

New approaches in the surgical treatment of breast cancer

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4/1/2011



- Intra-operative radiotherapy
- Breast conservation in the elderly
- Significance of minimal axillary disease
- Resection of the primary tumor in women with metastatic disease

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Targit-A Trial

TARGIT : **TARGET**ed **I**ntra-operative radio-**T**herapy
External **B**eam **R**adio-**T**herapy

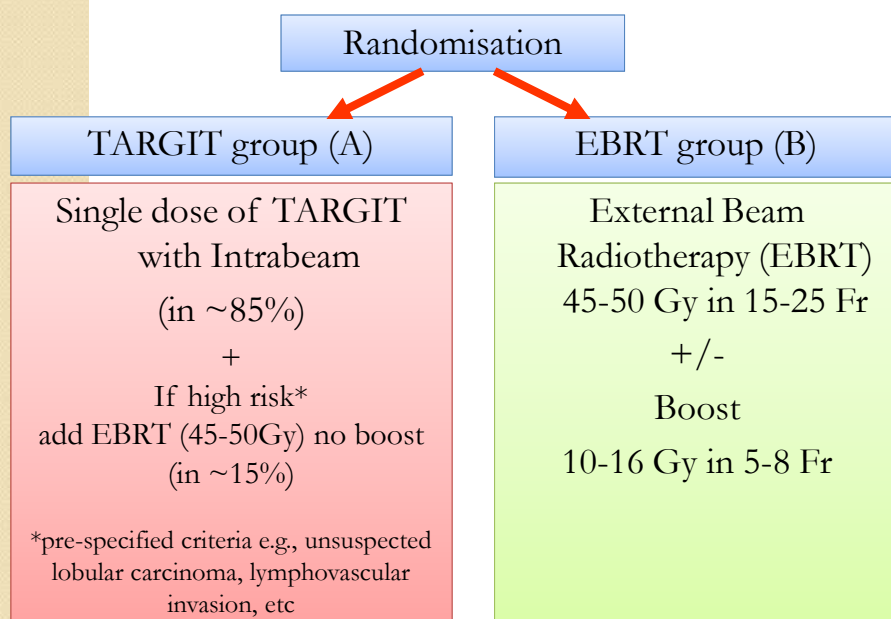
TARGIT-A trial is an international multicentre randomised clinical trial comparing TARGIT with EBRT , reported in 2010 with 10 years maximum follow-up

Michael Baum, David Joseph, Jeffrey S Tobias, Frederik K Wenz, Mohammed Keshtgar, Michael Alvarado, Max Bulsara, Wolfgang Eiermann, Norman Williams and Jayant S Vaidya on behalf of the TARGIT Trialists' group

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Breast cancer being treated with Breast Conserving Surgery



Power Calculations to demonstrate non-inferiority

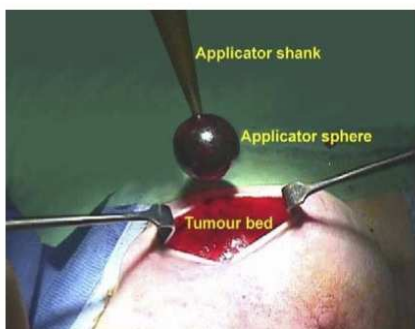
Scenario	Background Recurrence rate	Background + non-inferiority margin of 2.5%	Total sample size required (80% power 95% alpha)	Median follow up of this sample at present
Expected 10 years ago	6%	8.5%	2232	25.3 m
Expected following recent publications (e.g. START trial)	3%	5.5%	1151	43.0 m
Actually found in the control arm (EBRT group) of the TARGIT trial	1.5%	4%	585	54.0 m

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The TARGIT technique



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TARGIT- A trial recruitment

The 1st patient was randomised on 24 March 2000



Low risk population
 Mostly over 45 years in age
 10-15% of patients had tumors >2 cm, grade III, or node positive

Extent of surgery

	TARGIT group n=1113	EBRT group n=1119
Margins at first excision		
Free	970 (90.5%)	968 (90.2%)
DCIS only	46	43
Invasive	56	62
Unknown	41	46
Specimen weight		
Weight in gm (median)	45.5	47
Interquartile range	29 - 76	28 - 72
Re-excision for margins		
Performed in	79 (7.1%)	106 (9.2%)

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Clinically important wound complications

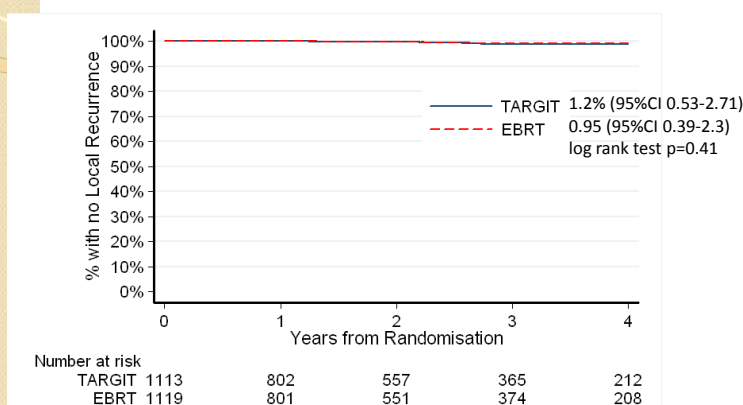
	TARGIT	EBRT	
Hematoma requiring surgical evacuation	11 (0.99%)	7 (0.63%)	p= 0.34
Seroma requiring more than 3 aspirations	23 (2.07%)	9 (0.8%)	p= 0.012
Infection requiring intravenous antibiotics or surgery	20 (1.9%)	14 (1.3%)	p= 0.29

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Kaplan-Meier Plot of Survival without local recurrence in the conserved breast – TARGIT vs. EBRT



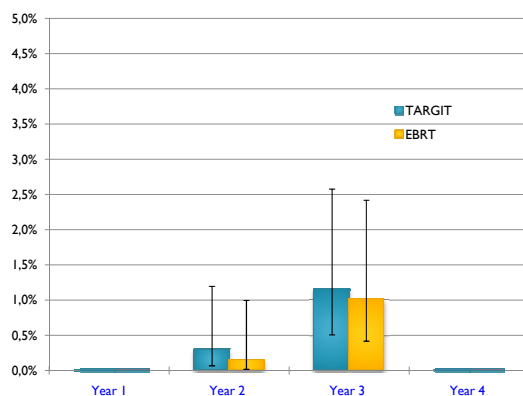
These graphs are restricted to 4 years as less than 420 (<20%) patients have a follow up beyond this point; however, all patients (with a maximum follow up of 10 years) are included in the analysis. As recommended by Pocock et al. *Lancet* 2002; **359(9318)**: 1686-9.

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Annual Hazards of local recurrence in the conserved breast – TARGIT vs. EBRT



There were no recurrences in the year 1 and year 4. These graphs are restricted to 4 years as less than 420 (<20%) patients have a follow up beyond this point; however, all patients (with a maximum follow up of 10 years) are included in the analysis.

As recommended by Pocock et al. *Lancet* 2002; 359(9318): 1686-9.

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Is it reasonable to use intra-operative RT in clinical practice?

- TARGIT data provides Level I evidence of quality of local control
- Other data on partial breast radiotherapy continues to show equivalence with whole breast RT.
- Caveats
 - PBRT has been used in low risk patients
 - Follow-up remains short
 - Data on new tumors outside the RT field still needed

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**DOES BREAST
CONSERVATION IN THE
ELDERLY REQUIRE
RADIOTHERAPY?**

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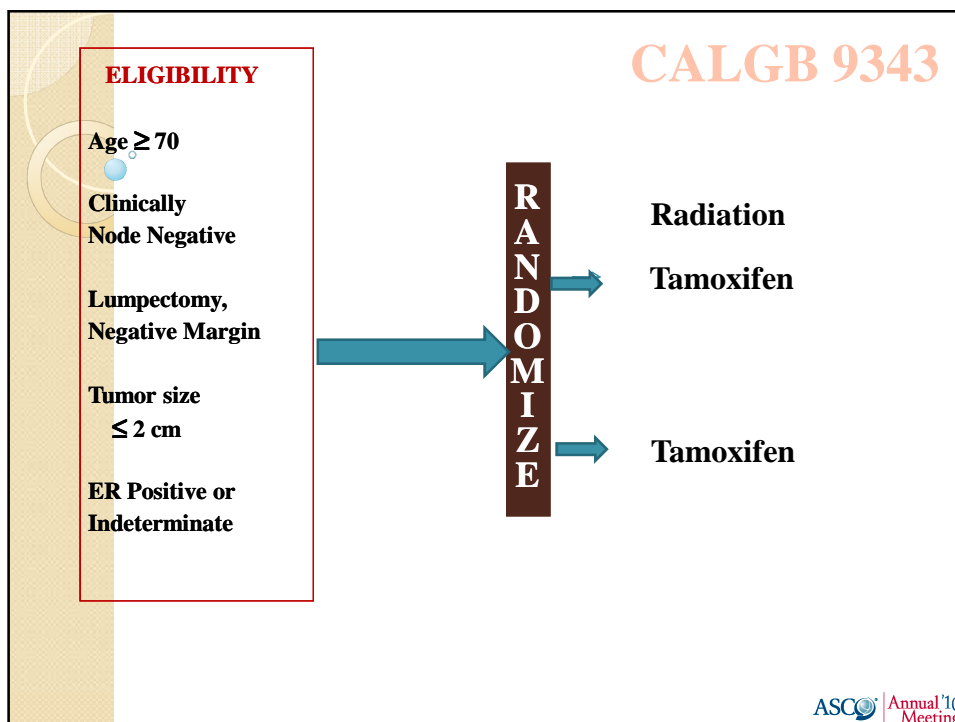


CALGB 9343

**Comparison of Lumpectomy Plus Tamoxifen With and Without
Radiotherapy in Women 70 or Older Who Have Clinical Stage
I, ER+ Breast Carcinoma**

Kevin S. Hughes, Lauren A. Schnaper, Constance Cirrincione, Donald
Berry, Beryl McCormick, Hyman B. Muss, Clifford Hudis, Eric Winer,
Barbara L. Smith

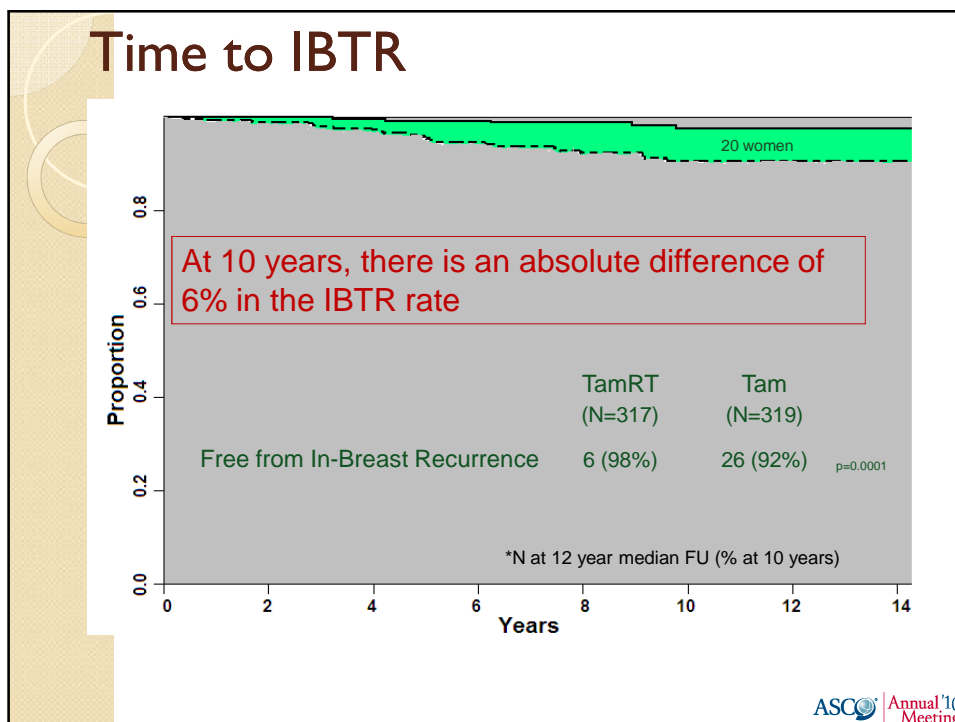
Cancer and Leukemia Group B
Radiation Therapy Oncology Group
Eastern Cooperative Oncology Group



Patient characteristics

	TamR	T+Tam
Total treated	317	319
Age >75	176 (56%)	172 (54%)
ER Positive	308 (97%)	310 (97%)
Size ≤ 2 cm	295 (93%)	296 (93%)
No Ax dissection	200 (63%)	203 (64%)

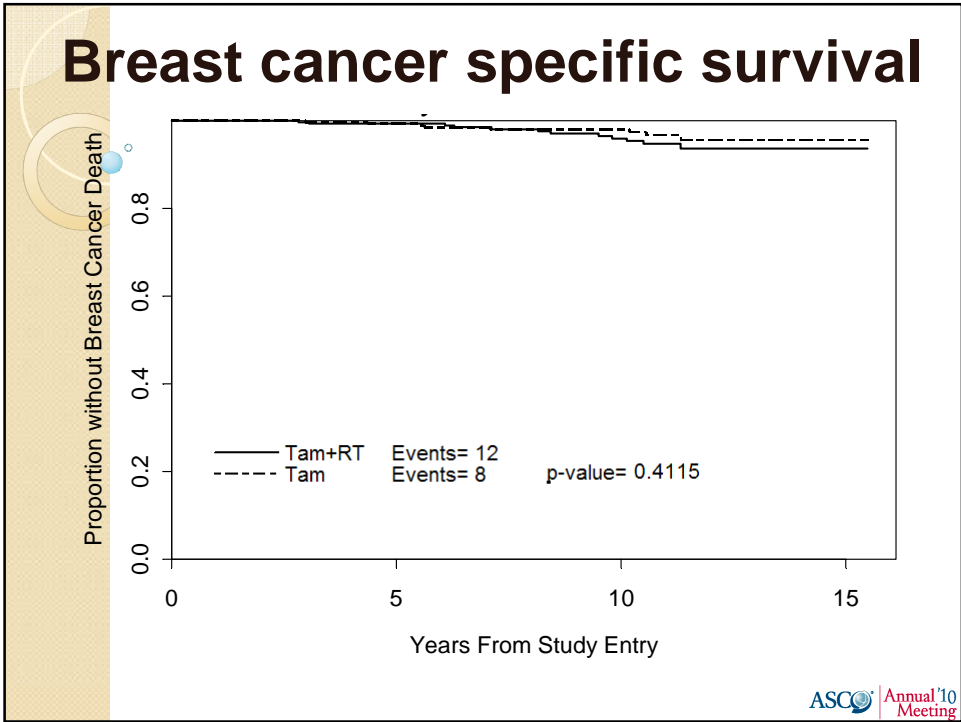
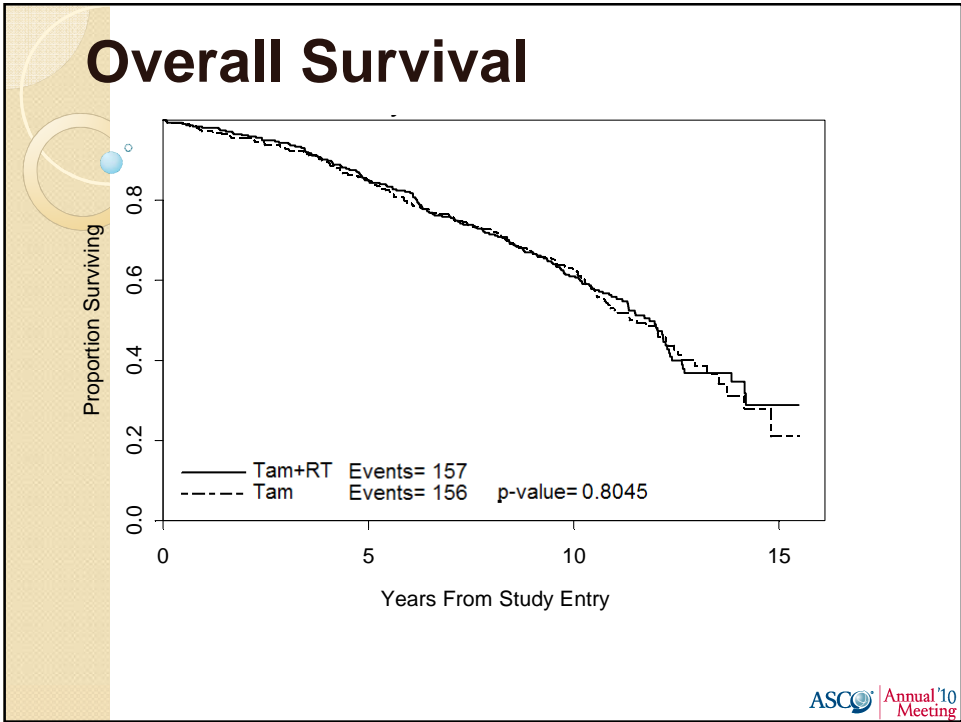
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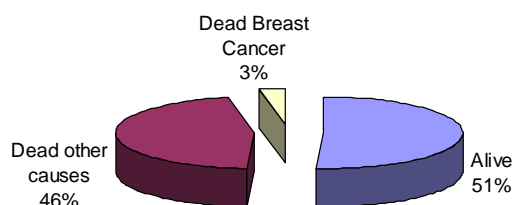
Axillary recurrence

	Tam	RT+Tam
No Ax dissection	200 (63%)	203 (64%)
Axillary Recurrence	0	6 (3%)

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Survival



- Comorbidities are a more important hazard in this age group than breast cancer
- Treatment recommendations should include a consideration of life expectancy
- The absolute risk of in-breast recurrence in this age group is low even without RT
- This data applies only to cT1 cN0 disease.

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Sentinel nodes: significance of IHC positivity

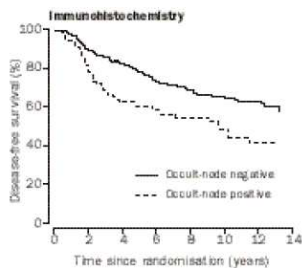
- When SN are negative by H&E, 10-15% of women will demonstrate presence of epithelial cells with immunohistochemical stains for cytokeratins.
 - The prognostic significance of this has been debated.
- The prognostic importance of IHC+ bone marrow aspirates has been seen in several studies.

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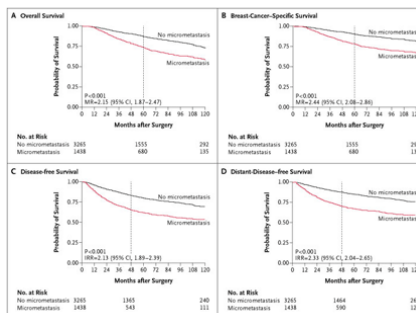
IHC Detected Occult Metastases to LN and BM is Associated with Outcome in Patients with Operable Breast Cancer

Outcome associated with IHC detected LN occult mets



Disease-free survival for 343 postmenopausal pts
Cote R et al. *Lancet* 1999

Outcome associated with IHC detected BM occult mets



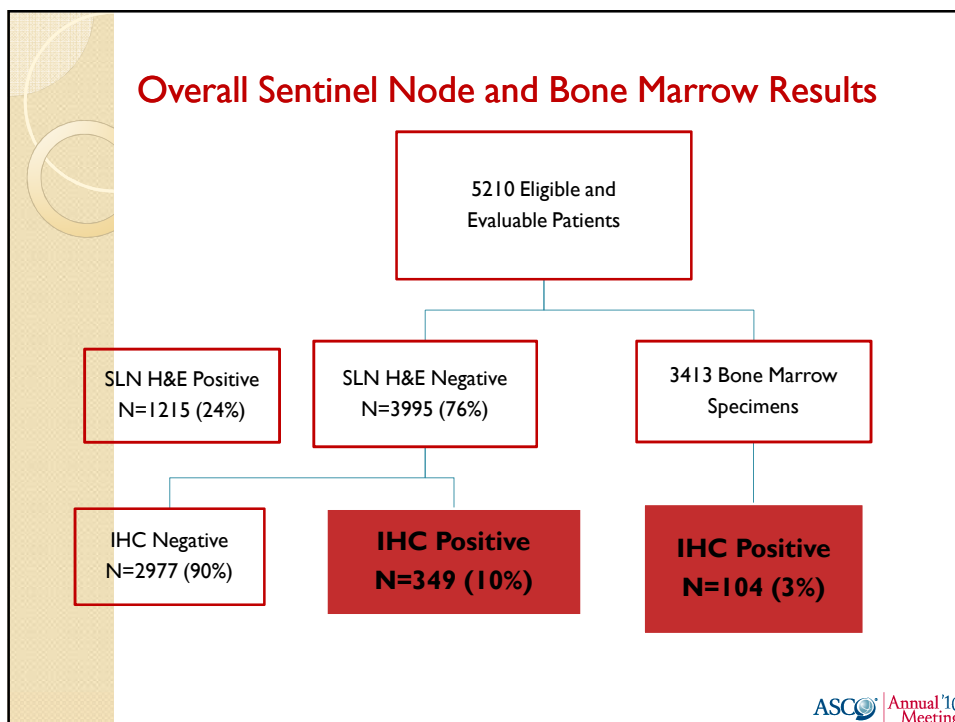
Disease free and overall survival in 4703 patients
Braun et al *NEJM* 353:8:793-802, 2005



ACOSOG Z0010 - Methods

- Bone marrow aspiration prior to SLN bx
- Bone marrow specimens subjected to IHC (investigators blinded to results)
- SLNs processed - standard pathology and H&E staining
- SLNs neg by H&E subjected to IHC for cytokeratin (investigators blinded to results)





Overall Survival by Histologic SLN and BM Status: All Patients

Variable	univariable		multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
SLN H&E negative	1.00 (ref)	0.0003	1.00 (ref)	0.007
SLN H&E positive	1.47 (1.19, 1.80)		1.44 (1.11, 1.88)	
BM IHC negative	1.00 (ref)	0.016	1.00 (ref)	0.017
BM IHC positive	1.90 (1.13, 3.20)		1.88 (1.12, 3.17)	

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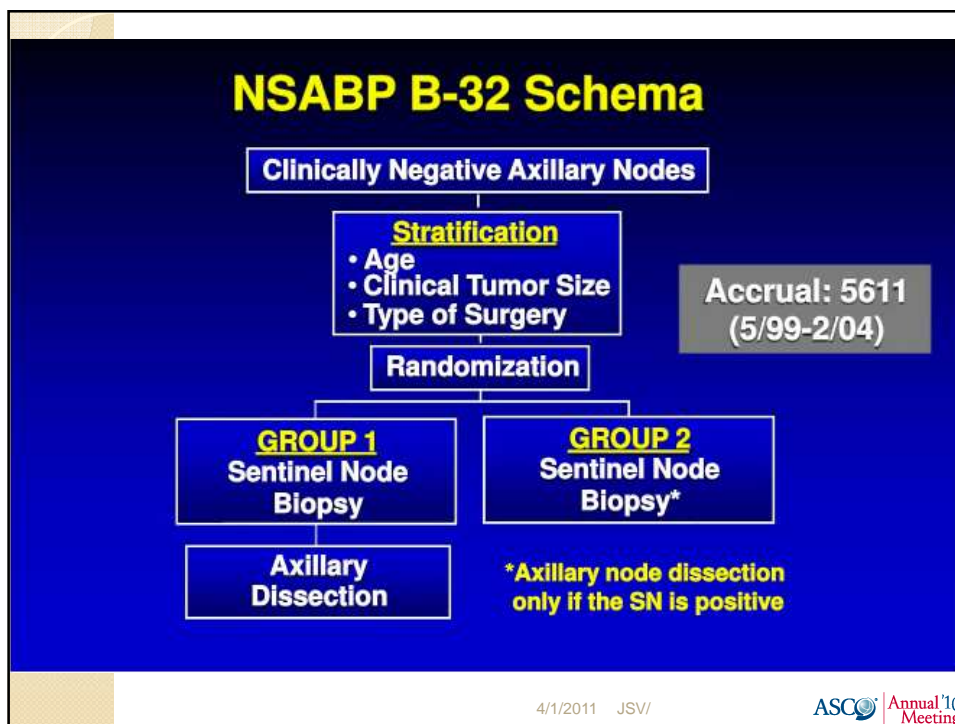
Overall Survival by SLN IHC and BM Status: SLN H&E- Patients

Variable	univariable		multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
SLN IHC				
negative	1.00 (ref)	0.65	1.00 (ref)	0.93
positive	0.92 (0.63, 1.33)		0.98 (0.62, 1.54)	
BM IHC				
negative	1.00 (ref)	0.016	1.00 (ref)	0.011
positive	1.90 (1.13, 3.20)		2.22 (1.21, 4.10)	

ACOSOG Z0010 IHC Sentinel node and bone marrow

Conclusions

- Outcome in this population was excellent, with 5 year overall survival of 93% in pts with H&E+ SLN
- Detection of BM occult mets by IHC identifies clinical T1,2N0M0 pts at significantly increased risk for death
- IHC detected SLN metastases do not appear to impact overall survival.
- Routine examination of SLN by IHC is not supported in this patient population by this study.
- This multi-institutional study supports prior single institution studies on the prognostic value of IHC detection of BM occult metastases



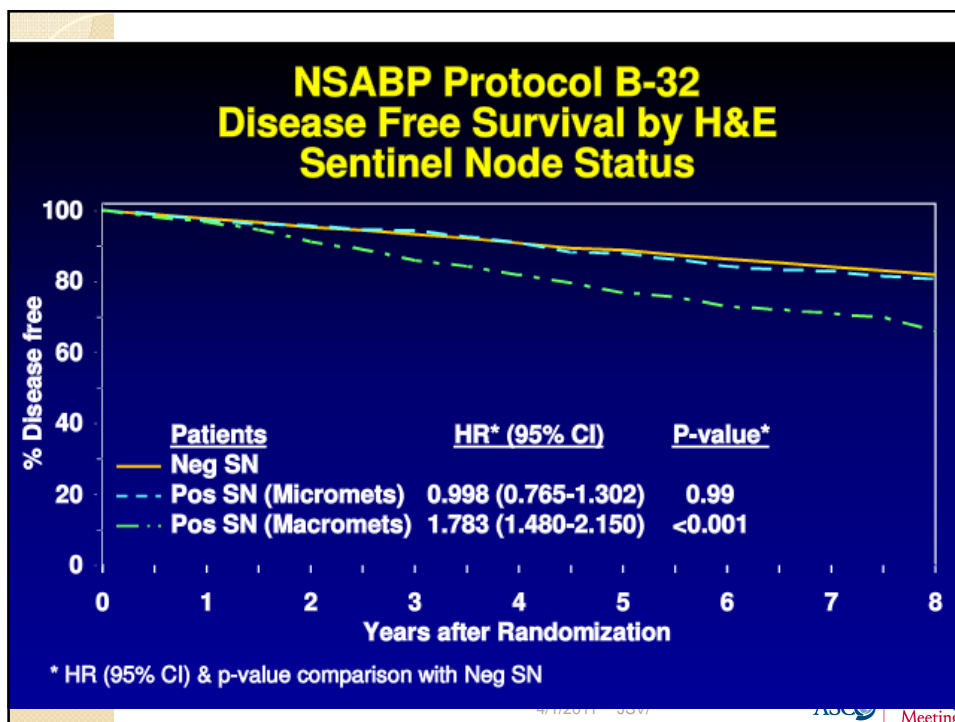
NSABP Protocol B-32 1390 SN Positive Patients

SN Micro and Macro Metastases (Hematoxylin and Eosin)

Variable	Category	# Patients
Type of metastasis	Micro	312
	Macro	422
	Unknown	626

Of the 734 known patients, 718 patients had complete data

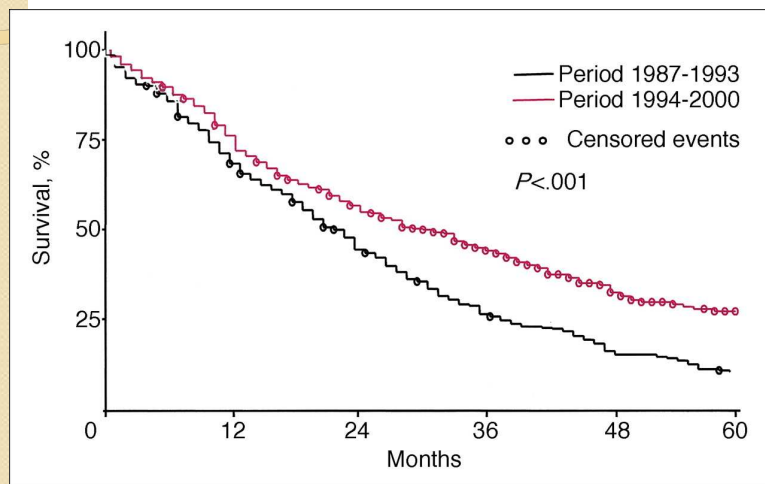
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Newly diagnosed Stage IV breast cancer with intact primary tumor

- Conventional approach
- Incurable disease
- Standard of care consists of systemic therapy
- Primary tumor does not need treatment unless it is uncontrolled by systemic therapy and is symptomatic.

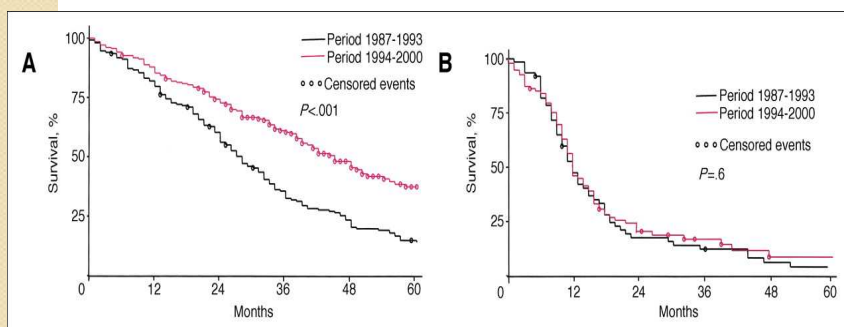
Time trends in the survival of women with de novo Stage 4 breast cancer



Andre, F. et al. J Clin Oncol; 22:3392-3398, 2004
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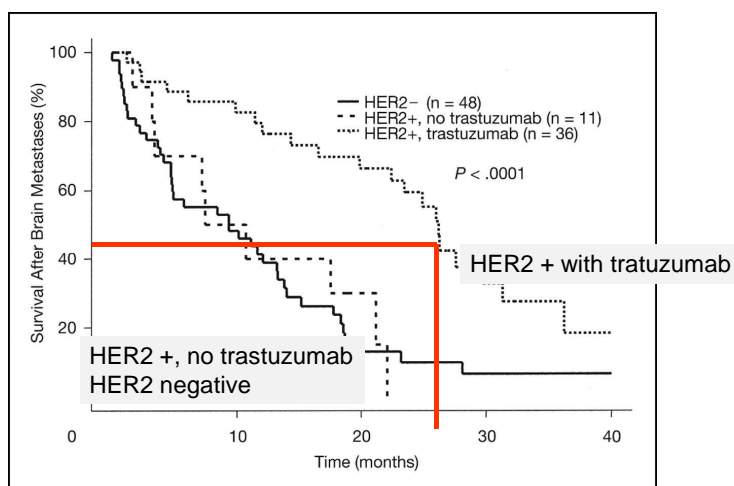
Time trends in survival of Stage IV breast cancer patients

Hormone receptor pos Hormone receptor neg



Andre, F. et al. J Clin Oncol; 22:3392-3398, 2004
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Overall survival by HER2 status in women with brain metastases: effect of trastuzumab.



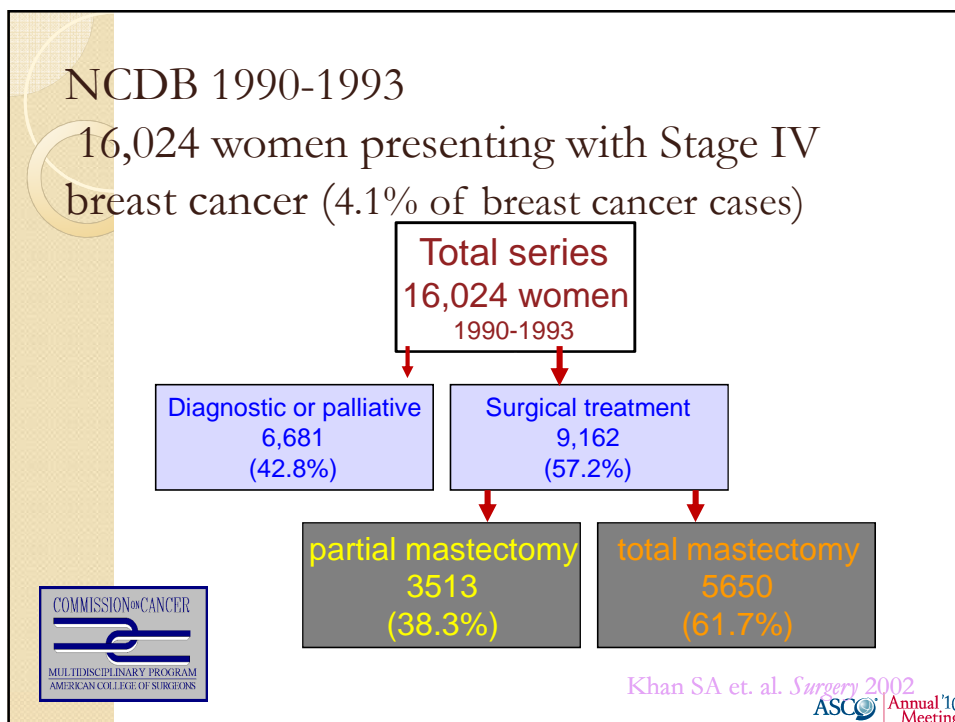
Kirsch, D. G. et al. J Clin Oncol; 23:2144-2116, 2005

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Targeted therapy prolongs survival in both metastatic and non-metastatic disease.

The list of targets is growing
 Estrogen & progesterone receptor
 Her-2/nue
 EGFR?
 Tyrosine kinase inhibitors?
 Others?

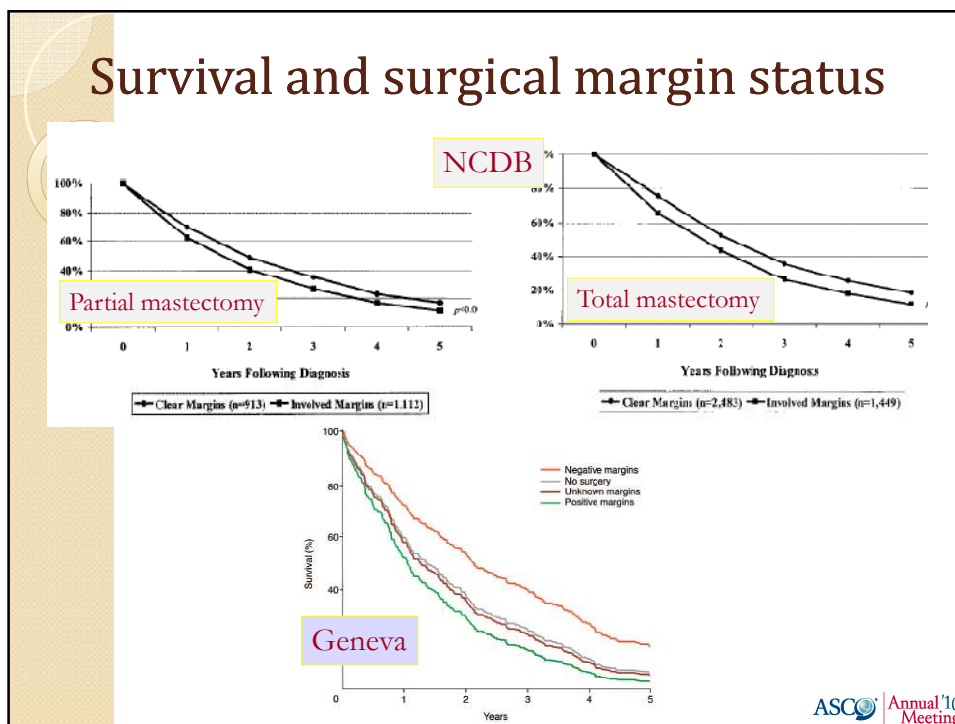
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NCDB: Multivariate Cox Model

	#Cases	HR	95% CI
Type of Metastasis (reference category visceral mets)			
Soft Tissue/bone	6216	0.75	0.71 - 0.78
Metastatic Burden (reference category single organ site)			
2 Sites	2352	1.25	1.19 - 1.32
3 Sites	1318	1.52	1.42 - 1.63
Systemic Therapy (reference category no therapy)			
Chemotherapy	3419	0.72	0.68 - 0.77
Hormonal Therapy	2837	0.73	0.69 - 0.78
Both	1620	0.61	0.57 - 0.66
Surgical Margin Status (reference category no surgery)			
Negative Margins	3099	0.61	0.58 - 0.65
Positive Margins	2326	0.75	0.71 - 0.79

Khan SA et al. ASCO Annual Meeting



Patterns of care for de novo Stage IV disease

Study	N	Time period	Surgery/RT
NCDB (Khan)	16,024	1990-93	56%
Geneva (Rapiti)	300	1977-1996	42%
<p>MI ~30,000 patients seen over periods ranging from 1970-2005</p> <p>W ~ 50% received some form of local therapy for the primary tumor</p>			
Boston (Cady)	622	1970-2002	56%
Boston (Bafford)	147	1998-2005	41%
Rene Huguenin **(LeScodan)	581	1980-2004	55%

** primary RT

Summary of positive retrospective studies

Study (N)	Adjusted 3-year survival		difference
	no surgery	Surgery or RT	
NCDB (16,024)	17%	35%	18%
Geneva (300)	22%*	41%*	19%
Wash U/Barnes (409)	28%*	46%*	18%
SEER (9,734)	19%*	37%*	18%
Baylor	24%	44%	20%
Huguenin, France**	27%	43%	16%
Netherlands	25%	42%	17%

* Estimated from published survival curves. ** primary RT

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Summary of survival benefit in positive studies

Study (N)	T 1-2 tumors	Free margins	HR local therapy (95% CI)
NCDB (16,024)	45.7%	37%	0.6 (0.58-0.65)
Geneva (300)	31%	48%	0.6 (0.58-0.65)
MDACC (224)	38.4%	62%	..
SEER (9,734)	41.2%	NA	0.63 (0.60-0.66)
Wash U	35%	49%	0.53 (0.42-0.67)
Baylor (427)	82%	NA	0.71 (0.56-0.91)
Rene Huguenin	32%	NA	0.70 (0.58 to 0.85)
Netherlands	46%	NA	0.62 (.51-.76)

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de novo Stage IV breast cancer & survival

Negative(?) studies

Negative results for surgical therapy of primary tumor in *de novo* Stage IV disease

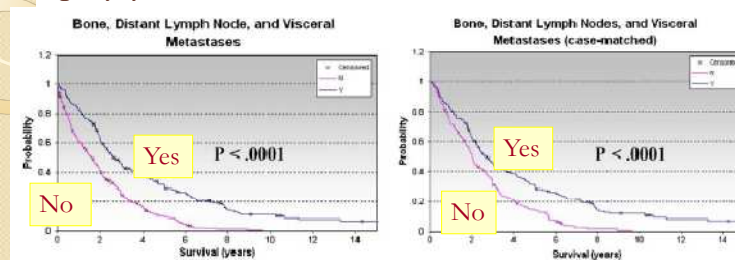
Study	N	Time period	Surgery
Boston (Cady)	622	1970-2002	38%
Boston (Bafford)	147	1998-2005	41%
Virginia (Leung)	157	1990-2000	33%

Matched Pair analysis from two Boston Hospitals (MGH + BWH)

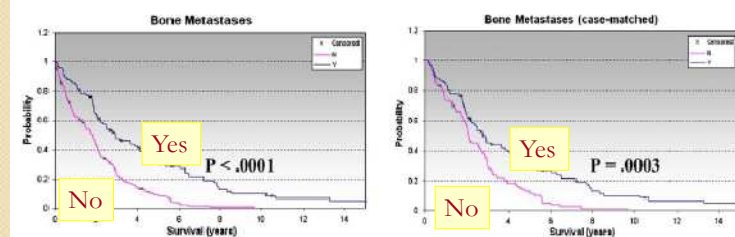
- 808/19,464 women over period 1970-2002
 - Exclusions for non-MA residence, AJCC 6th edition stage, other miscellaneous reasons.
- 622 eligible women
 - 388 (62%) underwent surgery
- Matched to women treated without surgery
 - Age (within 5 years),
 - Date of diagnosis (within 5 years),
 - Location of metastatic disease (bone, visceral, soft tissue),
 - Estrogen receptor status (positive versus negative),
 - Use of systemic therapy.



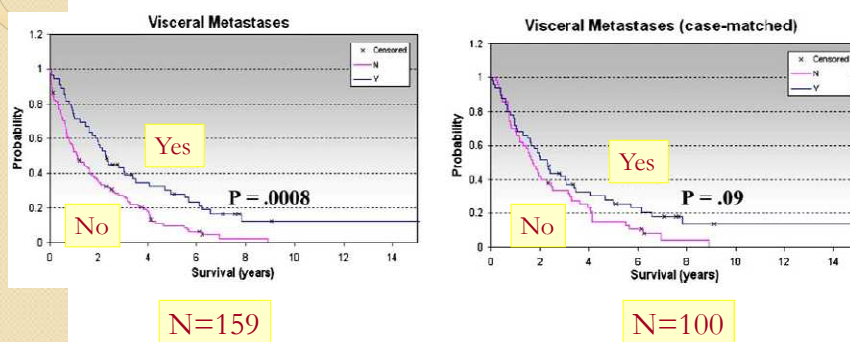
Main analyses with case-matching: surgery yes or no



survival analysis by multiple site (above) and bone only mets (below)



Matched pairs, visceral metastases only



Other subsets with non-significant results had under 20 patients in the surgical groups.

Cady et. al. Ann Surgical Oncol 2009
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Known biases in surgical series

- Younger age
- Smaller tumors
- Estrogen receptor positive
- Fewer organ sites involved
- Access to care
 - European ancestry, married
 - Insured
 - Surgery a surrogate for better care overall?
- Unknown biases cannot be adjusted for in retrospective studies.

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Ongoing prospective studies

- India Feb 2005, Tata Memorial Hospital
randomizing 350 pts who respond to 6 cycles to chemotherapy to surgery or no surgery (NCT00193778)
- Turkey November 2007
randomizing 270 patients to surgery or no surgery before chemotherapy(NCT00557986)
- Translational Breast Cancer Research Consortium
A registry for the prospective collection of clinical and pathological data, blood samples, paraffin-embedded and fresh frozen tissue samples from the primary tumor and distant metastatic sites. (TBCRC 0013)

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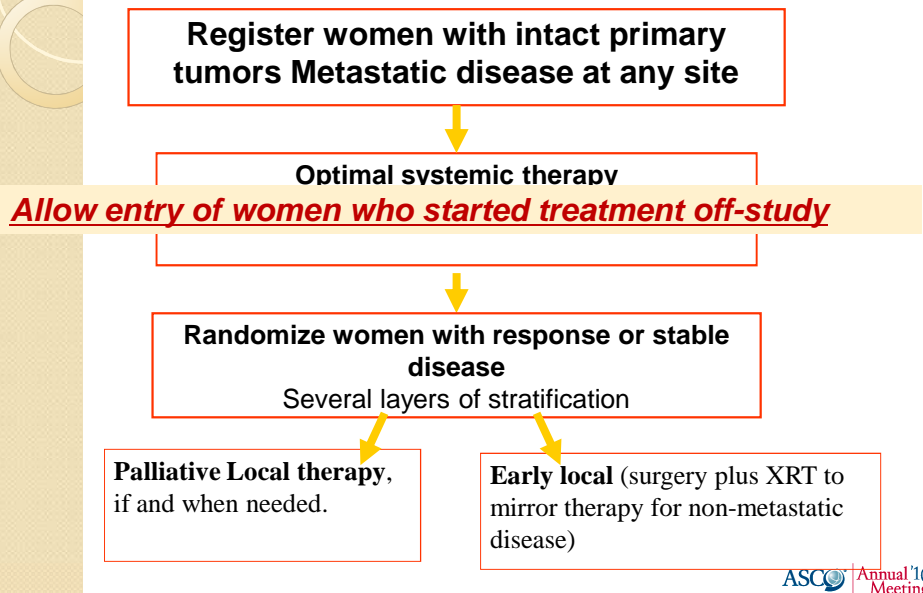
Activated in February 2011

Eastern Cooperative Oncology Group: E2108
A randomized trial of local therapy for the primary site in Stage IV breast cancer patients

CALGB/NCCTG
NSABP
RTOG
SWOG
NCIC
AVAILABLE THROUGH CTSU

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E2108 schema



Eligibility

- Women with intact primary tumors and Stage IV disease.
- Anticipated survival of at least 6 months.
- Core needle biopsy of the primary tumor (preferred)
- If incisional surgical biopsy of large tumor, residual palpable or imageable tumor must be present.
- T stages T1-T4d, N1-3.

Systemic therapy based on patient and tumor characteristics

Allow flexibility

- Use of NCCN guidelines encouraged.
- Participation in trials of 1st line therapy for Stage IV disease allowed
- Interval of primary systemic therapy:
 - 4 cycles for cytotoxic regimen,
 - 4 months for endocrine regimen

Local therapy will mirror that used in non-metastatic disease

Surgery with radiotherapy according to standards of care

tumor resection with free margins
axillary dissection (unless SN negative)
radiotherapy according to standard guidelines
reconstruction allowed if desired

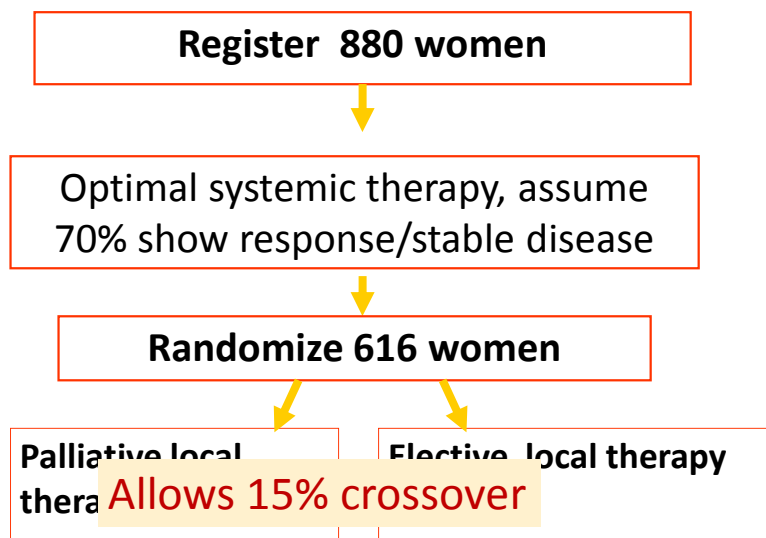
Health-related Quality of Life

- FACT-Breast Trial Outcome Index
 - With four added questions related to uncontrolled chest wall disease: skin nodules, ulcers, pain.
- Primary comparison 18-20 months post diagnosis
 - I.e. about one year after all primary site therapy complete.
- The change of FACT-B TOI scores over time will be compared between groups
 - Compare impact of local therapy to impact of uncontrolled local disease

Correlative science

- ▶ Form steering committee with representation from North American groups
- ▶ Chaired by Leyland-Jones, Khan
 - ▶ Questions to be prioritized as they are proposed
 1. Does primary site local therapy cause decrease in **circulating tumor cells**?
 2. Does **tumor stem cell** component in primary predict benefit from primary site therapy?
 3. The primary tumor secretes **proteins** that regulate metastatic tumor growth: RANTES, VEGF, G-CSF, osteopontin, SDF-1, PLGF and soluble VEGFR-2.

E2108 sample size



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Conclusions

- Local treatment of breast cancer continues to devolve towards less intervention.
 - Axillary dissection only for >2 involved nodes
 - No advantage to IHC testing of SN.
 - Partial breast radiotherapy with intra-operative approach provides excellent local control in low risk women
 - Elderly patients with small tumors have low risk of in-breast recurrence even when radiotherapy is not used
- Local therapy for the primary site may improve survival in Stage IV disease and is being tested in randomized trials.

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