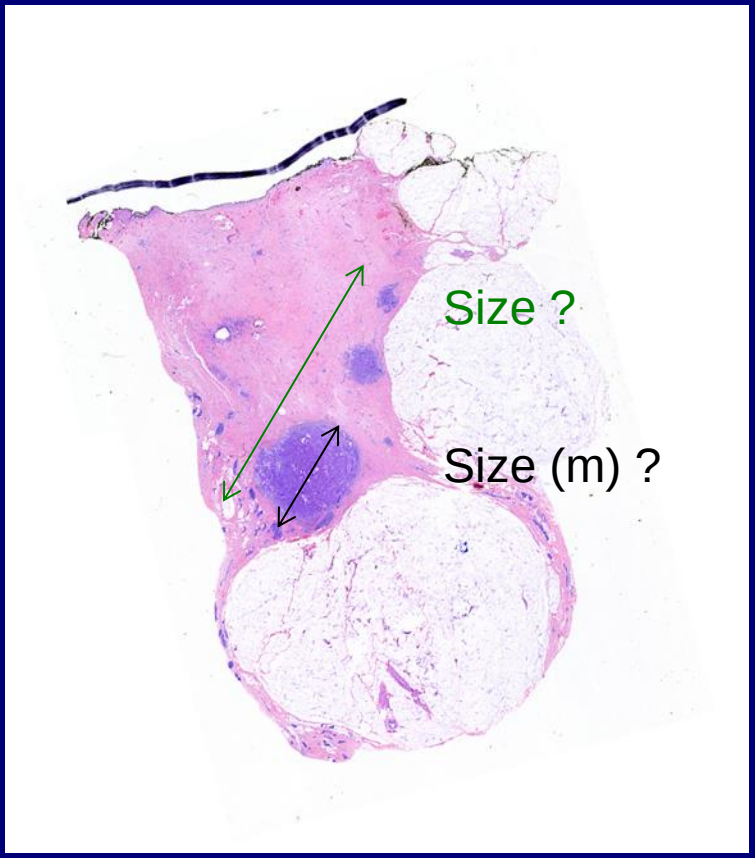
- Estimate the size of tumors that are unapparent by clinical modalities or gross pathologic examination by carefully mapping the relative positions of the tissue sections and determining which contain tumor
- **Pathologic (posttreatment) size should be estimated based on the best combination of gross and microscopic histological findings**
- **The posttreatment ypT will be defined as the largest continuous focus of invasive cancer as defined histopathologically with a subscript to indicate the presence of multiple tumor foci. Note: definition of posttreatment ypT remains controversial and an area in transition**

The Extent Of Residual Cancer Is Variable





AJCC Stage of Nodes and Neoadjuvant Treatment 7th edition, 2010

- Introduced the following specific recommendations:

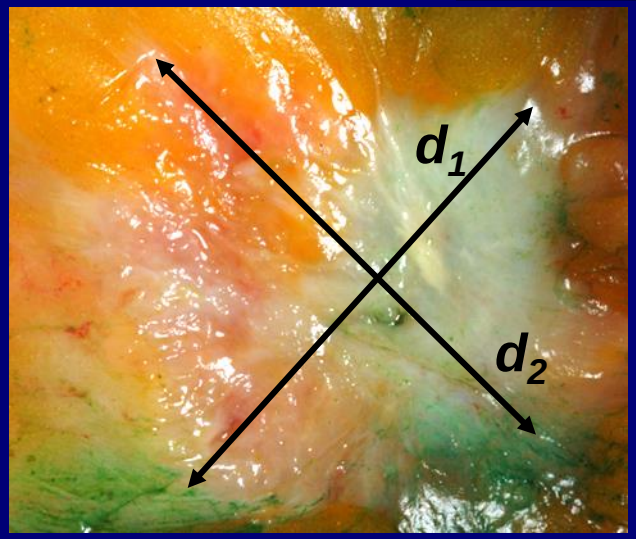
- Add subscript to clinical N Stage to indicate whether N was derived from clinical examination, FNA, core biopsy, or sentinel node biopsy

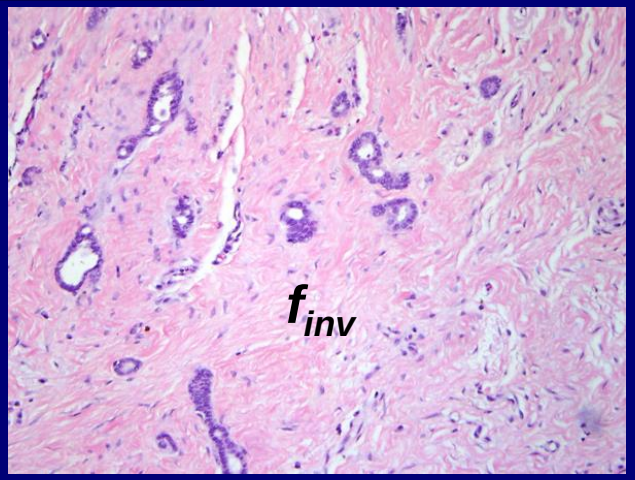
- Posttreatment nodal metastases ≤ 0.2 mm are classified as ypN0(i+)
  - No patients' outcomes data to support this recommendation

- Prone to subjectivity when residual metastasis consists of scattered remaining cells in fibrotic/treatment changes

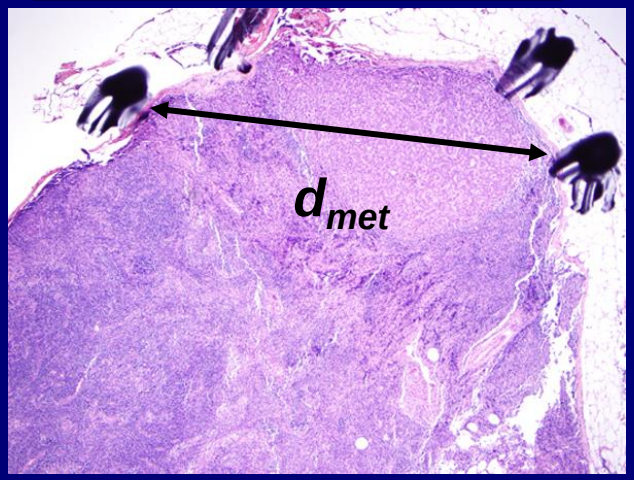
Residual Cancer Burden (RCB)

Primary Tumor Bed





Lymph Nodes



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

f_{inv} = % area with invasive CA

LN = Number of Positive Nodes

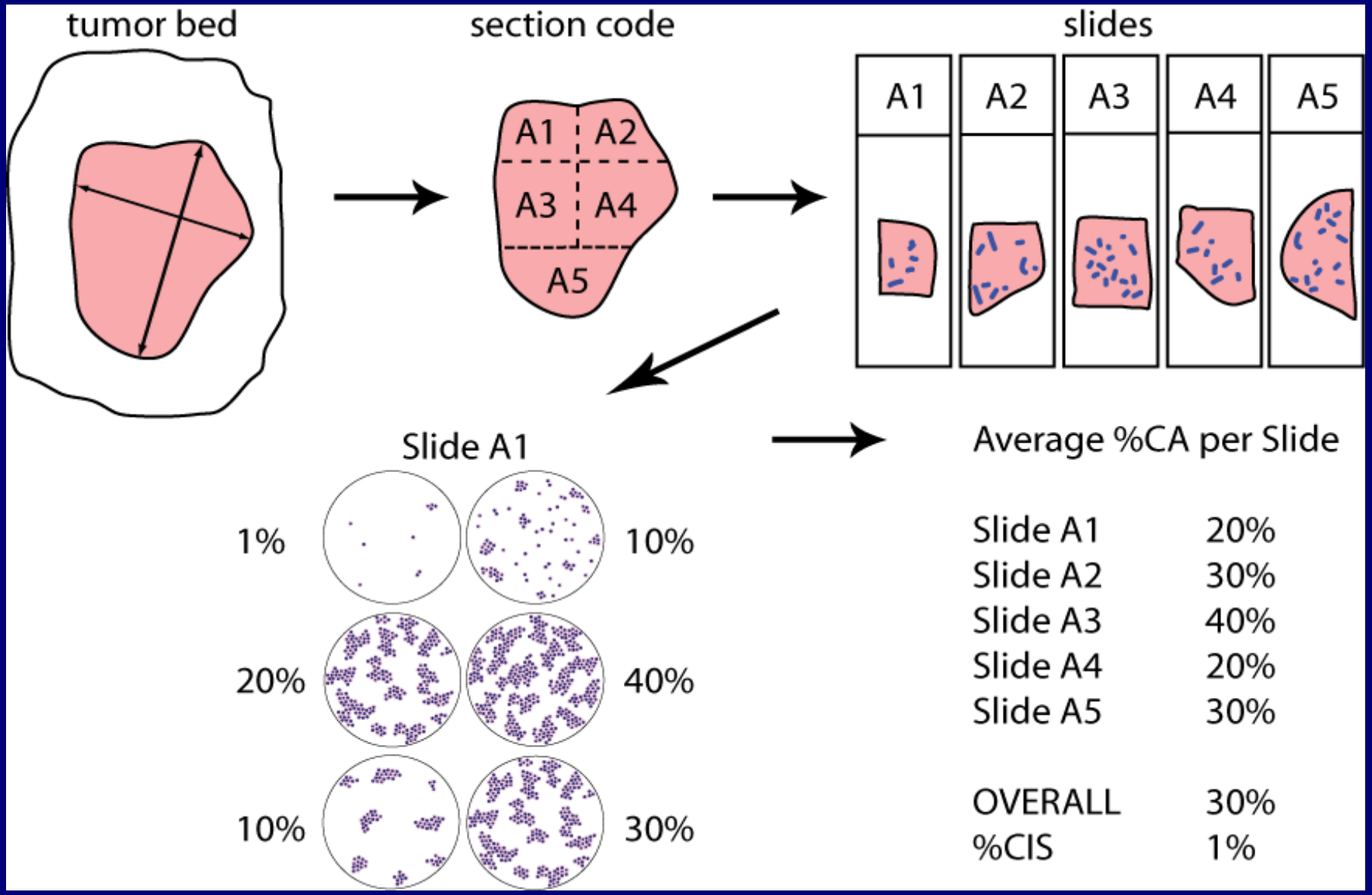
d_{met} = size largest metastasis

DRFS Following Neoadjuvant T/FAC Chemotherapy (N=241)

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 JCO 2007;25:4414-22

Pathologic Assessment Of The Primary Tumor Bed



See downloadable protocol and illustrations at www.mdanderson.org/breastcancer_RCB

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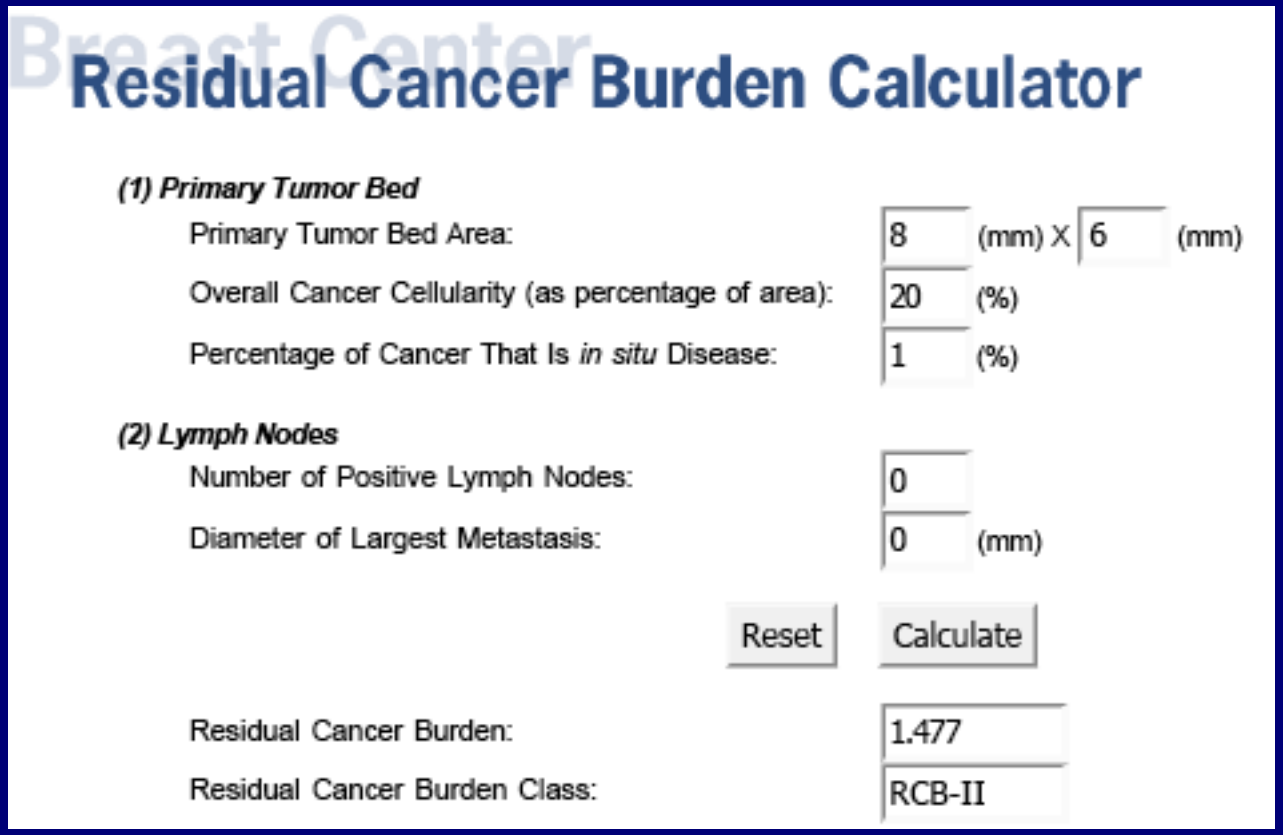


Residual Cancer Burden Calculator

(1) Primary Tumor Bed

Primary Tumor Bed Area:	8 (mm) X 6	(mm)
Overall Cancer Cellularity (as percentage of area):	20	(%)
Percentage of Cancer That Is *in situ* Disease:	1	(%)

(2) Lymph Nodes

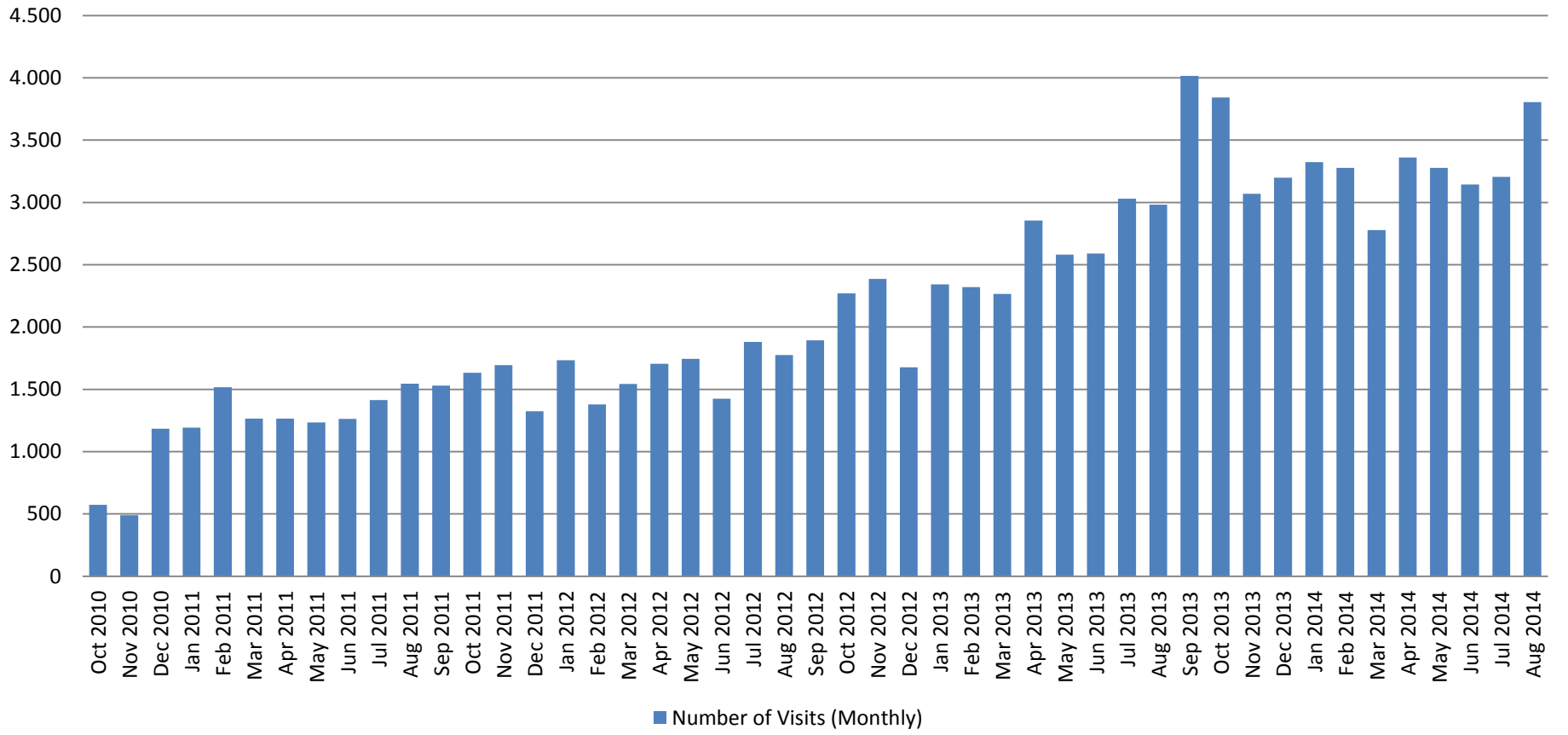
Number of Positive Lymph Nodes:	0	
Diameter of Largest Metastasis:	0	(mm)

Reset Calculate

Residual Cancer Burden:	1.477
Residual Cancer Burden Class:	RCB-II

Symmans et al JCO 2007;25:4414-22

Residual Cancer Burden Calculator



Prognostic Performance of RCB (continuous score)

Cohorts	Median F-up (years)	Relapse-Free Survival		Overall Survival	
		Hazard Ratio (95% CI)	C-Index (95% CI)	Hazard Ratio (95% CI)	C-Index (95% CI)
Validation FAC	16.4	2.01 (1.54, 2.63)	0.74 (0.68, 0.81)	1.91 (1.45, 2.52)	0.74 (0.67, 0.82)
Development T/FAC	12.7	2.20 (1.74, 2.79)	0.73 (0.67, 0.80)	2.08 (1.61, 2.70)	0.72 (0.64, 0.80)
Validation T/FAC	8.3	1.87 (1.56, 2.25)	0.73 (0.67, 0.78)	1.94 (1.59, 2.38)	0.75 (0.68, 0.81)
Combined T/FAC	10.1	2.00 (1.72, 2.31)	-	2.01 (1.72, 2.35)	-

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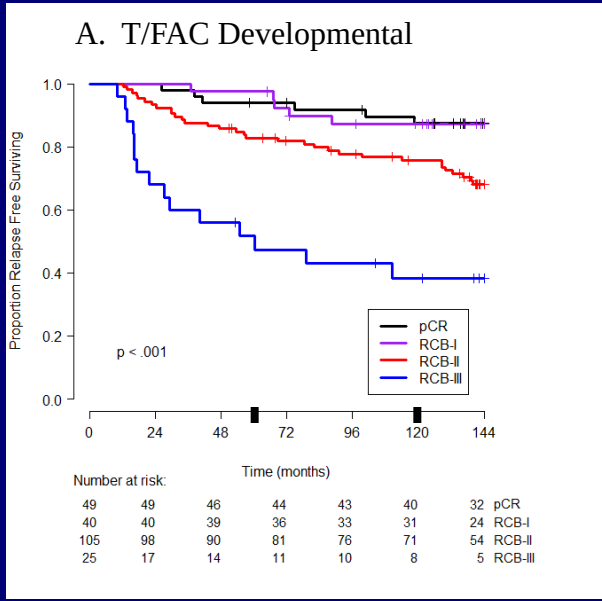
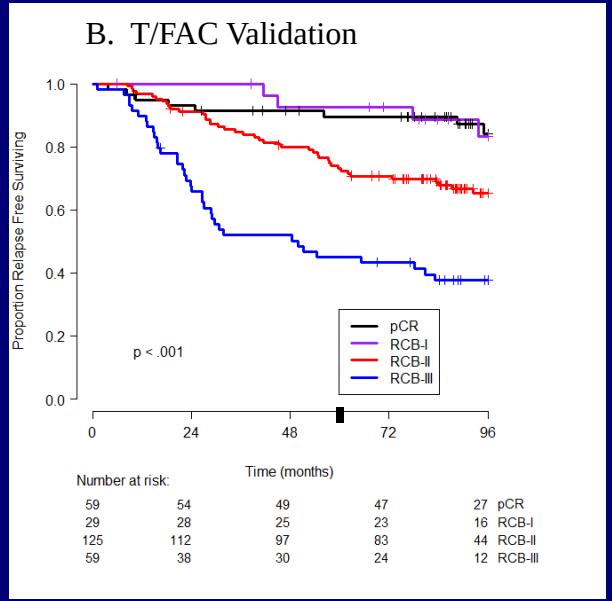
Prognosis According To RCB Categories (RFS)

Developmental Cohort T/FAC



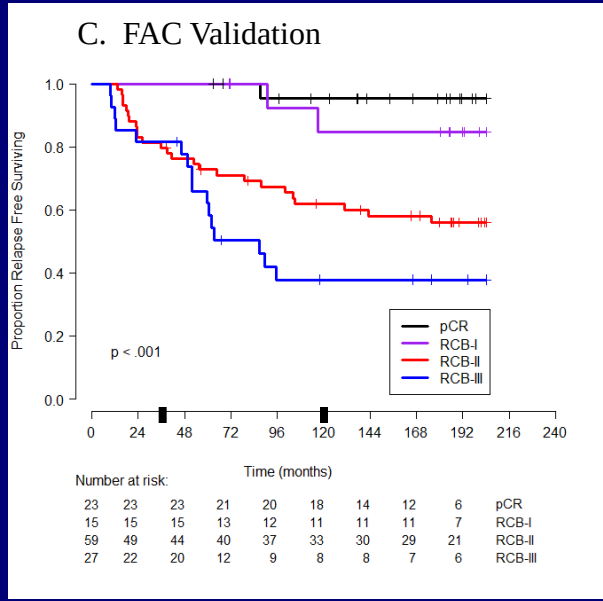
	Class	N	%
	pCR	49	22
	RCB-I	40	18
	RCB-II	105	48
	RCB-III	25	11

Validation Cohort T/FAC



	Class	N	%
	pCR	59	22
	RCB-I	29	11
	RCB-II	125	46
	RCB-III	59	22

Validation Cohort FAC



	Class	N	%
	pCR	23	18
	RCB-I	16	12
	RCB-II	60	46
	RCB-III	32	24

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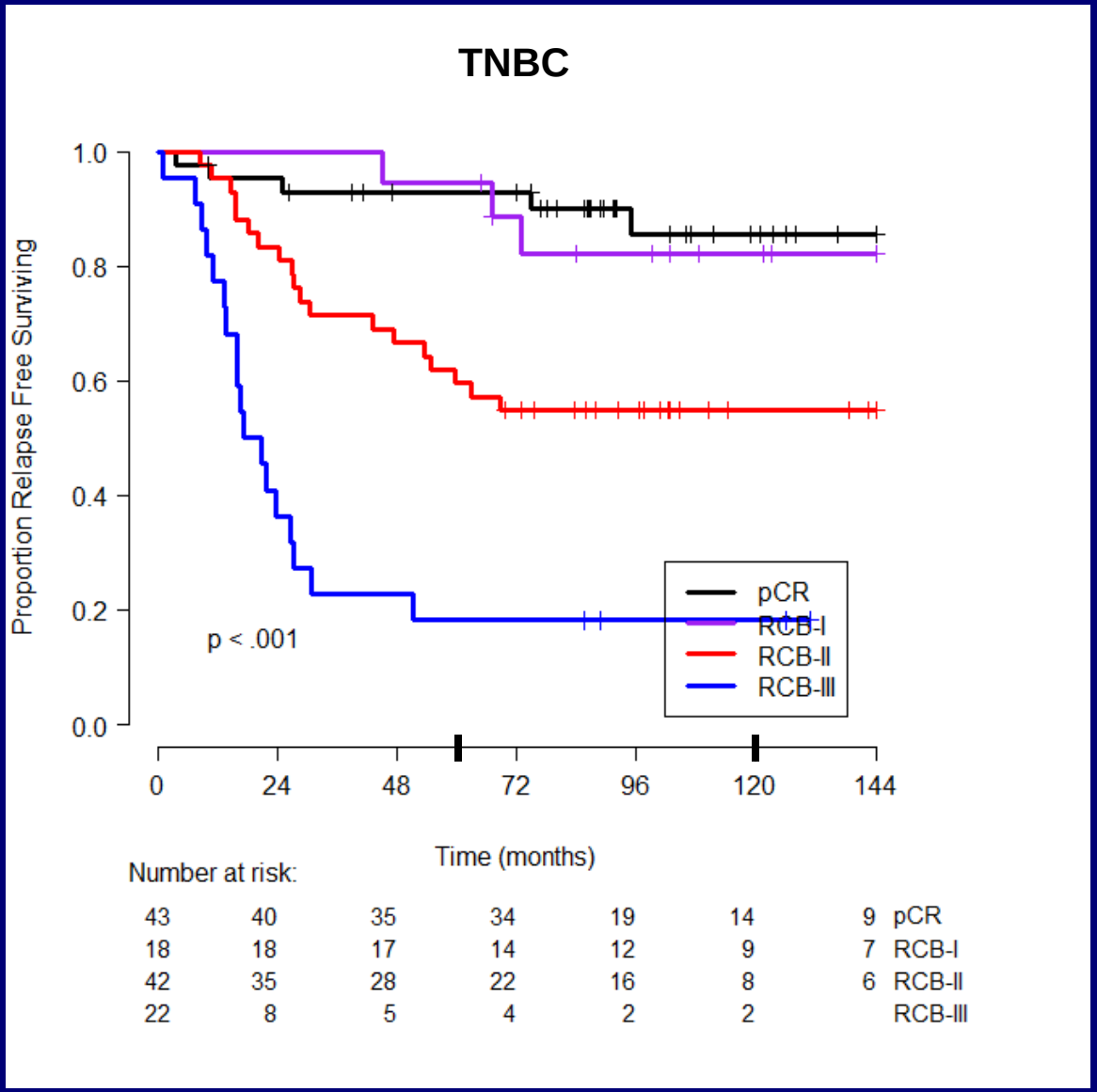
RCB Categories: Combined T/FAC Cohorts (RFS)



Class	N	%
pCR	43	34
RCB-I	18	14
RCB-II	42	34
RCB-III	22	18

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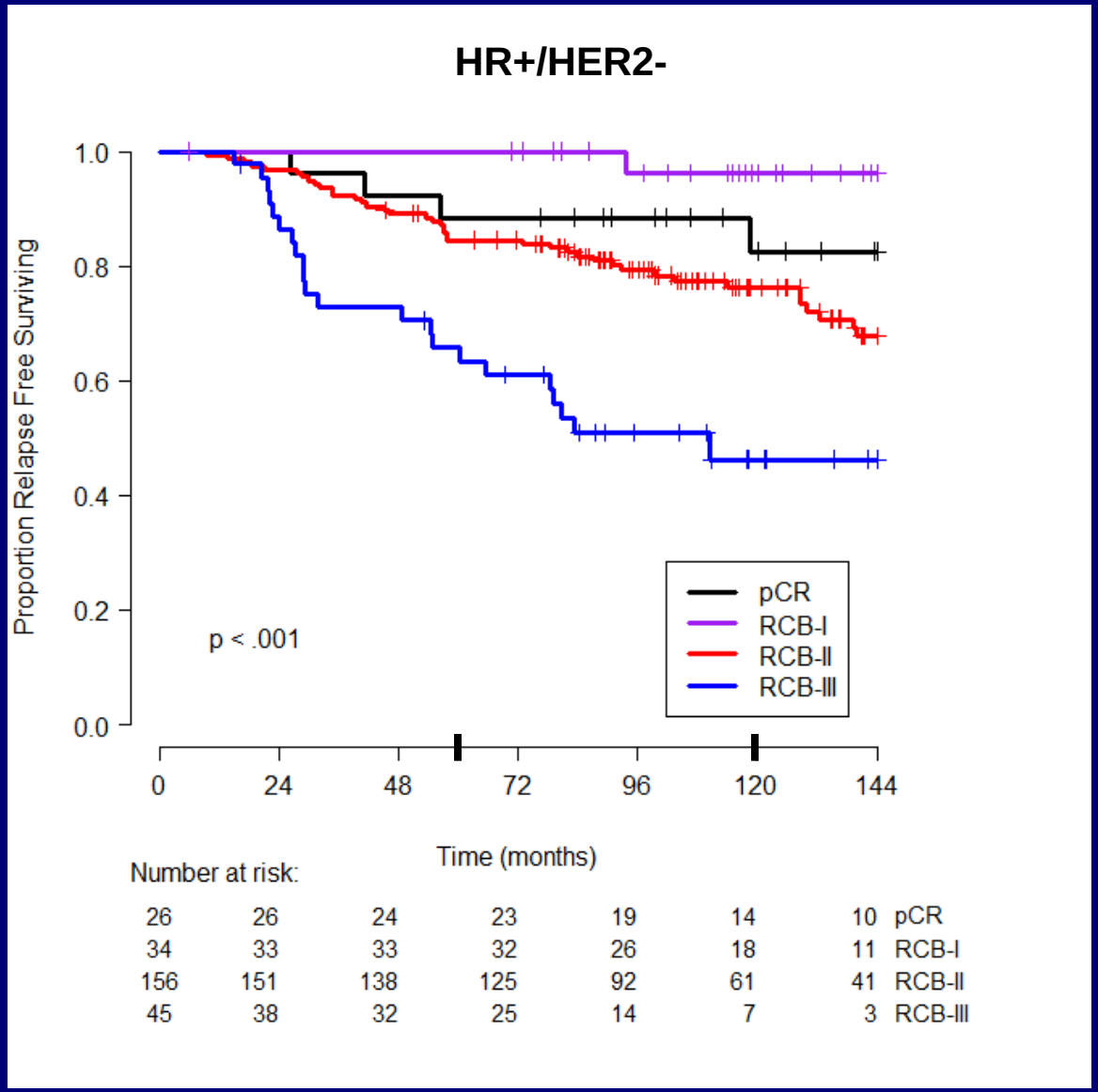
RCB Categories: Combined T/FAC Cohorts (RFS)



Class	N	%
pCR	26	10
RCB-I	34	13
RCB-II	156	60
RCB-III	45	17

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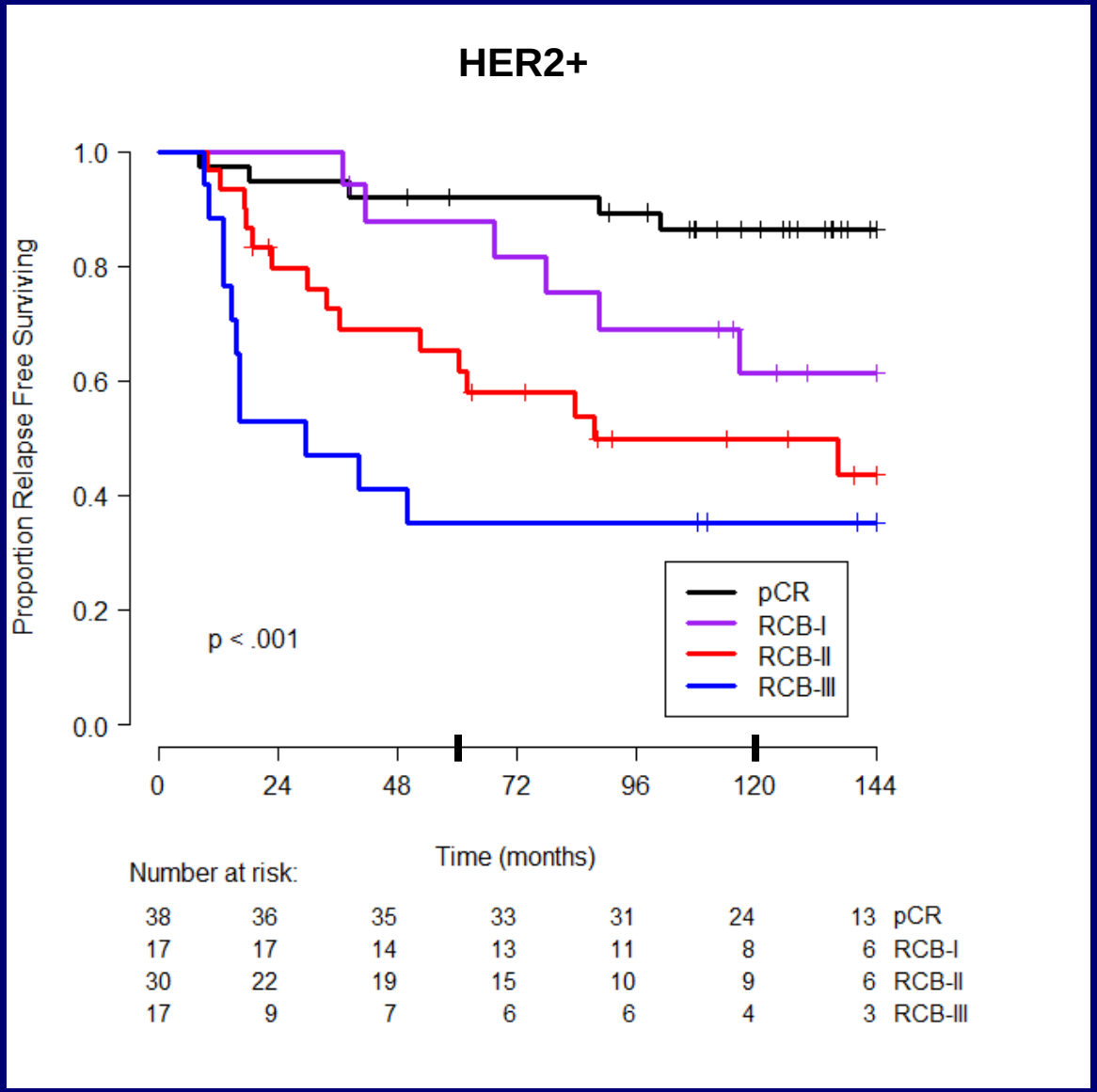
RCB Categories: Combined T/FAC Cohorts (RFS)



Class	N	%
pCR	38	37
RCB-I	17	17
RCB-II	30	29
RCB-III	17	17

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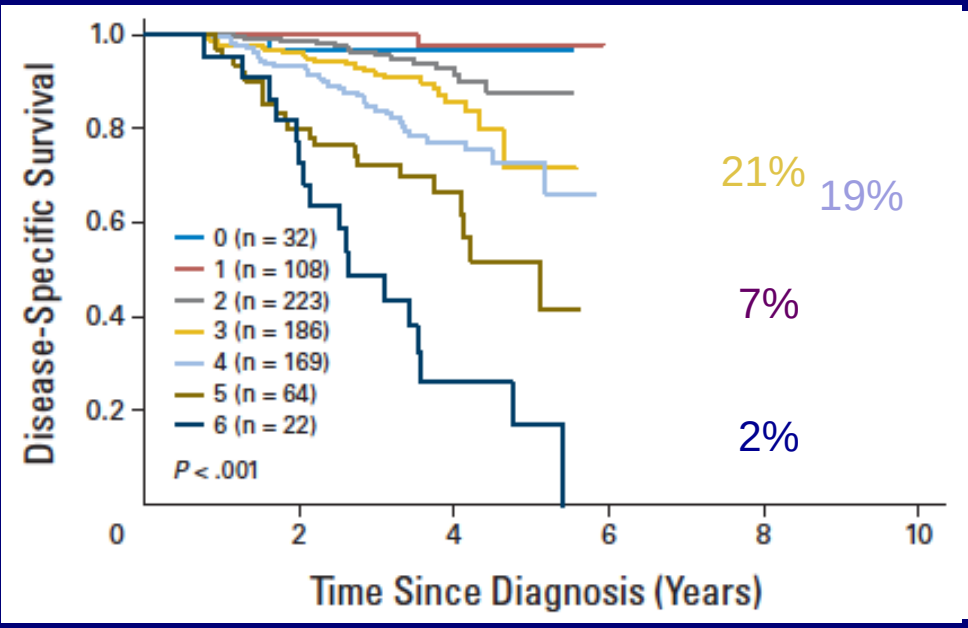
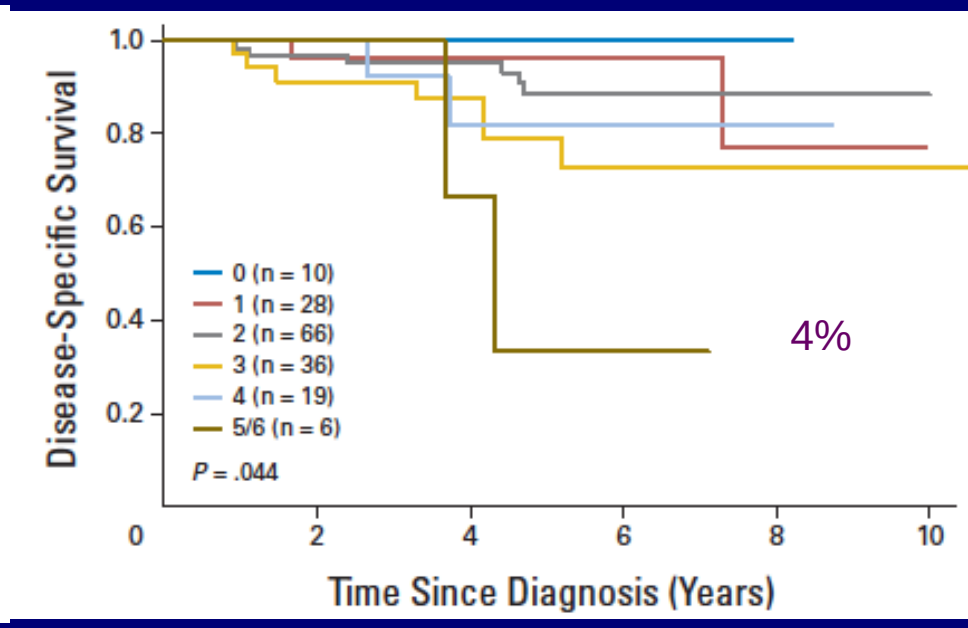
Clinical Stage + ER Status + Grade + Pathologic Stage (CPS-EG)

Pre-Rx Stage (c)		Pre-Rx Pathobiology				Post-Rx Stage (yp)	
c Stage	=	ER Status	=	N Grade	=	yp Stage	=
I - IIA	0	Positive	0	1 - 2	0	0 - I	0
IIB - IIIA	1	Negative	1	3	1	IIA - IIIB	1
IIIB - IIIC	2					IIIC	2

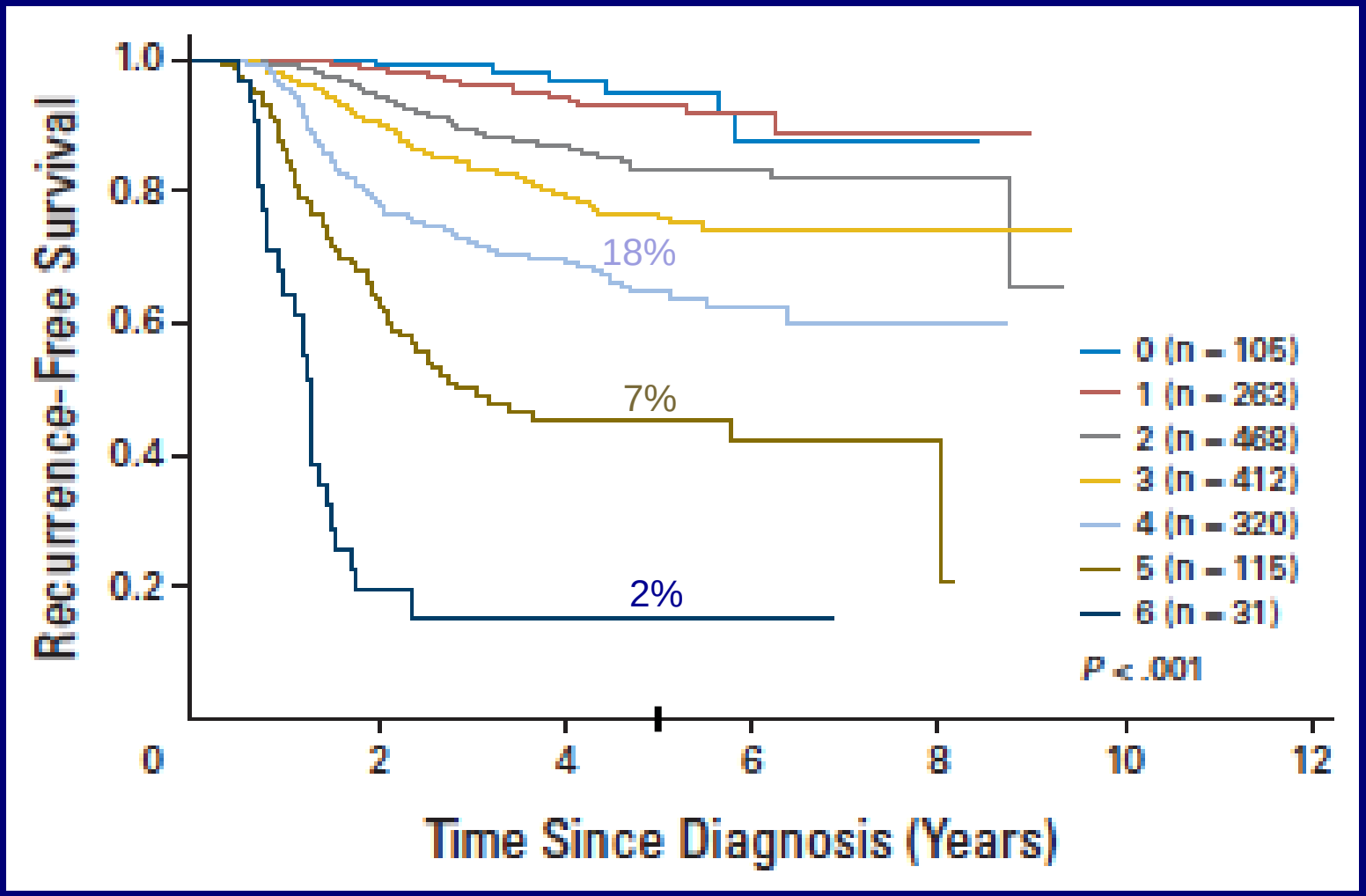




Based on 6th edition of AJCC Staging System (2003)

Mittendorf et al JCO 2011;29:1956-62

Prognosis (DFS) of CPS-EG Groups In MDACC T/FAC Cohorts: Development (n=932) and Validation (n=969)



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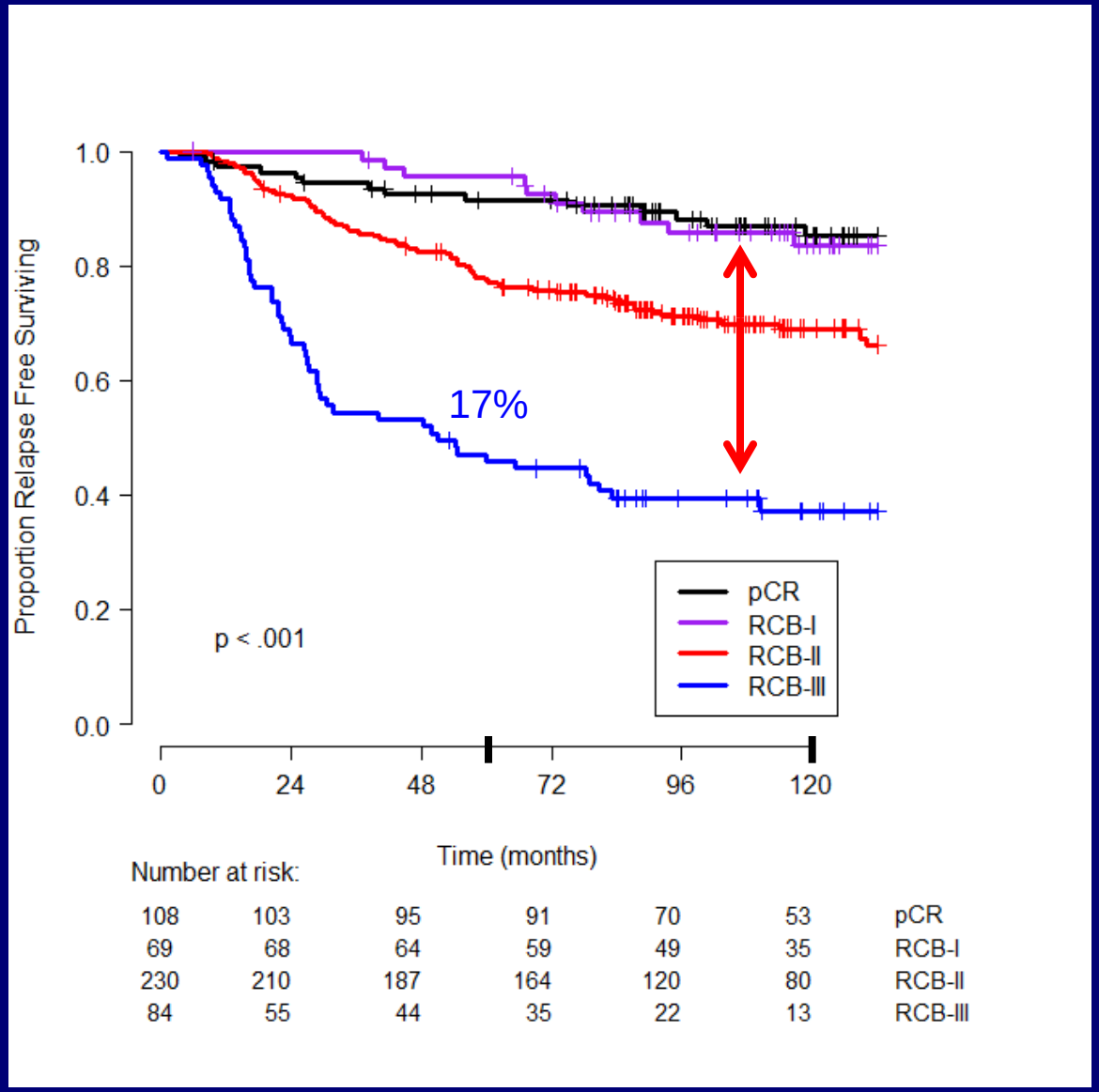
Mittendorf et al JCO 2011;29:1956-62

Prognosis (RFS) of RCB Categories MDACC T/FAC Cohorts



Class	N	%
pCR	108	22
RCB-I	69	14
RCB-II	230	47
RCB-III	84	17

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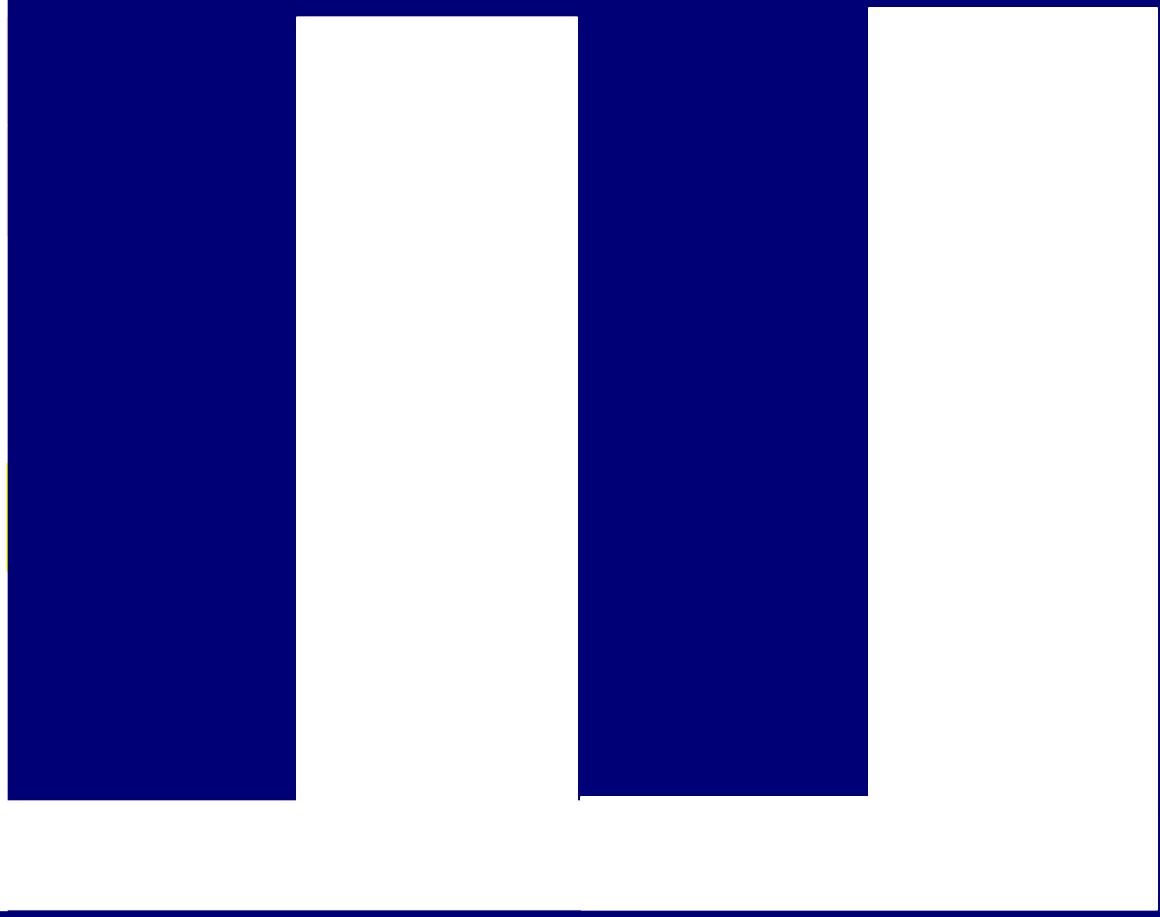
Addition Of RCB To Multivariate Prognostic Models (RFS)

HER2-Positive

RFS	Model	
	HR (95% CI)	P value
c-Stage (III vs I-II)	1.74 (0.86,3.54)	NS
Grade (3 vs 1-2)	1.96 (0.84,4.59)	NS
Multifocal (Yes vs No)	**2.61 (1.33,5.10)**	**<0.01**
pCR (Yes vs No)	**0.21 (0.07,0.59)**	**<0.01**



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Summary

- Record pretreatment cStage from clinical records
- Record pretreatment phenotype and grade
- pCR
  - pCR in breast and nodes
  - Report presence and extent of in situ residual disease
- Require standardized procedures to evaluate the gross specimen, record a map of the tissue sections related to the gross & imaging findings, and relate the histopathologic findings to that map
  - Multidisciplinary teamwork from surgeons, radiologists, and pathologists
- Then it becomes very easy to interpret and report
  - ypT Stage defined by largest continuous extent of invasive cancer
  - RCB from the dimensions and cellularity of primary tumor bed
  - Multifocality