



# NEOADJUVANT THERAPY AND LOCO-REGIONAL CONTROL:


## A SURGEON'S PERSPECTIVE

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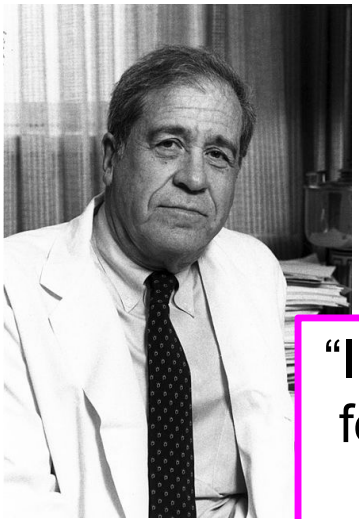
**Breast Surgical Oncology**

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# MULTIMODALITY TREATMENT IN BREAST CANCER



SYSTEMIC CHEMOTHERAPY AS AN ADJUVANT TO SURGERY IN THE TREATMENT OF BREAST CANCER  
 BERNARD FISHER, MD  
 STATUS OF ADJUVANT THERAPY: RESULTS OF THE NATIONAL SURGICAL ADJUVANT BREAST

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 APY AS AN ADJUVANT TREATMENT IN OPERABLE BREAST CANCER

“Increasing interest in determining whether there is a role for the use of preoperative (neoadjuvant) chemotherapy in patients with primary operable breast cancer.....  
 ...efficacy of lumpectomy followed by breast irradiation in such patients provided that interest.”

**Bernard Fisher, Surgeon at the University of Pittsburgh**

- In 1957, helped establish the Surgical Adjuvant Chemotherapy Breast Project, later known as the National Surgical Adjuvant Breast and Bowel Project (NSABP)

following radical mastectomy for breast cancer

**Phase 2: Expanded chemotherapy studies**

control trial stratified by age, positive lymph nodes (1-3 versus 4+), and extent of surgery (radical mastectomy versus extended radical mastectomy) (CMF)

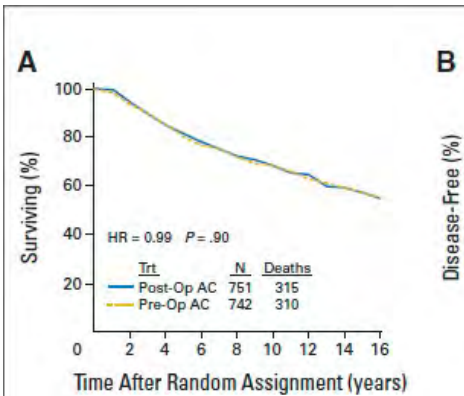
Failures	Control	CMF	p-value
Total	24%	5.3%	<10 <sup>-6</sup>
1-3 nodes	16.8%	3.6%	<10 <sup>-3</sup>
4(+) nodes	40.7%	8.8%	<10 <sup>-4</sup>

Fisher, Cancer 1969; 24(6): 1286-1289; Fisher, Cancer 1971;28(6):1654–1658; Bonadonna, et al., N Engl J Med 1976; 294: 405-410; Fisher and Mamounas, JCO 1995; 13(3): 537-540.

# NEOADJUVANT CHEMOTHERAPY

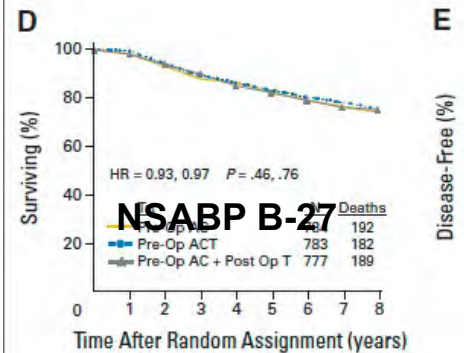
## Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27

Priya Rastogi, Stewart J. Anderson, Harry D. Bear, Charles E. Geyer, Morton S. Kahlenberg, André Robidoux, Richard G. Margolese, James L. Hoehn, Victor G. Vogel, Shaker R. Dakhil, Deimante Tamkus, Karen M. King, Eduardo R. Pajon, Mary Johanna Wright, Jean Robert, Soonmyung Paik, Eleftherios P. Mamounas, and Norman Wolmark



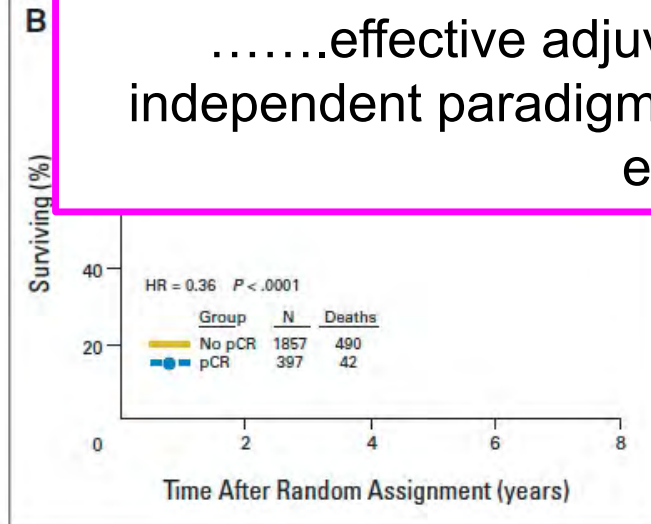
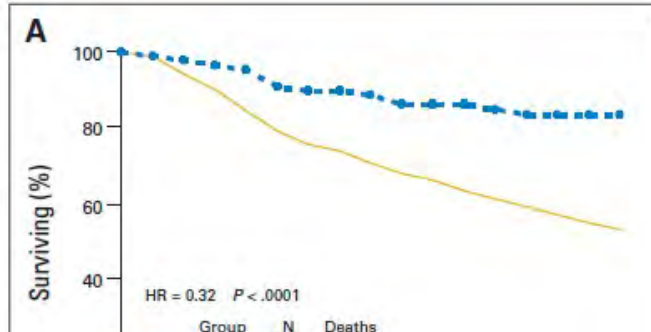
**B**

Disease-Free (%)



**E**

Disease-Free (%)



- No statistically significant differences in DFS or OS

“Two independent paradigms subsequently arose: one directed toward controlling local-regional disease and the other aimed at eliminating micrometastatic tumor .....effective adjuvant therapy.....these two independent paradigms have converged into a single exemplar.”

comes in patients < 50 years

RR 0.81, P=0.06 for OS

and a complete response superior DFS and OS  
a poorer response

- Confirmed by EORTC 10902 as well as Early Breast Cancer Trialists' Collaborative Group meta-analysis
  - Distant recurrence rate (38.2% vs 38%, RR 1.02, 0.92–1.14) and breast cancer mortality (34.4% vs 33.7%, RR 1.06, 0.95–1.18)

# CURRENT PARADIGM: NEOADJUVANT THERAPY

**Surgical**

Unresectable  
disease

- Allow for surgical therapy

Resectable but  
advanced

- Downstage the disease

Provide prognostic  
information

- pCR = better outcomes

**Non-Surgical**

Provide a guide to  
adjuvant treatments

- Katherine, CREATE-X, etc

# NEOADJUVANT THERAPY FROM A SURGEON'S PERSPECTIVE



# ALLOW FOR SURGICAL THERAPY

## Locally Advanced Breast Cancer

- Tumors that *may preclude* surgical upfront surgical resection
  - Skin involvement, ulceration
  - Chest wall involvement
  - Bulky axillary disease
- Much of the support of this approach extrapolated from the studies examining *resectable* locally advanced disease
  - Early study by Deo and colleagues examined T4bN0-2M0 patients (n=101)
    - Primary tumor response in 66%; axillary response 95% in the node positive group
  - NSABP B-18 and B-27 data
    - Tumor size markedly reduced in 80% of patients
      - *Possible conversion to resectable*
      - *Not always a limited resection.....*

Deo, et al., JCO 2003; 84: 192-197; Fisher, et al., JCO 1997; 15(7): 2483-2493; Rastogi, et al., JCO 2008; 26(5): 778-785

# ALLOW FOR SURGICAL THERAPY

## Inflammatory Breast Cancer

- **Early reports in the 1900s noted dismal survival with local therapy alone**
  - **Survival**
    - **12 to 32 months for mastectomy**
    - **9 to 29 months for radiation**
    - **7 to 42 months for combined treatments**
- **Combined modality introduced in the 1970s**
  - **Survival with the addition of chemotherapy markedly improved**
    - **>24 months with 5-year survival rates into the 70% range**
- **Chemotherapy, surgery, radiation now the standard approach**

DeLena et al., Cancer Chemother Pharmacol 1978; 1: 53-59; Jaiyesimi, et al., JCO, 1992; 10: 1014-1024

# DOWNSTAGE THE BREAST

## Istituto Nazionale Tumori, Milan

- Tumors >3 cm
  - CMF/FAC/FEC – quadrantectomy – adjuvant chemo / radiation 4-6 weeks later
- "Full-dose primary chemotherapy.....allowing for breast-conserving surgery"

## Royal Marsden Hospital

- Randomized to adjuvant versus neoadjuvant
- Noted that even small tumors can be decreased in volume to allow for breast conservation

## NSABP B-18

- Noted 80% of patients with a reduction in tumor size after neoadjuvant therapy
- 36% had a pCR (remember this is 4 cycles of AC alone)
- Increased rate of breast conservation candidates, most pronounced in the T3 category

**Table 3. Clinical Downstaging and Surgical Requirements According to Clinical Stage and Tumor Size**

Primary regimen	Tumor Characteristic	No. of Adjuvant Patients (n = 99)	No. of Neoadjuvant Patients	
			Prechemotherapy (n = 101)	Postchemotherapy (n = 101)
CMF × 3 CMF × 4 FAC × 3 FAC × 4 FEC × 3	<b>Clinical size (cm)</b>			
	0.1-1.0	2	2	62
	1.1-2.0	8	7	20
	2.1-3.0	42	43	11
	3.1-4.0	32	25	3
	4.1-5.0	7	21	4
	> 5.0	8	3	1
	<b>Tumor stage</b>			
	T0-T1	10	9	82*
	T2	81	89	18
	T3	8	3	1
	<b>Node stage</b>			
	N0	85	79	98†
N1a	8	14	0	
N1b	6	8	3	
<b>P</b>				
Response (complete or partial)		.15	.33	.04
Complete response		.18	< .001	.16

Bonadonna, et al., JNCI 1990; 82(19): 1539-1545; Powles, et al., JCO 1995; 13: 547-552; Fisher, et al., JCO 1997; 15(7): 2483-2493



# DOWNSTAGE THE BREAST

Therapy done	Clinical response				Total
	Complete*	Partial†	Stable or progressive disease‡	Unknown	
<b>Planned mastectomy</b>					
Breast-conserving	75 (60%)	121 (41%)	30 (12%)	26 (36%)	252 (33%)
Mastectomy	49 (40%)	175 (59%)	231 (88%)	47 (64%)	502 (67%)
Unknown	0	1 (NA)	2 (NA)	11 (NA)	14 (NA)
Total response§	124/684 (18%)	297/684 (43%)	263/684 (38%)	84 (NA)	768 (100%)
<b>Unknown planned therapy</b>					
Breast-conserving	162 (83%)	164 (76%)	97 (56%)	28 (49%)	451 (70%)
Mastectomy	33 (17%)	53 (24%)	76 (44%)	29 (51%)	191 (30%)
Unknown	2 (NA)	3 (NA)	8 (NA)	38 (NA)	51 (NA)
Total response§	197/598 (33%)	220/598 (37%)	181/598 (30%)	95 (NA)	693 (100%)

## EBCTCG Meta-analysis

- Marked increase in the rate of breast conservation
- Did note an increased local recurrence rate – but this did not equate to changes in survival
  - And interestingly, some of the breast conservation patients included radiation alone.....

## More recent meta-analysis

- 7 RCTs with 1452 patients
- BCT rates increased from 43.3% to 60.4% (p<0.0001)
  - Of note: only 31% converted to BCT eligible opted for lumpectomy

	Eligibility for BCS (%)		oCR (%)	BCS performed (%)	Shift to BCS (%)
	Before NAT	After NAT			
CALGB 40601	41.4	63.7	63.7	49.0	12.9
CALGB 40603	54.2	68.1	68.1	47.3	-10.9
CHER-LOB	43.8	n.a.	89.9	64.7	39.7
IMPACT	43.6	61.8	34.6	41.5	32.3
NeoALTO	29.8	46.9	75.4	43.6	28.2
TEAM IIA	61.8	75	64.6	65.7	23.1
TRYPHAENA	46.2	n.a.	92	58.7	21.9
Pooled values	43.3 (41.3, 45.9)	60.4 (57.8, 62.9)	74.8 (72.5, 77.0)	51.8 (49.5, 54.2)	16.6 (14.4, 19.0)

Asselain, et al., Lancet Oncol 2018; 19(1): 27-39 ; Krakatsanis, et al., Br J Surg 2018; 105(5): 469-481

# DOWNSTAGE THE BREAST

## Points to Remember:

- 1) The resection volume relates to current tumor size
- 2) All suspicious microcalcifications need to be removed

## ”Simple” Lumpectomy

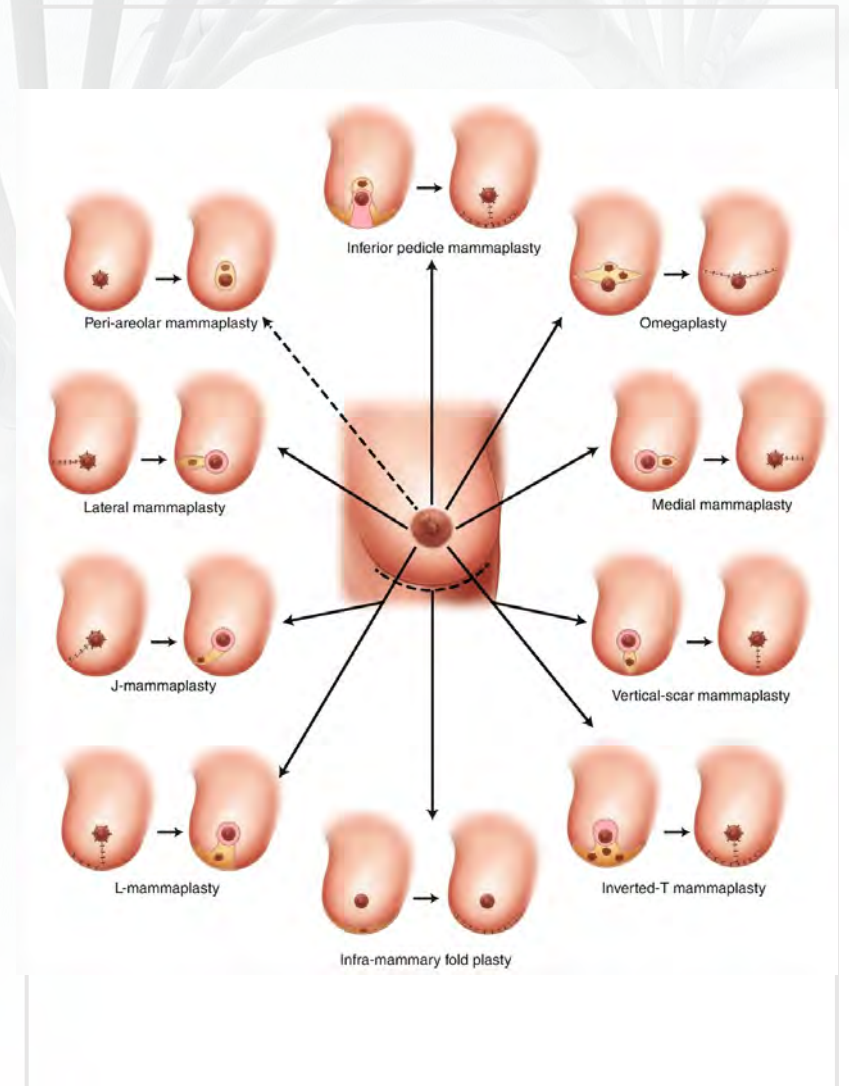
- 1) Partial mastectomy with minimal dead space coverage or tissue re-arrangement
- 2) Ideal for small defects in larger breasts

## Lumpectomy with Level 1 or 2 Oncoplastic Reconstruction

- 1) Partial mastectomy with tissue re-arrangement often performed by the breast surgeon
- 2) Local tissue rearrangement to maintain volume and minimize dead space

## Lumpectomy with Advanced Level Oncoplastic Reconstruction

- 1) Partial mastectomy with large volume loss in a medium to large size breast
- 2) Plastic surgery support for large tissue rearrangements often combined with a contralateral reduction



Douvetzemis, S.E., Kovacs, T. (2020). Concept, Principles and Indication of Oncoplastic Breast Surgery: Fashion or Necessity. In: Kimberg, V., Kovacs, T., Rubio, I. (eds) Oncoplastic Breast Surgery Techniques for the General Surgeon. Springer, Cham.

# DOWNSTAGE THE AXILLA

- Importance of the nodal status
  - Guide adjuvant systemic therapy
  - Guide radiation therapy
- Importance of neoadjuvant therapy
  - Downstage the “microscopically positive axilla”
  - Downstage the clinical positive axilla
    - Decrease axillary morbidity
      - Shoulder dysfunction, sensory nerve issues, and.....

	SLN	SLN/AxDx	AxDx	AxDx/XRT		AxDx versus XRT (AMAROS)
Risk of Lymphedema (1,811 prospective patients)	7.7%	10.8%	29%	38.7%		23% versus 11%

Ashikaga et al., J Surg Oncol 2010; 102(2):111-118; Naoum et al., Int J Radiat Oncol 2019; 105: S42; Donker et al., Lancet Oncol 2014; 15: 1303-1310

# DOWNSTAGE THE AXILLA

## NSABP B-2

- 428 p
- SLN p
- R
- Succ
- 84
- 87
- SLN p
- A

Conversion of cN1 (non-matted nodes) to cN0				
Study	N	Identification Rate	False Negative Rate	
SENTINA	642	87.8%	Overall: 2+ SLN removed	14.2% 9.6%
SN FNAC	145	87.6%	Overall: 2+ SLN removed	8.4% 4.9%
Z1071	649	92.7%	Overall: 2+ SLN removed (+) clipped node	12.6% 8.7% 6.8%

Manoumas et al., J Clin Oncol 2005; 23(12): 2694-2702; Kuehn et al., Lancet Oncol 2013; 14(7): 609-618; Boughey et al., JAMA 2013; 310(14): 1455-1461; Boileau et al., J Clin Oncol 2015; 33(3): 258-264

# DOWNSTAGE THE AXILLA

## Targeted Axillary Dissection

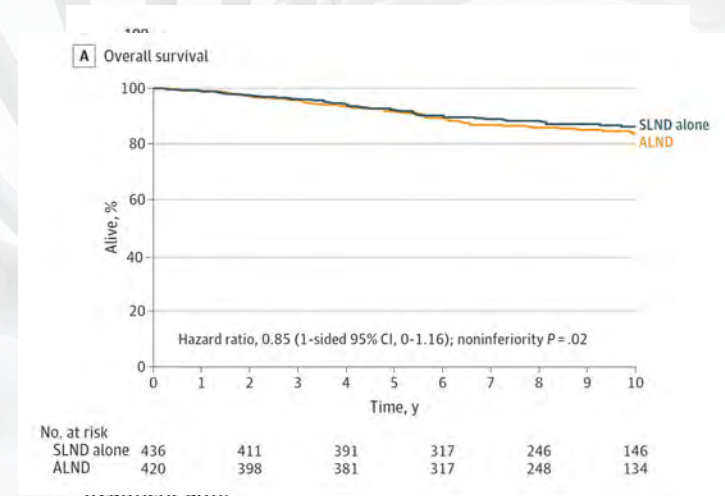
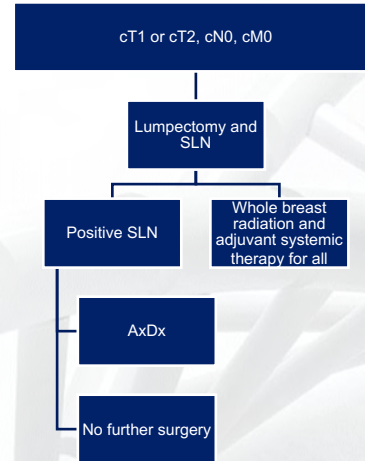
- Placement of a marker into the clipped node (the index nodal disease)
  - Radioactive seed, ferrous compounds, SAVI Scout reflector, wires
- Allows for a false negative rate of <5%
- Provides a more accurate and complete picture of the nodal response to therapy
- Also helps the multimodality team in the planning of adjuvant treatments
  - Radiation oncology can assess need for nodal irradiation
  - Medical oncology can assess need for adjuvant systemic therapies



This is all well and good – but who cares – there is no proof that retrieving the clipped node matters in terms of loco-regional recurrence.....

# DOWNSTAGE THE AXILLA

## What about ACOSOG Z-0011?



### Interesting dilemma:

- Patient with T1/2 tumors and clinically negative axilla are eligible for limited axillary surgery for <2 positive lymph nodes in the systemic therapy naïve patient
  - Post-NAT - even isolated tumor cells warrant axillary dissection.....
- Interestingly, the rate of suspected additional nodal disease in both scenarios is ~25%
- Best approach for cT1-2N0 TNBC or HER 2+ patients that are eligible for upfront breast conservation.....
  - See the debate @ 9:25 between Drs. Gogineni and Bhave “Stage I TNBC” Neoadjuvant Therapy?
  - For now, the right answer is a multidisciplinary discussion.....

Giulliano et al., Ann Surg 2016; 264(3): 413-420, and JAMA 2017; 318(10): 918-926

# TIMING OF SURGICAL THERAPY

- **Emory experience:** Trend towards improved overall and disease-free survival if surgery performed 4-6 weeks following completion of chemotherapy
- **MD Anderson experience:** “In multivariable analysis, compared with an interval of  $\leq 4$  weeks, patients who underwent surgery at 4-6 or  $>6$  weeks had equivalent OS, LRFS, and RFS; a sensitivity analysis suggested worse OS in patients who underwent surgery at  $>8$  weeks.”
- **Meta-analysis of all available studies:** Optimal timing is 4-8 weeks with increased overall and disease-free survival

Covariate	Level	N	Disease-free survival (mo)		
			Hazard ratio (95% CI)	HR P-value	Type 3 P-value
Time to Surgery (wk)	$>8$	44	1.23 (0.64-2.37)	.528	.407
	$>6, \leq 8$	55	1.42 (0.78-2.59)	.252	
	$>4, \leq 6$	152	0.91 (0.55-1.51)	.725	
	$\leq 4$	98	—	—	

Covariate	Level	N	Overall Survival (mo)		
			Hazard Ratio (95% CI)	HR P-value	Type 3 P-value
Time to Surgery (wk)	$>8$	44	1.11 (0.52-2.35)	.784	.615
	$>6, \leq 8$	55	1.11 (0.59-2.10)	.739	
	$>4, \leq 6$	152	0.79 (0.47-1.33)	.382	
	$\leq 4$	98	—	—	

TABLE 4 Multivariable Cox proportional hazards model

Weeks from neoadjuvant chemotherapy to surgery	Overall survival			Relapse-free survival			Locoregional relapse-free survival		
	Hazard ratio	95 % CI	p	Hazard ratio	95 % CI	p	Hazard ratio	95 % CI	p
[4, 6] weeks versus [0, 4] weeks	0.89	(0.68, 1.16)	0.38	0.97	(0.74, 1.26)	0.80	0.80	(0.47, 1.36)	0.42
$>6$ weeks versus [0, 4] weeks	1.14	(0.84, 1.56)	0.40	1.16	(0.85, 1.58)	0.35	1.26	(0.70, 2.27)	0.45
$>8$ weeks versus [0, 8] weeks	1.62	(1.07, 2.36)	0.02	1.42	(0.92, 2.10)	0.09	1.75	(0.75, 3.50)	0.16

Variables included in multivariable model: age, race, clinical stage, LVI, breast cancer subtype, pCR, type of breast surgery, and number of comorbidities including hypertension, hyperlipidemia and diabetes

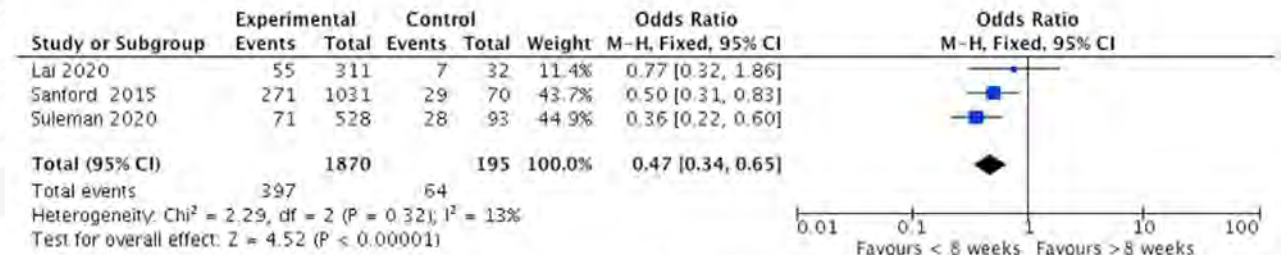


Fig. 2. Overall survival:  $< 8$  weeks versus  $> 8$  weeks.

# IMAGING AND NEOADJUVANT THERAPY

## Complete imaging prior to treatment is crucial:

- Breast imaging (mammogram, ultrasound, MRI if indicated)
- Axillary imaging (ultrasound)
- Clip placement  
*If clip not placed at initial biopsy, place prior to treatment*

## Complete imaging prior to surgical intervention:

- A guide for surgeons
- Timing not crucial – close to end is ideal
- Generally, utilize the same imaging modalities

## Important considerations:

- Resection volume is based on current tumor size
- All suspicious calcifications must be excised
- All previous biopsy clips must be excised



# CAN WE DELAY / AVOID SURGERY?

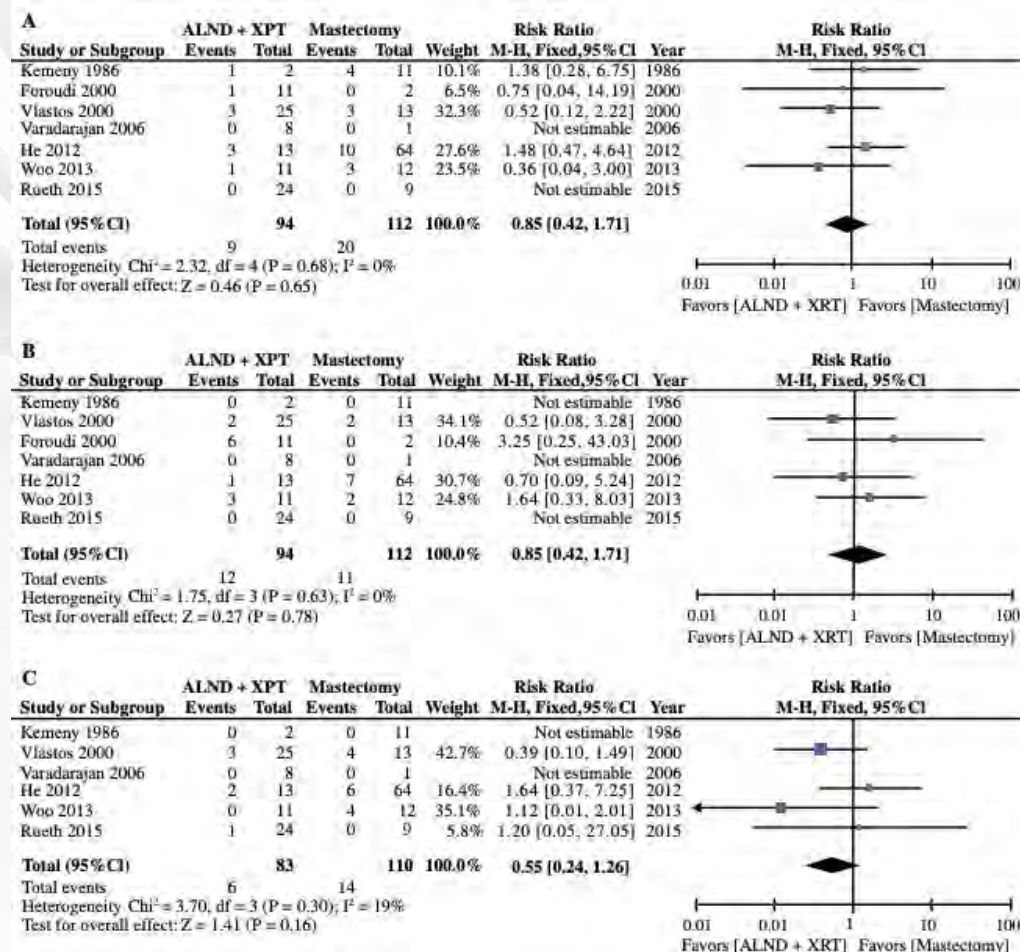
## Delay.....yes?

- COVID era learning points
  - Endocrine therapy adopted in patients to delay surgery.....but outcome data maturing.....

## Avoid surgery (the ultimate in breast conservation)

- Bonadonna and colleagues treated unresectable disease (T3-T4) with chemotherapy and radiation
  - "surgery may be resumed to achieve a better local-regional control"
- NSABP B-18/B-27 and EORTC 10902, pointed to good results with tri-modality approaches and pCR
- Occult primary disease now known to have equivalent outcomes when comparing mastectomy with whole breast radiation

## So why not avoid surgery for patients with pCR?



# CAN WE DELAY / AVOID SURGERY?

First, you need to be able to accurately determine pCR without a surgical resection

- 3 studies released interim results at SABCS 2019
  - Heil, et al.: FNR=17.8% (95% CI 12.8-23.7%) thus core biopsy not sufficient
  - Tasoulis, et al.: FNR=18.7% (95% CI 9.8-26.8%) lowered to FNR 3.2% (95% CI 0-8.8%) if residual abnormality <2cm
    - TNBC and HER2+ subgroups with FNR 4.2% (95% CI 0-10.7%)
    - Basik, et al., (NRG BR-005): NPV only 77.5%
- Additional studies .....

For now, only in clinical trials and patient selection is key

Table 2. Ongoing clinical feasibility trials utilizing percutaneous biopsy after neoadjuvant therapy to select patients for omission of breast cancer surgery (partially adapted from Kuerer et al.<sup>69</sup>)

Group/author/PI	Eligibility criteria/lesion size criteria	Type of biopsy	Number of patients	Study unique characteristics	Performance results
MD Anderson Cancer Center/Kuerer et al. <sup>69</sup>	TN- or HER2-positive initial imaging size 5 cm and final size 2 cm and/or 90% of lesion sampled after NST; N0 or biopsy-confirmed N1 with four or less abnormal nodes on initial ultrasound	Minimum of 12× 9G VAB; image guidance dependent on radiologist decision	50	No breast surgery treatment trial	Primary end point is local recurrence with continuous monitoring and early stopping rules
Netherlands Cancer Institute/MICRA Trial Vrancken-Peeters et al. <sup>69</sup>	Invasive breast cancer patients; nonmetastatic; with radiologic partial or complete response on CE-MRI after NST/no lesion size criteria	Ultrasound-guided 14 G biopsies targeted around pre-NST-placed marker (four central; four peripheral)	525 (150 with partial radiologic response on CE-MRI and 375 with complete radiologic response on CE-MRI)	All breast cancer subtypes; response monitoring with CE-MRI	Primary end point is a specificity of 92% (proportion of patients with residual disease in the surgical specimen that is also confirmed by biopsy). In addition, FNR will be calculated
University of Heidelberg/RESPONDER trial Heil et al. <sup>69</sup>	Invasive breast cancer after NST; clinical partial or complete response; target lesion visible on ultrasound or mammography/no lesion size criteria	Ultrasound- or mammographic-guided VAB	600	Confirmative analysis to identify a pCR using VAB	Primary end point <10% FNR. Standardization of histopathological evaluation of post-NST samples.
University of Birmingham/Rea/NOSTRA feasibility	ER-negative or HER2-positive invasive breast cancer receiving NST/lesion size must be >1 cm on ultrasound or node-positive	Ultrasound-directed biopsy, minimum of six	150	Microcalcifications will not be targeted; no upper limit of size criteria	FNR <10%
NRG/Basik and De Los Santos	Operable local or multifocal (T1–T3, stage II and IIIA) invasive ductal carcinoma with no size criteria (all receptor phenotypes); completed NST with a clinical complete response (by clinical examination); patients must have achieved a complete or near-complete radiologic tumor response on breast imaging with mammogram, ultrasound, and MRI; patients must be undergoing breast conserving therapy; patients must have a biopsy marker placed within the tumor bed with imaging confirmation (preferably mammogram but ultrasound or MRI is acceptable) of marker placement prior to NST	6× 8–11G VAB, stereotactic	175	Multicenter cooperative group study with trimodality imaging required	NPV = 90% and FNR = 10%

CE, contrast enhanced; FNR, false-negative rate; MRI, magnetic resonance imaging; NST, neoadjuvant systemic treatment; pCR, pathologic complete response; PI, principal investigator; VAB, vacuum-assisted biopsy.

# SUMMARY: NEOADJUVANT THERAPY FROM A SURGEON'S PERSPECTIVE

## \*\*\*\*\*TAKE HOME POINTS\*\*\*\*\*

### Unresectable Disease

- Allow for Surgical Therapy

### Resectable but Large

- Downstage the breast to broaden surgical options

### Resectable with Axillary Disease

- Downstage the axilla to reduce morbidity

### Timing of Surgery

- 4 - 8 weeks after completion of systemic therapy

### Post-treatment Imaging

- Identify all disease up front
- Imaging near end of therapy

### Can we delay / avoid surgery?

- Delay surgery yes....sometimes
- Avoid surgery....not yet.....

# CASE:

65-year-old woman presents with a 5 cm mass with associated microcalcifications in the upper outer quadrant of her right breast. Diagnostic imaging and core biopsy confirms an ER(-)PR(-)HER2(+) invasive ductal carcinoma (cT2N1M0). She receives neoadjuvant systemic therapy consisting of Docectaxel / Carboplatin / Trastuzumab / Pertuzumab (TCHP) with an outstanding clinical response. Follow-up imaging (MMG/US/MRI) reveals the biopsy clip in the breast with no residual mass, persistent microcalcifications and clinically her lymph nodes are now negative. Her surgical options include:

- 1) Lumpectomy and targeted axillary dissection
- 2) Lumpectomy alone
- 3) Radiation alone
- 4) Active surveillance (no local therapy)
- 5) Radical mastectomy



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## A SURGEON'S PERSPECTIVE

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