

PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

Surgical Therapy after Preoperative Chemotherapy

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Surgical Decisions

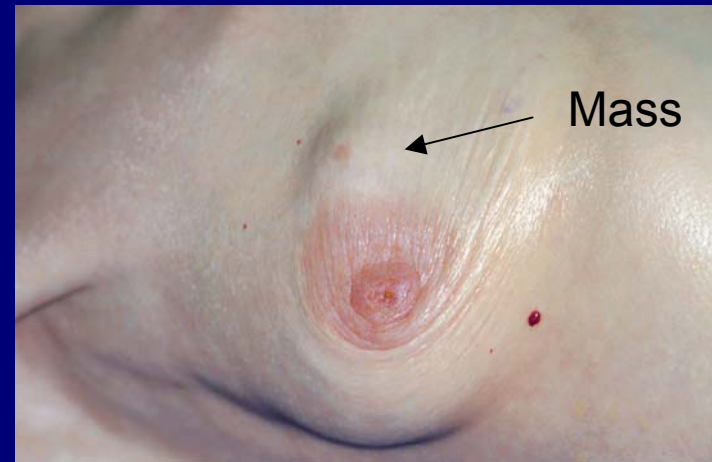
- Breast Conservation Therapy
- Mastectomy
- Sentinel Lymph Node Biopsy
- Breast Reconstruction

Goals

- Increase the rate of breast conservation therapy (BCT)
 - 80-90% of patients will undergo a response to preoperative chemotherapy
 - Large percentage can then be offered BCT
- Obtain prognostic information

Pre-Therapy Assessment

- A surgeon should evaluate the patient at least prior to chemotherapy and before surgery
 - Thorough, documented physical exam
 - Clinical tumor size
 - Location of tumor
 - Lymph node involvement
 - Skin erosion
 - Fixation to the chest wall
 - Skin inflammation



Pre-Therapy Assessment

- All patients need to undergo thorough radiographic evaluation prior to chemotherapy and before surgery
 - Mammogram
 - Supplemental ultrasound and MRI
 - All suspicious areas should be biopsied prior to the initiation of chemotherapy
 - Multiple biopsies may be necessary
 - Especially important for patients contemplating BCT

Pre-Therapy Assessment

- Location of the tumor needs to be “marked” in some manner prior to initiation of chemotherapy
 - Even in patients who want mastectomy
 - “Patients change their minds”
 - Radiologic clip(s) or coil(s)
 - Outline the extent of tumor on the breast and then photograph the patient
 - Outline extent of tumor on clear sheet of plastic with appropriate breast markings
 - Extent of tumor tattooed on skin
 - Usually 4 points tattooed
 - Calcifications will not disappear after preoperative chemotherapy
 - Can be used as target

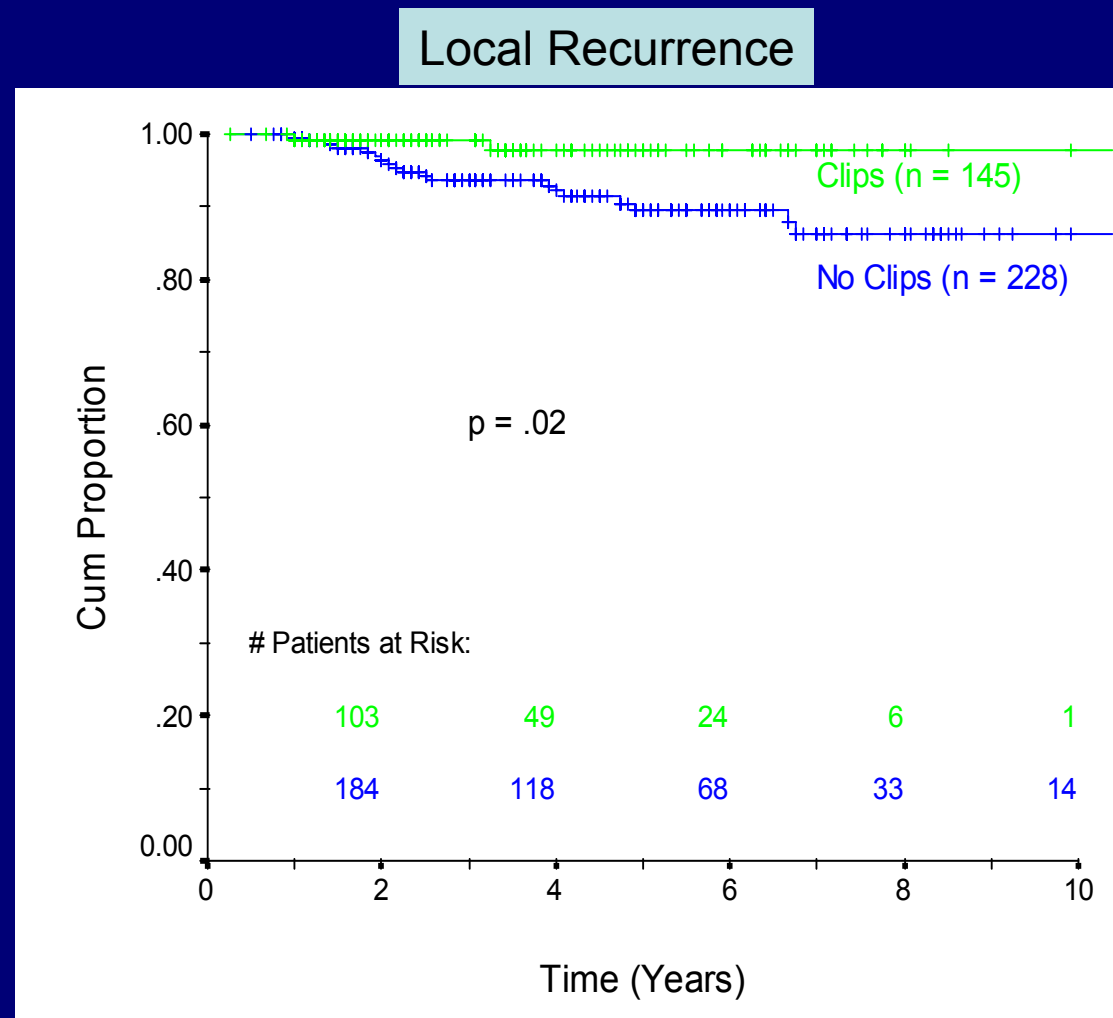
Pre-Therapy Assessment

- If tumor is not marked before chemotherapy, subsequent localization for BCT may prove difficult
 - May compromise overall local control
 - Adequate localization may be impaired in up to 30% of cases
 - If patient desires BCT and the tumor was not marked, attempts to localize the tumor based on post-treatment imaging has to be performed
 - Recent study observed that more breast volume excised
 - Quadrantectomy

Dash N, Am J Roentgenol, 1999;173:911
Chattopadhyay R, SSO, Abstract #P191

Pre-Operative Clip Placement

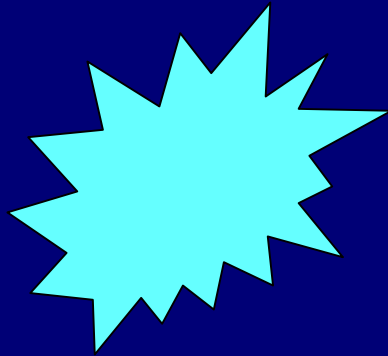
On multivariate analysis, the omission of tumor bed clips was associated with a hazard ratio of 3.69 for increased local recurrence compared to patients who did have radiopaque clips placed
($p=.083$, 95% CI 0.84-16.16).



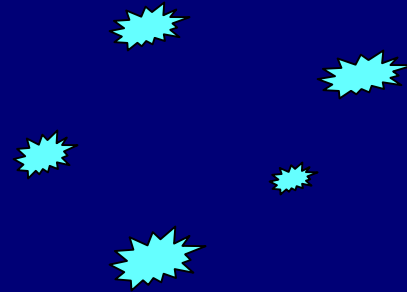
Timing of Surgery

- Surgery should be performed after pre-determined chemotherapy is completed
 - Includes patients with dramatic responses to chemotherapy
 - Patients prefer to complete chemotherapy if possible before surgery
 - Prior to surgery hematologic ramifications need to be assessed
 - All repeat imaging needs to be performed

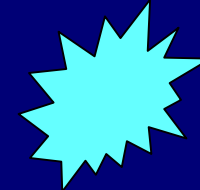
Tumor Response to Chemotherapy



“Honeycomb or Swiss Cheese” Shrinkage



Concentric Shrinkage



Pre-Chemotherapy Tumor

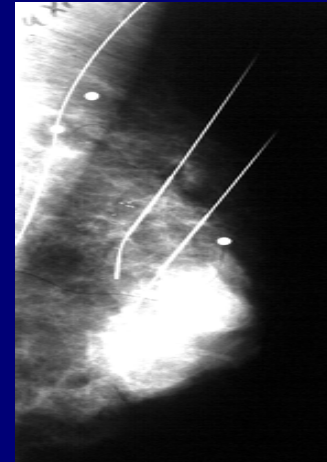
Post-Chemotherapy Tumor

BCT Selection

- Same selection criteria used for patients undergoing preoperative chemotherapy or primary surgery
 - Absence of multicentric cancer
 - Selected cases of multifocal cancer appropriate
 - Wide-spread malignant appearing calcifications
 - Ability to excise the residual tumor with negative margins and acceptable cosmetic result
 - Patient able and willing to undergo radiation therapy
- Decision for BCT is made after completion of chemotherapy

BCT

- Technique for BCT is the same as for patients who do not undergo preoperative chemotherapy
 - Key: need to excise all residual palpable and radiologic abnormalities
 - Multiple guidewires or radioactive seeds maybe needed
 - Oncoplastic techniques may facilitate BCT
 - Meticulous assessment of the margins is critical
 - Specimen margins should be inked
 - Adequate margins: controversial
 - Most agree 1-10 mm
 - » My preference is 2 mm



Outcomes of BCT after Preoperative Chemotherapy

BCT Outcomes

- GEPARDUO Trial
 - Phase III randomized trial with operable breast ca (\geq 2 cm) to preoperative dose dense doxorubicin + docetaxel vs. doxorubicin + cyclophosphamide followed by docetaxel
 - 607 Patients
 - 493 (81%) BCT attempted
 - 450 (74%) BCT successful
 - Tumor size
 - T1 5 (0.8%)
 - T2 438 (72.2%)
 - T3 157 (25.9%)

BCT Outcomes GERPARDUO Trial

Pre-Operative Predictors of BCT

Variable	No. Patients <i>N</i> (%)	<i>P</i> value	
		Univariate	Multivariate
Clinical tumor size before chemotherapy (palpation)		< .0001	< .0001
≥40 mm (n = 415)	329 (79.3)		
> 40 mm (n = 185)	118 (63.8)		
Clinical N classification before chemotherapy		.10	
N0 (n = 364)	280 (76.9)		
≥N1 (n = 243)	170 (70.0)		
Histology		< .0001	.003
Ductal (n = 444)	349 (78.6)		
Lobular (n = 105)	64 (61.0)		
Grade		< .0001	.46
1 (n = 34)	25 (73.5)		
2 (n = 297)	216 (72.7)		
3 (n = 195)	164 (84.1)		
Estrogen receptor		.029	.47
Positive (n = 382)	281 (73.6)		
Negative (n = 160)	128 (80.0)		
Type of neoadjuvant chemotherapy		.028	.047
ADOC (n = 306)	215 (70.3)		
AC-DOC (n = 301)	235 (78.1)		
Clinical response (palpation)		< .0001	< .0001
CR (n = 260)	215 (82.7)		
PR (n = 210)	153 (72.9)		
SD (n = 98)	62 (63.3)		
PD (n = 13)	5 (38.5)		
Clinical tumor size after chemotherapy (palpation)		< .0001	< .0001
≤20 (n = 443)	355 (80.1)		
> 20 (n = 146)	60 (56.8)		
Center size *		< .0001	.001
≥10 patients/center (n = 469)	365 (77.8)		
< 10 patients/center (n = 138)	86 (62.3)		

BCT Outcomes

GERPARDUO Trial

Post-Operative Factors Predicting Successful BCT

Variable	No. Patients (%)	<i>P</i> value	
		Univariate	Multivariate
Pathologic response rate		.002	.004
pCR (n = 71)	62 (87.3)		
No pCR (n = 536)	388 (72.4)		
Pathologic nodal status		<.0001	<.0001
Negative (n = 356)	288 (80.9)		
Positive (n = 250)	161 (64.4)		
Lymphovascular space invasion		.026	.047
Not present (n = 357)	272 (76.1)		
Present (n = 40)	24 (60.0)		
Multifocality		.001	<.001
Unifocal disease (n = 339)	269 (79.4)		
Multifocal/multicentric disease (n = 57)	27 (47.4)		

BCT Outcomes

GERPARDUO Trial

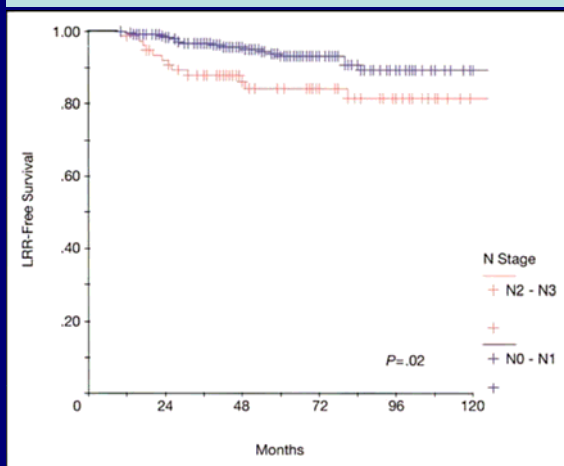
- Trial Conclusions
 - Majority of patients can undergo BCT after preoperative chemotherapy for operable breast cancer
 - Factors associated with BCT rate were
 - Initial and residual tumor size
 - Response to chemotherapy
 - Histology
 - Invasive lobular carcinoma
 - » Lower BCT rate 56%
 - » Lower clinical response rate (only 5% CR rate)
 - Lymphovascular invasion
 - Pathologic nodal status
 - Multifocality
 - Center size

Risk of Local Recurrence after BCT

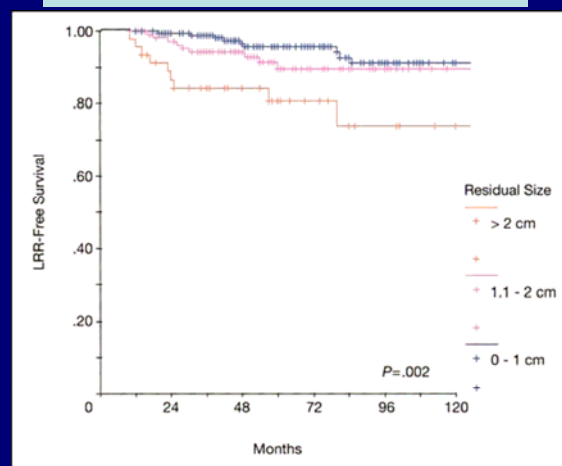
- Analysis of 340 Patients
- 1987-2000
- Single institution – MD Anderson Cancer Center
- Overall local recurrence was 9%
- Increased risk of local recurrence with:
 - Clinical N2 or N3 disease
 - Pathologic residual tumor > 2 cm
 - Multifocal residual tumor pattern
 - Lymphovascular invasion

Risk of Local Recurrence after BCT

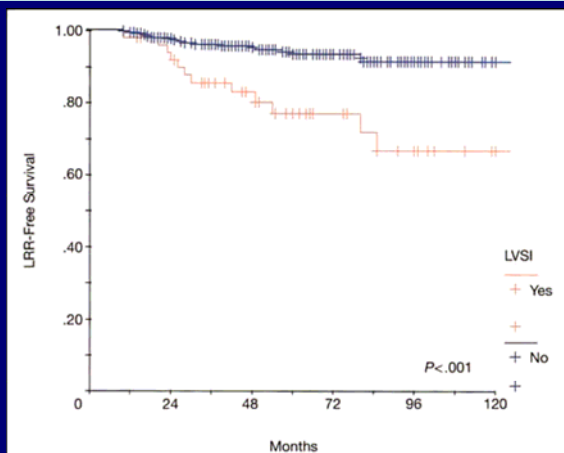
Clinical N0-N1 vs N2-N3



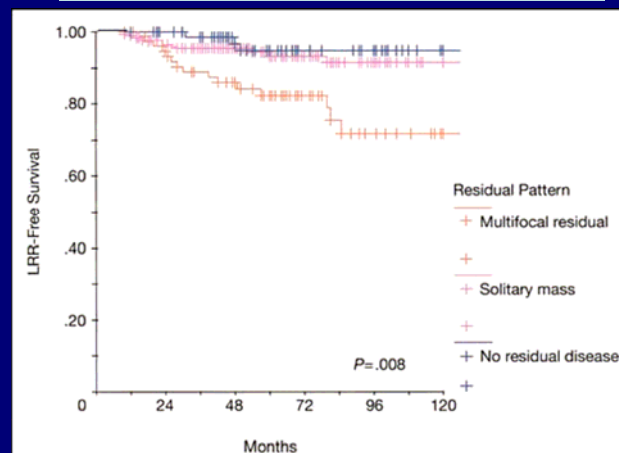
Residual Tumor Size



Lymphovascular Invasion



Residual Tumor Pattern



Risk of Local Recurrence after BCT

- This led to the development of a prognostic index score
 - 1 point for each factor present
 - Prognostic score of 0 or 1 had a very low risk of local recurrence
 - Prognostic score of 3 or 4 had a high risk of local recurrence
 - Mastectomy should be considered for these patients
- The prognostic index score still needs to be validated on other data sets

Chen Am, Cancer, 2005;103:689

Huang EH, Int J Rad Onc Biol Phys, 2006;66:352

Risk of Local Recurrence after BCT

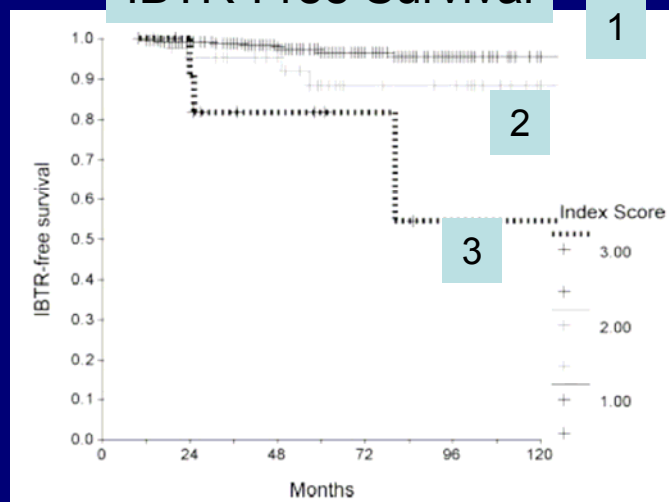
Rates of IBTR and IBTR-Free Survival According to MDAPI Score

MDAPI score	No. of patients	No. of patients with IBTR (%)	No. expected	RR	5-yr IBTR-free rate (%)
0	157	2 (1)	7.0	0.3	99
1	119	6 (5)	5.5	1.0	94
2	43	4 (9)	2.0	2.0	88
3	12	3 (25)	0.7	7.0	82
4	0	0 (0)	0	NA	NA

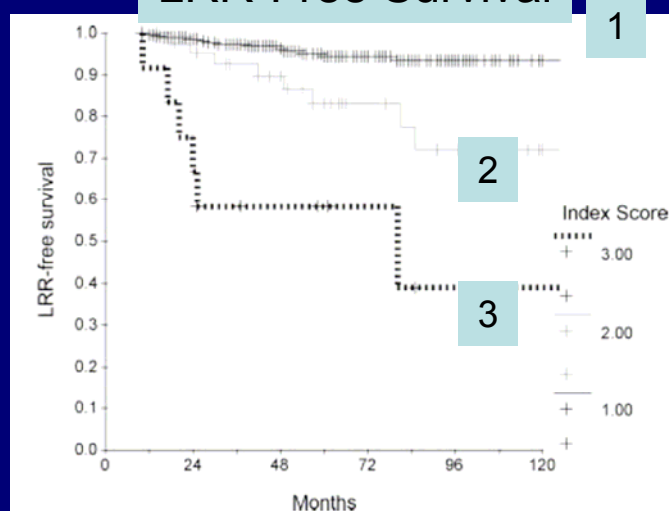
Rates of LRR and LRR-Free Survival According to MDAPI Score

MDAPI score	No. of patients	No. of patients with LRR (%)	No. of expected	RR	5-Yr LRR-free rate (%)
0	157	4 (3)	12.8	0.3	97
1	119	9 (8)	9.9	0.9	91
2	43	8 (19)	3.6	2.2	83
3	12	6 (50)	0.7	8.2	58
4	0	0 (0)	0	NA	NA

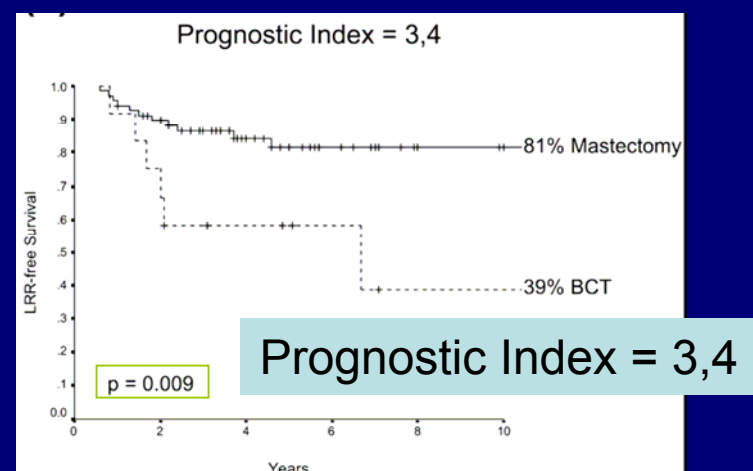
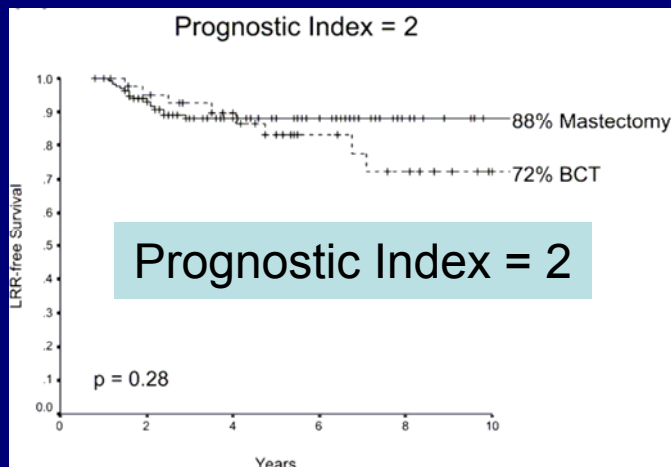
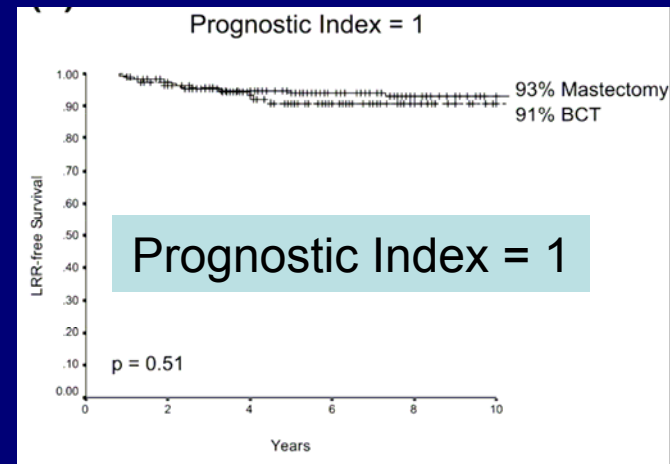
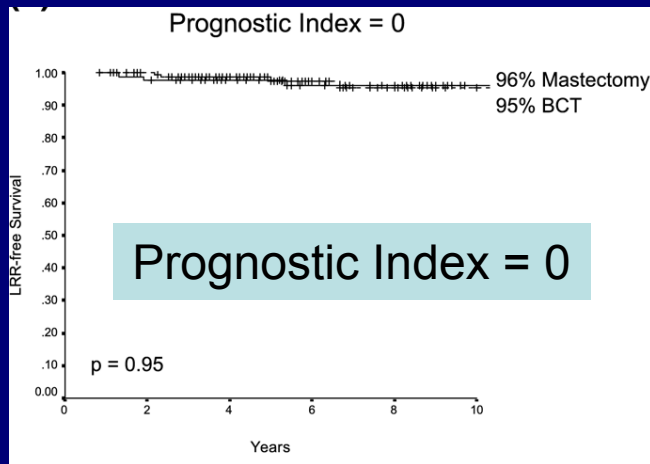
IBTR-Free Survival



LRR-Free Survival



Local Recurrence Mastectomy vs. BCT Based on Prognostic Index Score



Patients with a prognostic index score of 0-1 are equally well served by BCT or mastectomy

Local Recurrence after BCT

- Retrospective review 257 patients treated with BCT (1985-1994)
 - A variety of chemotherapy regimens
 - A variety of radiotherapy regimens
 - T stage
 - T1 15 (6%)
 - T2 216 (84%)
 - T3 26 (10%)
 - 159 (62%) were clinical N0
 - 92% infiltrating ductal

Local Recurrence after BCT

- Local failure at 5 and 10 years is 16% and 21.5%
- Factors associated with local recurrence were age, margin status, S-phase, and tumor size at surgery
- Pre-chemotherapy factors did not play a role
- Local recurrence negatively impacted overall survival

Covariate	RR	95% Confidence Interval	P
Age			
> 40 years	1		
≤ 40 years	3.55	1.89-6.67	< .001
Margin status			
> 2 mm	1		
≤ 2 mm	2.48	1.26-4.86	.04
Positive	0.94	0.35-2.54	
S-phase fraction			
≤ 4%	1		
> 4%	2.64	1.19-5.85	.03
Size at surgery			
≤ 2 cm	1		
> 2 cm	2.09	1.08-4.03	.04

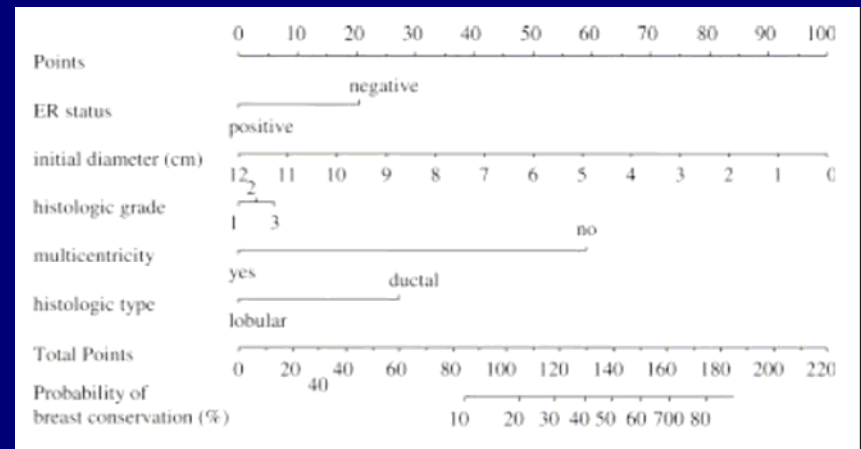
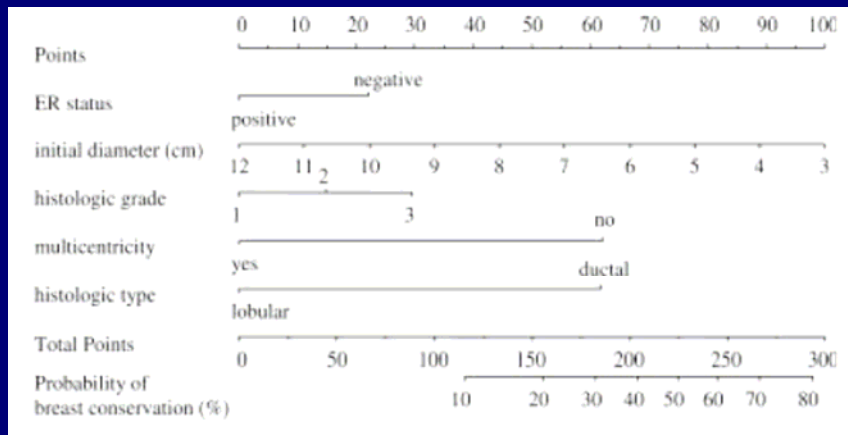
Margin status:

Positive	11%
Close (≤ 2 mm)	18%
Negative	67%
Unknown	4%

Nomograms

- 3 published preoperative nomograms
 - Prediction of CR
 - Prediction of residual tumor < 3 cm
 - Surrogate for the ability to perform BCT
 - Prediction of BCT after preoperative chemotherapy

Nomogram - BCT



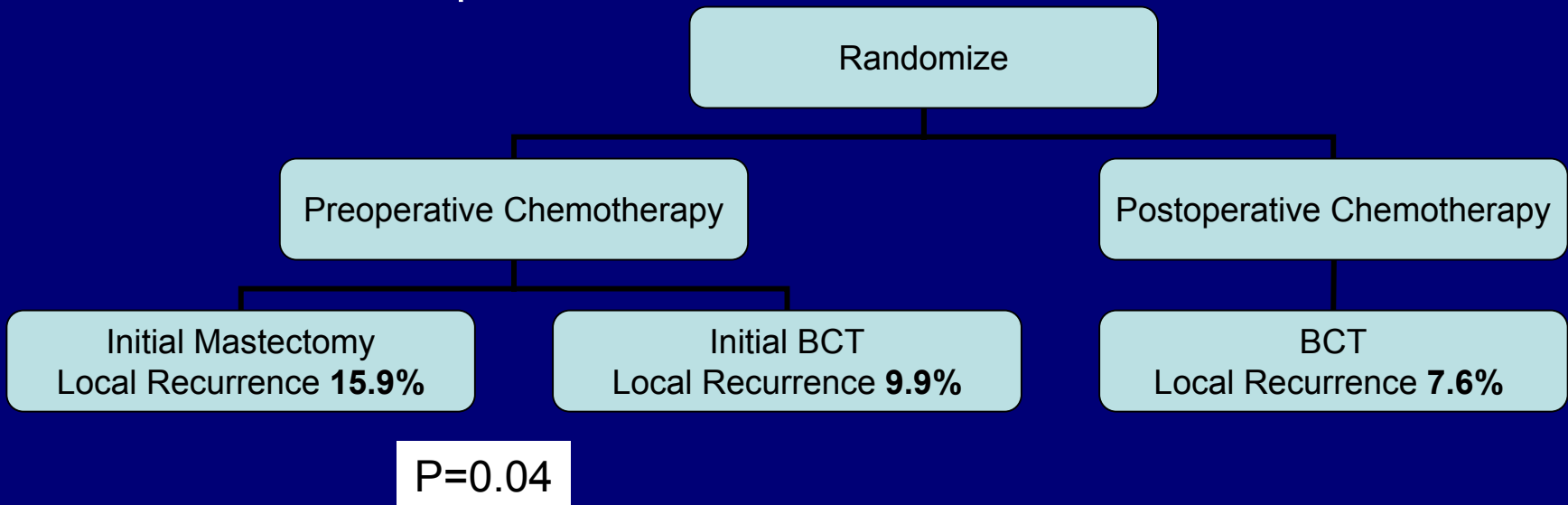
- Prediction of BCT after anthracycline or anthracycline + taxane chemotherapy was based on tumor characteristics
 - ER status, tumor diameter, histologic grade, multicentricity, histologic type
- Concordance index was 0.67

Conversion of Mastectomy to BCT

- Data regarding local recurrence is conflicting
- Some studies demonstrate increase rate of local recurrence other do not

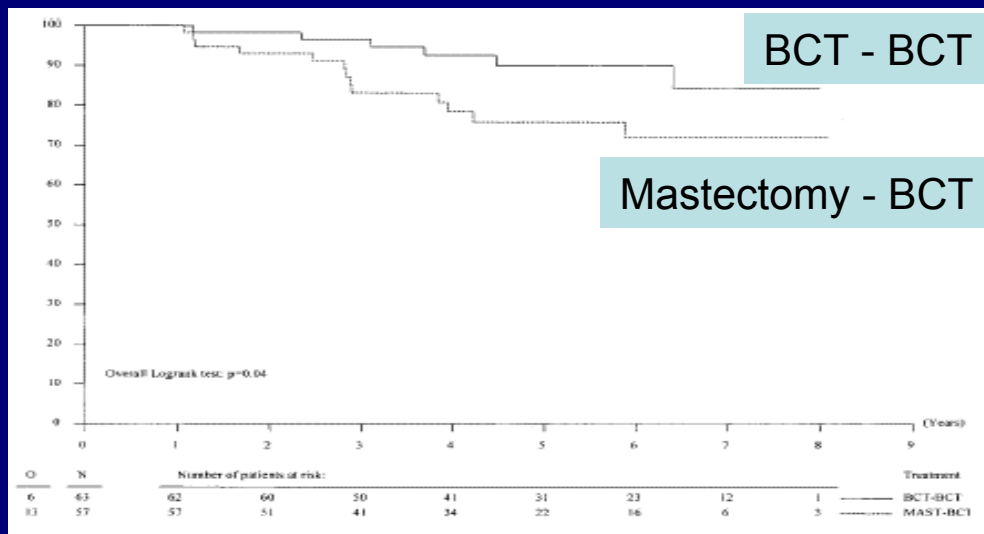
NSABP B18

- Overall, no difference in local recurrence in BCT patients
 - pre-operative (10.7%) vs. post-operative (7.6%) chemotherapy
- Difference in preoperative chemotherapy group determined to be secondary to:
 - Age
 - Tumor size at presentation



EORTC 10902

- Randomized patients to preoperative and postoperative chemotherapy
- 698 Patients
- 199 underwent BCT
- Overall Local Recurrence 10% in both groups (BCT + Mastectomy)
- Only patient who underwent BCT after chemotherapy analyzed
 - Patients who converted from mastectomy to BCT had worse overall survival than those who were initially BCT eligible



Impact of Margin Status

- Retrospective review 390 patients
 - 1994-2002
 - Single institution – European Institute of Oncology, Milan, Italy
 - All T2 or T3 tumors
 - 76% T2
 - All patients mastectomy only candidates
 - 195 (63%) underwent BCT
 - 72% T2
 - 34% T3
 - Median F/U 41 months

Impact of Margin Status

- BCT patients
 - 19% pCR
 - 44% tumors <2 cm
 - 24 (12%) +margins on final pathology (not re-excised)
 - 13 (7%) local recurrence
 - 5% with –margins
 - 13% with +margins
 - Local recurrence did not influence overall survival
 - Short F/U
- Conclusion: margin status important in overall local control

Local Recurrence after BCT

- Many single center studies report much lower local recurrence rates than multi-institutional trials
 - Not all have addressed initial surgical options
 - Lower incidence of local recurrence attributed to:
 - Multi-disciplinary approach
 - Strict BCT guidelines
 - Large volume centers

Special Considerations

Multifocal or Multicentric (MFMC) Breast Cancer

- Retrospective analysis of 706 patients treated with preoperative chemotherapy
- 97 (14%) had MFMC disease
 - Diagnosed before starting chemotherapy
- Patients where all tumor could be removed through one lumpectomy were offered BCT

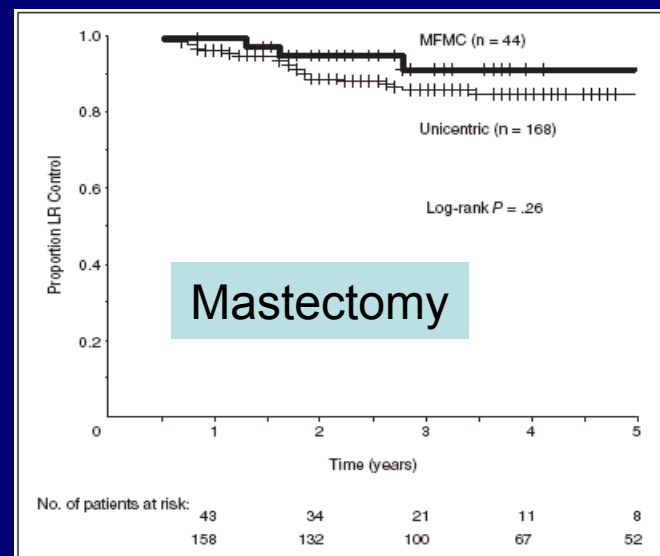
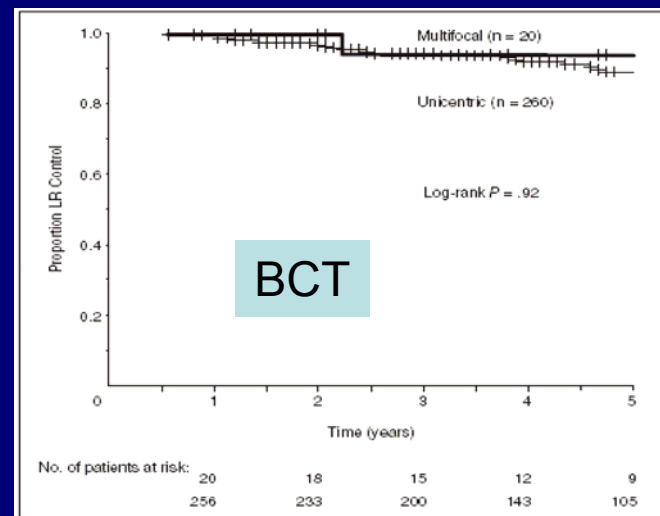
Table 1. Patient and Tumor Characteristics

Characteristic	Patients				χ^2 test <i>P</i>
	Unicentric (n = 609)		MFMC (n = 97)		
	No.	%	No.	%	
Age, years					
< 35	96	16	18	19	.487
≥ 35	513	84	79	81	
Nuclear grade					
1-2	388	64	63	65	
3	133	22	28	29	.192
Unknown	88	14	6	6	
Tumor stage					
1	51	8	11	11	.689
2	272	45	47	49	
3	185	30	26	27	
4	101	17	13	13	
Node stage					
0	184	30	37	38	.293
1	279	46	39	40	
2-3	146	24	21	22	
Stage					
II	313	51	59	61	.084
III	296	49	38	39	
Estrogen receptor					
Negative	247	41	38	39	.535
Positive	271	44	48	50	
Unknown	91	15	11	11	

Abbreviation: MFMC, multifocal and multicentric.

Multifocal and Multicentric (MFMC) Breast Cancer

- Mean F/U was 66 months
- Overall locoregional failure was 7% in patients with MFMC disease and 10% in patients with unifocal disease
 - Equal success with BCT or mastectomy
- Only 20 patient with multifocal disease underwent BCT



Infiltrating Lobular Carcinoma

Study	N	Pathologic CR	BCT
Tubiana-Hulin, 2006	ILC 118 14% IDC 742 88%	1% 9%	30% 48%
Cristofanilli, 2005	ILC 122 (12%) IDC 912 (88%)	3% 15%	16% 29%
Cocquyt, 2003	ILC 26 (19%) IDC 101 (75%)	0% 15%	38% 50%

Tubiana-Hulin M, Ann Oncol, 2006;17:1228

Cristofanilli S, J Clin Oncol, 2005;23:41

Cocquyt VF, Eur J Surg Oncol, 2003;29:361

NSABP B27

IDC vs. ILC

Ipsilateral Breast Tumor Recurrence

Histologic Type	# Pts	# IBTR	Annual IBTR Rate (%)
Ductal	989	41	3.72
Lobular	151	2	2.09
P-value in Cox proportional hazards = 0.09			

Clinical Prediction of pCR

Variable	Coeff	SE	P-value	Odds Ratio	95% CI
Treatment (Pre-OP AC [†] , Pre-OP AC+T)	0.774	0.166	< 0.0001	2.167	1.566 – 2.999
Clinical Nodal Status (Negative [†] , Positive)	0.366	0.173	0.034	1.443	1.028 – 2.024
Histologic Type (Ductal [†] , Lobular)	0.543	0.289	0.060	1.721	0.977 – 3.030
† Baseline for comparison Model based on 1108 patients for whom all covariates were known					

Conclusions

- Surgeons are integral in the multi-disciplinary approach to breast cancer patients
 - Need to evaluate patients before preoperative chemotherapy and after
- Breast conservation therapy safe and effective after pre-operative chemotherapy
 - Increases the options for women with breast cancer

Conclusions

- Appropriate selection criteria for BCT must be employed
 - Thorough pre-operative assessment is critical
 - Factors consistently associated with successful BCT (not absolute criteria)
 - Residual tumor
 - Vascular invasion
 - Residual disease
 - Histology – IDC
 - Negative margins
 - Mastectomy specimen



Thank You

Questions?

