Can We Eliminate Surgery in Exceptionally Excellent Responders?

Mark Basik, MD
Breast Surgical Oncologist
Segal Cancer Center
Associate Professor of Oncology & Surgery
McGill University
Montreal, Canada

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NOT YET

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Financial Disclosure

- None relevant to this talk

Background

- Use of neoadjuvant chemotherapy (NAC) has increased, especially recently since CREATE-X and KATHERINE results

- Pts with HER2+ or triple negative (TN) disease have high pCR rates (> 50%) to NAC +/- HER2 targeted therapies compared with ER+ (<15%) (Buzdar et al., *JCO*, 2005; Gianni et al., *Lancet*, 2010; Liedtke et al., *JCO*, 2008)

- Lower rates of LR in pCR patients (7% at 10 years) (Mamounas, *JCO*, 2012)

- pCR predicts excellent survival

BREAST + AXILLA

- Breast surgery:
  - Lumpectomy
  - Mastectomy
- Axillary surgery
  - Sentinel lymph node biopsy
  - Axillary Dissection

SURGERY OF THE BREAST

Eliminating breast surgery: Why?

- Morbidity = breast deformity (5-30%: raison d'être of oncoplastic surgery), acute and chronic pain, hematoma, fat necrosis, seroma, anesthesia risks
- Cost (Outpatient surgery = $ 12K/pt -Blumen et al, 2016 Am Health Drug Benefits), use of limited hospital resources
- Patients ask the question: why do I need surgery if my tumor has disappeared?

Historical series comparing surgery vs. radiation alone following neoadjuvant chemotherapy

Study	Study Period	n	cCR	Locoregional Treatment		5-Year Overall Survival		5-Year LRR	
				Surgery	RT alone	Surgery (%)	RT alone (%)	Surgery (%)	RT alone (%)
De Lena et al. [11]	1975-1980 prospective	132 T3b-4 N0-2	100% RT group; 60% surgery group	65	67	49.1[a]	51.7[a]	29.6	31.1
Perloff et al. [9]	1978-1983 prospective	87	18%	43	44	63[b]	50[b]	19	27
Scholl et al. [8]	1986-1990	200	?	36 Mtx ± RT, 62 BCS + RT	102	-	-	24	
Touboul et al. [6]	1982-1990 prospective	97	33	37 rD (>3 cm), Mtx 27 rD (<3 cm), BCS	33	83.3	75.7	16 after BCS, 5.4 after Mtx	16
Ellis et al. [12]	1985-1994	185	39	120; 29 Mtx, 91 BCS	39	76	84	7	21
Mauriac et al. [7]	1985-1989	134 T2-3		89; 40 BCS = RT, 49 Mtx	44	-	-	22.5 BCS + R, 22.4 after Mtx	34
Ring et al. [13]	1986-1999	453	136	67	69	74	76	10	21
Daveau et al. [10]	1985-1999	1477 T2-3	165	65	100	82	91	12	23
Swain et al.	1977-1986		77		28				21

[a] Four-year overall survival

[b] Overall survival at 39 months

BCS breast conserving surgery, cCR clinical complete remission, LRR locoregional recurrence, Mtx mastectomy, rD residual disease, RT radiotherapy

van la Parra R, et al. *Breast Cancer Res*, 2016

Ring et al (2003)

- N=136 retrospective series using cCR
- No surgery arm 21% 5 yr LRR
- Ultrasound to determine cRR
- 8% 5 yr LRR in pts with cCR and cRR

Randomized Trial in Women with complete response after neoadjuvant systemic therapy

BCS + RT **RT alone**

- Can we define a group who can safely be treated with primary chemo-radiotherapy by developing a tool highly predictive of pCR?
- Or at least pCR with a 90% certainty!

SELECTING PATIENTS TO AVOID SURGERY

- HOW CAN WE RELIABLY IDENTIFY pCR BEFORE SURGERY?
  - Imaging
  - Biopsy
  - Others? Biomarkers?

FNR and NPV for predicting breast pCR in mammography, MRI, and ultrasound

Study	Mammography		Ultrasound		Magnetic resonance imaging		PET/CT	
	NPV (%)	FNR (%)	NPV (%)	FNR (%)	NPV (%)	FNR (%)	NPV (%)	FNR (%)
Breast								
Schott et al. [19]	91	9	91	9	94	6	–	–
Peintinger et al. [18]	NPV 93, FNR 7				–	–	–	–
Chen et al. [38]	–	–	–	–	74	26	–	–
Bhattacharyya et al. [39]	–	–	–	–	96	–	–	–
Keune et al. [17]	86	–	85	–	–	–	–	–
Croshaw et al. [20]	30	70	33	67	44	56	–	–
De Los Santos et al. [16]	–	–	–	–	47[a]	–	–	–
Schaefgen et al. [21]	52	13	51	24	60	4	–	–

van la Parra R, et al. *Breast Cancer Res*, 2016.

Performance of Post-treatment MRI in the Breast

Subtype	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
Total Group	470/567 (83)	85/179 (47)	85/182 (47)	470/564 (83)	555/746 (74)
HR+/ HER2 -	243/283 (86)	20/44 (45)	20/160 (33)	243/267 (91)	263/327 (80)
HR-/ HER2+	52/63 (83)	18/38 (47)	18/29 (62)	52/72 (72)	70/101 (69)
HR+/ HER2+	86/111 (77)	18/37 (49)	18/43 (42)	86/105 (82)	104/148 (70)
TN	79/98 (81)	28/57 (49)	28/47 (60)	79/108 (73)	107/155 (69)
p value	0.02	NS	0.014	<0.0001	0.0103

*pCR: resolution of invasive disease *and* DCIS

TBCRC 017

De Los Santos et al., *Cancer* 2013

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CASE REPORT # 1

- 38 yr old with 5 cm ER + invasive ductal carcinoma and palpable nodes (T2N1)
- Complete clinical response to NAC (AC/wTaxol)
- Refuses surgery in Jan 2018
- Refuses radiotherapy as well
- MRI August 2018 = no residual disease
- MRI January 2019 = 5.6 tumor with + nodes!

Imaging alone is insufficient to identify a group that may safely omit surgery

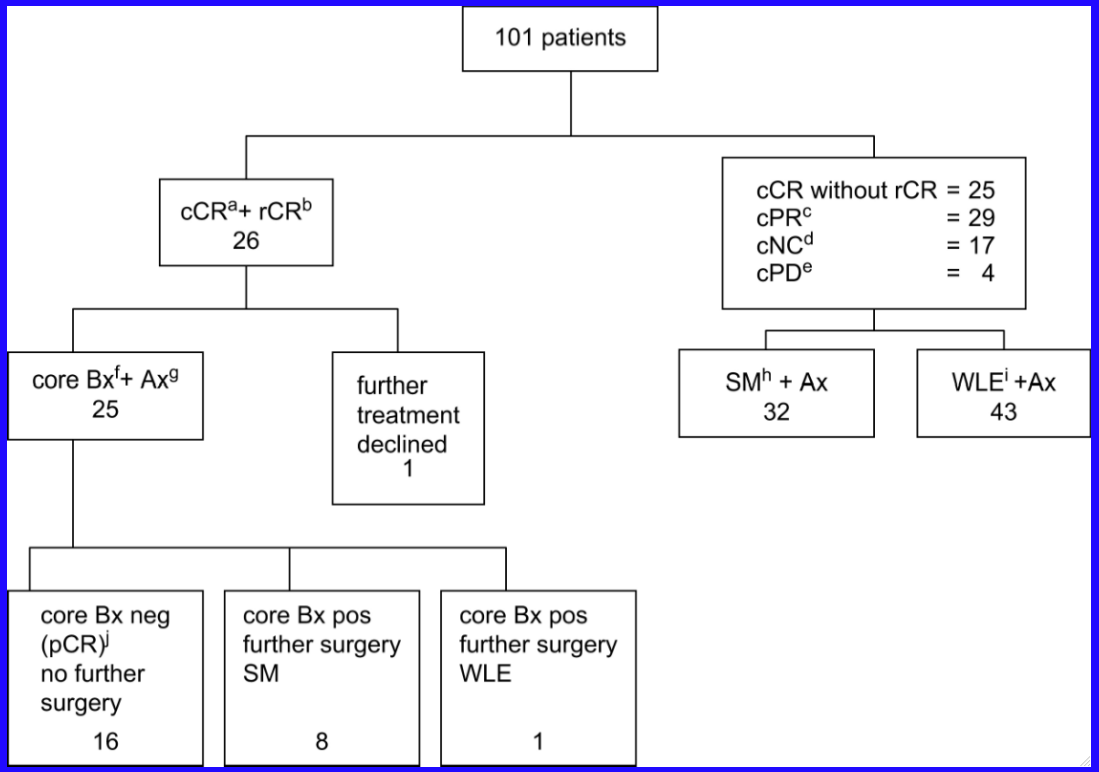
ADDING THE BIOPSY OF THE TUMOR BED POST-NCT

Post-NAC Biopsy

- Enabled by the presence of clip or marker
- Large needles / Vacuum-assisted biopsies now available

Clouth et al (EJSO, 2007)

- Non-randomized, pre-treatment size 5.2 cm, AC followed by q3wkT ; 3 pts received Herceptin
- Multiple core biopsies (6+6) + axillary clearance
- Negative biopsy no surgery in 16 pts: LR in 2 of 16 (13%) at 33 months follow up vs 9.5% in the non-pCR group



Completed Clinical Feasibility Trials Utilizing Percutaneous Biopsy after Neoadjuvant Therapy to Select Patients for Potential Omission of Breast Cancer Surgery

Status	Group/PI	Eligibility Criteria/Lesion Size Criteria	Type of Biopsy	# Patients	Performance Results
Completed Trials	MDACC/ Kuerer et al.	TN; HER2+ lesions <5 cm on imaging after NST	Image guided VACB and FNA; (63% by stereotactic and 37% by ultrasound)	40	Accuracy=98%; FNR=5%; NPV=95%
	German Breast Group/Heil et al.	St I-III IDC; clinical imaging after neoadjuvant chemotherapy	Core cut (CC) and vacuum-assisted biopsy (VACB)	164 (111 with CC and 46 with VACB)	Entire cohort (n=164): NPV 71.3%; FNR 49.3%; MMG guided VACB (n=16): NPV 100%; FNR 0%
	University of Heidelberg/Heil et al.	St I-III IDC; clinical partial or complete response to NST	Ultrasound-guided VACB	50	Entire cohort (n=50): NPV 76.7%; FNR 25.9%;
	Univ of Bham/ Rea-Francis et al.	Invasive breast cancer with any receptor subtype receiving NST	Ultrasound guided core biopsy	22	Number of patients with a false-negative result (4 of 18 total patients)

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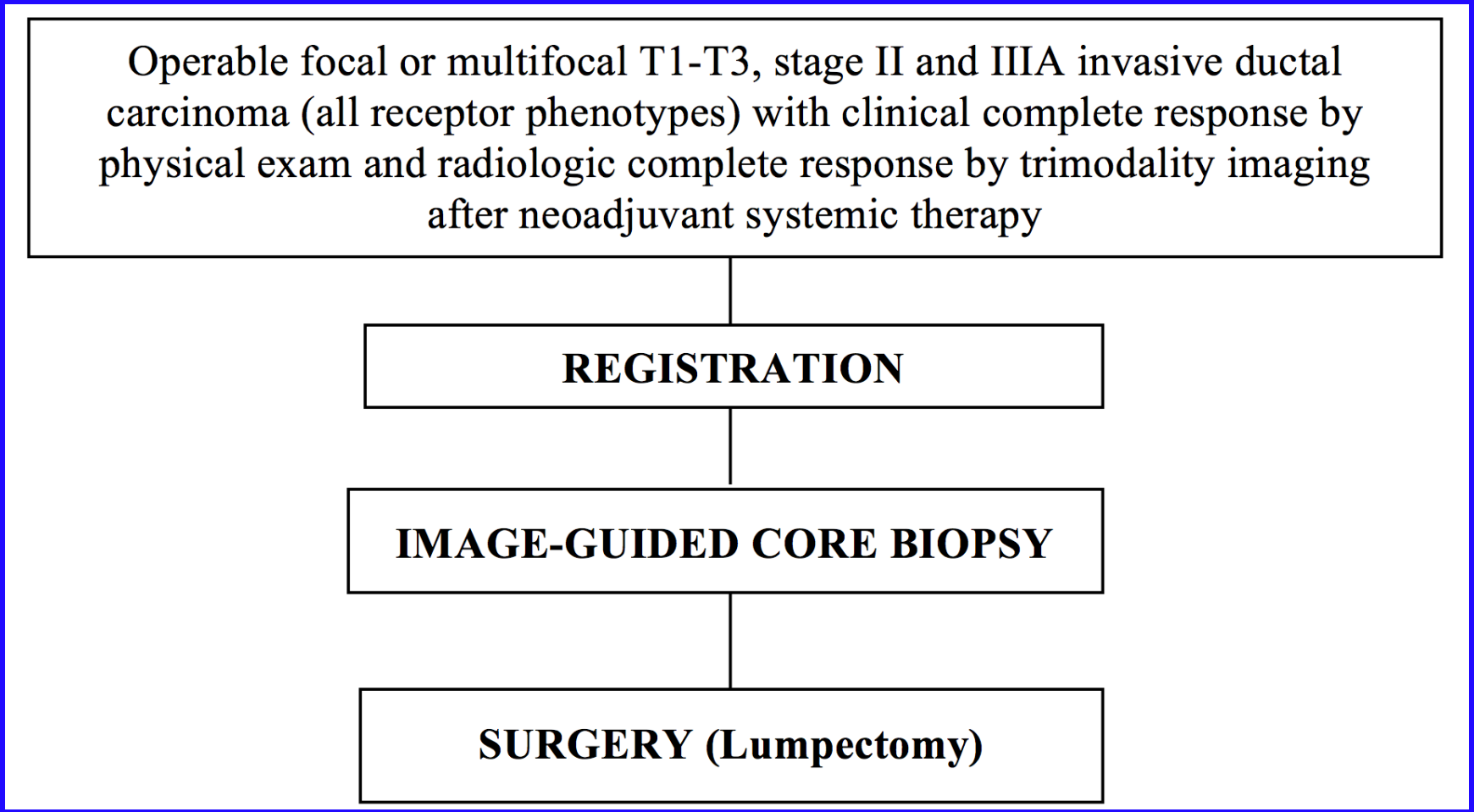
NRG BR005 Schema



Rationale

- Develop an approach combining clinical exam, the best imaging with a biopsy to
  - Predict with > 90% a pCR
  - To detect >50% of residual disease after cRR with trimodality imaging
- N=175

Patient Eligibility

- Operable focal or multifocal (T1-T3, stage II and IIIA invasive ductal carcinoma [all receptor phenotypes]) who have completed NAC with a clinical complete response (cCR by clinical examination).
- rCR or near complete response by SOC imaging (DCE-MRI, mammography and ultrasound post-chemo) – Trimodality imaging required
- Biopsy marker placed within the tumor bed with image confirmation of marker placement.
- Patients who are undergoing breast conserving therapy.
- Completion of $\geq$ 8 weeks of standard neoadjuvant chemotherapy that includes either an anthracycline and/or a taxane-based regimen.

Imaging Criteria for Eligibility are defined under *Ineligibility Criteria*

- Patients with one or more of the following imaging criteria from any of the 3 imaging modalities after completion of NCT are not eligible:
    - Mammogram with malignant appearing calcifications or mass > 1 cm; or
    - Ultrasound with a hypoechoic area > 2 cm; or
    - Breast MRI demonstrating a residual mass with rapid rise and washout type III kinetics.

CC6: asking the patients and the physicians

- Feasibility of larger trial:
- The objective of the study is to explore the attitudes and perceptions of patients and physicians regarding the development of a nonsurgical approach to breast cancer therapy, including the factors of greatest importance to them.
- Selected physician and patient interviews

Performing the biopsy

- The biopsy may be done at any time prior to the breast conserving surgery but after completion of neoadjuvant therapy.
- The biopsy clip should be targeted for biopsy while optimizing tumor bed tissue sampling, and this is best achieved with review of mammography documenting biopsy clip placement prior to neoadjuvant chemotherapy when possible.
- An 8 to 11 G vacuum-assist device should be used for the biopsy.
- Four cores should be obtained at 90 degree intervals with 2 additional cores directed in the area of the targeted clip, if possible.
- If the clip is not retrieved in the specimen, a second site biopsy clip should be placed to differentiate the two clips.
- Post-clip mammogram should be obtained with documentation of distance between the two clips if baseline clip is not retrieved.

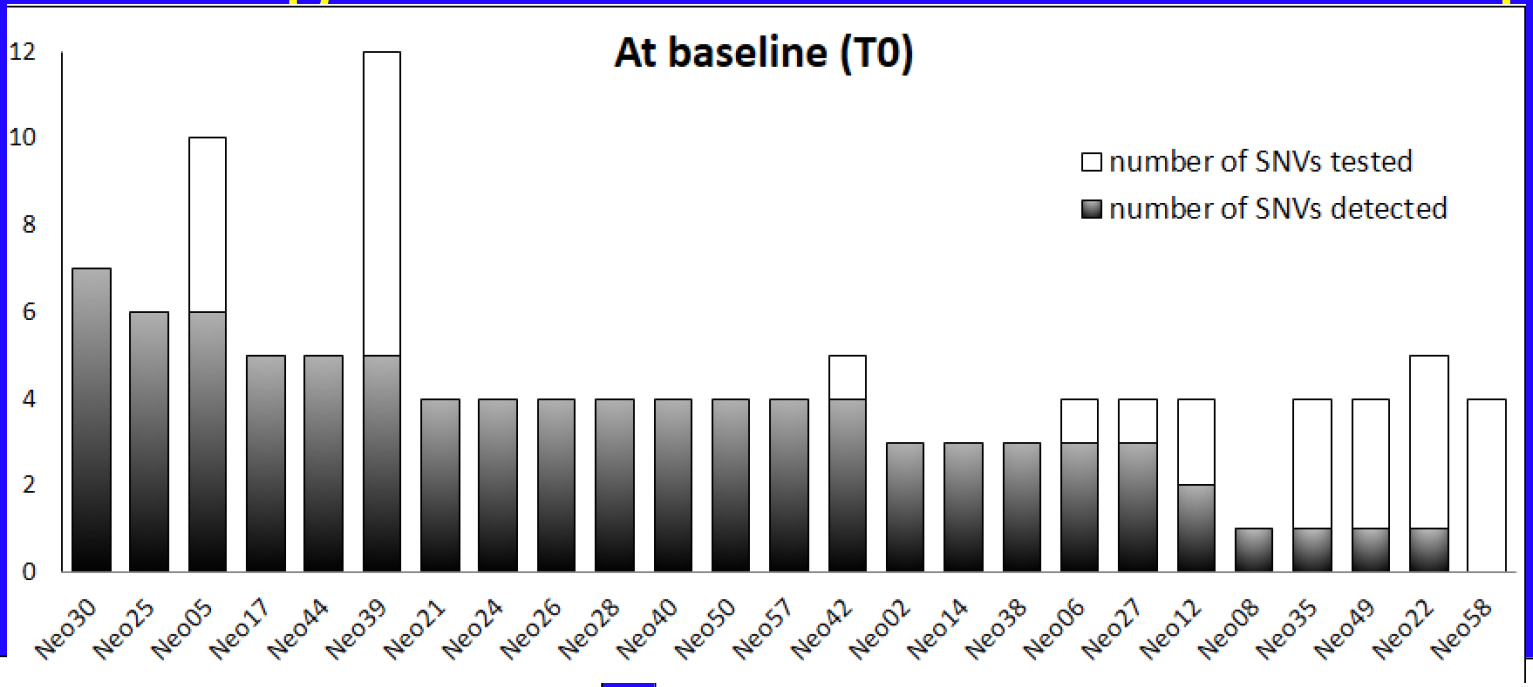
NRG BR005 to date

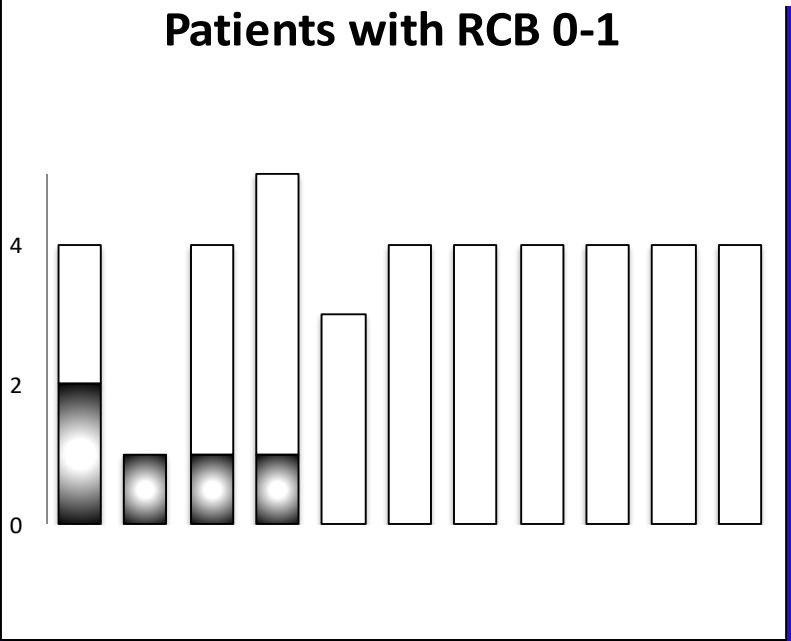
- 91 pts (March 31, 2019) accrued
- 45% ER +
- 50% HER2 +
- 19 pts non-pCR of 78 (24%)

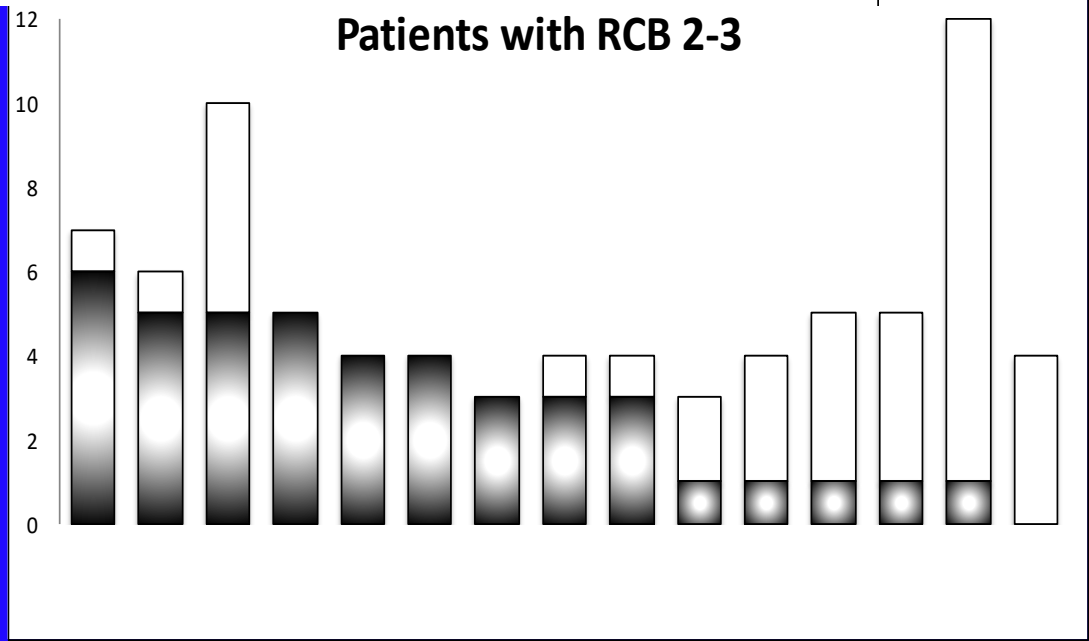
Other biomarkers?

- More sophisticated imaging
- Circulating tumor DNA

Circulating Tumor DNA Post-chemotherapy







THE AXILLA

Can we not operate the axilla?

- Depends on original axillary response
- Imaging is very poor guide to axillary response

The axilla in breast pCR cases

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Table 3. Pathologic Node Status by Response Stratified by Clinical Tumor and Nodal Category

Response					
Breast pCR			Residual Breast Disease		
	Pathologic Node Status, No. (%)[a]			Pathologic Node Status, No. (%)[a]	
Biologic Subtype	ypN0	ypN Positivity	Biologic Subtype	ypN0	ypN Positivity
cN0 Status					
HR-positive/*ERBB2*-positive			HR-positive/*ERBB2*-positive		
cT1 N0	NR (98.3)	NR (1.7)	cT1 N0	689 (85.1)	121 (14.9)
cT2 N0	NR (97.8)	NR (2.2)	cT2 N0	1647 (80.0)	413 (20.0)
cT1/cT2 N0 combined	1696 (97.9	36 (2.1)	cT1/cT2 N0 combined	2336 (81.4)	534 (18.6)
HR-negative/*ERBB2*-positive			HR-negative/*ERBB2*-positive		
cT1 N0	NR (99.7)	NR (0.3)	cT1N0	197 (88.7)	25 (11.3)
cT2 N0	NR (98.8)	NR (1.2)	cT2 N0	575 (88.7)	73 (11.3)
cT1/cT2 N0 combined	1317 (99.0	13 (1.0)	cT1/cT2 N0 combined	772 (88.7)	98 (11.3)
TNBC			TNBC		
cT1 N0	581 (98.1	11 (1.9)	cT1 N0	788 (86.2)	126 (13.8)
cT2 N0	1698 (98.5	25 (1.4)	cT2 N0	2627 (87.8)	366 (12.2)
cT1/cT2 N0 combined	2279 (98.4	36 (1.6)	cT1/cT2 N0 combined	3415 (87.4)	492 (12.6)
HR-positive/*ERBB2*-negative			HR-positive/*ERBB2*-negative		
cT1 N0	NR (94.9)	NR (5.1)	cT1 N0	572 (66.5)	288 (33.5)
cT2 N0	NR (96.3)	NR (3.7)	cT2 N0	2387 (67.0)	1176 (33.0)
cT1/cT2 N0 combined	620 (96.0	26 (4.0)	cT1/cT2 N0 combined	2959 (66.9)	1464 (33.1)
cN1 Status					
HR-positive/*ERBB2*-positive			HR-positive/*ERBB2*-positive		
cT1 N1	209 (84.3)	39 (15.7)	cT1 N1	118 (31.9)	252 (68.1)
cT2 N1	622 (87.5)	89 (12.5)	cT2 N1	463 (35.6)	839 (64.4)
cT1/cT2 N1 combined	831 (86.7)	128 (13.3)	cT1/cT2 N1 combined	581 (34.7)	1091 (65.3)
HR-negative/*ERBB2*-positive			HR-negative/*ERBB2*-positive		
cT1 N1	182 (87.9)	25 (12.1)	cT1 N1	56 (42.1)	77 (57.9)
cT2 N1	565 (89.0)	70 (11.0)	cT2 N1	252 (45.2)	306 (54.8)
cT1/cT2 N1 combined	747 (88.7)	95 (11.3)	cT1/cT2 N1 combined	308 (44.6)	383 (55.4)
TNBC			TNBC		
cT1 N1	264 (81.5)	60 (18.5)	cT1 N1	105 (28.1)	269 (71.9)
cT2 N1	792 (87.5)	113 (12.5)	cT2 N1	632 (37.4)	1058 (62.6)
cT1/cT2 N1 combined	1056 (85.9)	173 (14.1)	cT1/cT2 N1 combined	737 (35.7)	1327 (64.3)
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cT1 N1	127 (61.4)	80 (38.6)	cT1 N1	132 (14.2)	800 (85.8)
cT2 N1	367 (72.8)	137 (27.2)	cT2 N1	653 (18.0)	2975 (82.0)
cT1/cT2 N1 combined	494 (69.5)	217 (30.5)	cT1/cT2 N1 combined	785 (17.2)	3775 (82.8)

Abbreviations: HR, hormone receptor; NR, numbers not reported; TNBC, triple negative breast cancer.

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- In patients with cN0 *HER2*+ disease or TNBC with breast pCR, the nodal positivity rate was less than 2%, which supports consideration of omission of axillary surgery in this subset of patients.
- In cN1 patients, the rates are 11-14% in TNBC and HER2+….
  - Could a post-NAC Axillary Bx help? (40-50% FNR for Axillary US)

CONCLUSIONS

- High rates of breast pCR suggest that surgery can be avoided in a significant proportion of breast cancer patients undergoing NAC
- Modern imaging is insufficient to select patients for surgery avoidance
- Trials to evaluate the addition of post-NAC tumor bed biopsy and imaging are ongoing
- Avoiding axillary surgery is more complicated but reasonable in cN0 patients with breast pCR.

THANK YOU!
고맙습니다!