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Appropriate Margins for Breast-conserving Surgery in Patients With Early Stage Breast Cancer: A Meta-analysis

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Mastology

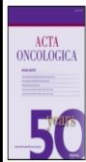




TOTAL MASTECTOMY VERSUS LUMPECTOMY

TWENTY-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING TOTAL MASTECTOMY, LUMPECTOMY, AND LUMPECTOMY PLUS IRRADIATION FOR THE TREATMENT OF INVASIVE BREAST CANCER

Similar Survival



Acta Oncologica



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Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol

Mogens Blichert-Toft, Maja Nielsen, Maria Düring, Susanne Møller, Fritz Rank, Marie Overgaard & Henning T. Mouridsen

Long-Term Results of a Randomized Trial Comparing Breast-Conserving Therapy With Mastectomy: European Organization for Research and Treatment of Cancer 10801 Trial

Joop A. van Dongen, Adri C. Voogd, Ian S. Fentiman, Catherine Legrand, Richard J. Sylvester, David Tong, Emmanuel van der Schueren, Peter A. Helle, Kobus van Zijl, Harry Bartelink

Mastectomy Versus Breast-Conserving Therapy in the Treatment of Stage I and II Carcinoma of the Breast: A Randomized Trial at the National Cancer Institute

By Allen S. Lichter, Marc E. Lippman, David N. Danforth, Jr, Teresa d'Angelo, Seth M. Steinberg, Ernest deMoss, Harold D. MacDonald, Cheryl M. Reichert, Maria Merino, Sandra M. Swain, Kenneth Cowan, Lynn H. Gerber, Judith L. Bader, Peggine A. Findlay, Wendy Schain, Catherine R. Gorrell, Karen Straus, Steven A. Rosenberg, and Eli Glatstein

Margins

Recurrences

>10%

Re-operations

Local Recurrence (LR)

LR < 5%:

1- Better Radiology

2- Better Pathology

3- Systemic Therapy

Systemic Therapy and Local Recurrence

NSABP B-14

- **RL 10 Years**
- **Positive RH Tumors**
- **TAM Vs Placebo**
- **14.7 → 4.3%**

NSABP B-13

- **RL 10 anos years**
- **Negative RH Tumors**
- **QT vs Placebo**
- **13.4% → 2.6%**

Margins Definition: No ink on Tumor

Margins

Recurrences

>10%

Re-operations

20-25%

Clinical Investigation: Breast Cancer

**Society of Surgical Oncology—American Society for
Radiation Oncology Consensus Guideline on Margins for
Breast-Conserving Surgery With Whole-Breast Irradiation
in Stages I and II Invasive Breast Cancer**

Meena S. Moran, MD,^{*} Stuart J. Schnitt, MD,[†] Armando E. Giuliano, MD,[‡]
Jay R. Harris, MD,[§] Seema A. Khan, MD,^{||} Janet Horton, MD,[¶] Suzanne Klimberg, MD,[#]
Mariana Chavez-MacGregor, MD,^{**} Gary Freedman, MD,^{††}
Nehmat Houssami, MD, PhD,^{‡‡} Peggy L. Johnson,^{§§} and Monica Morrow, MD^{|||}

**28.162 patients in 33 estudies
(1506 local recurrences – 5.3%)**

**Positive margins:
OR 1.96 (CI 1.72-2.24)**

Model 1

**Bigger margins was not associated with
better local control
(1, 2 and 5mm)**

Model 2

**Appropriate margins for
breast-conserving surgery in
patients with early stage
breast cancer:**

A meta-analysis

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Beth Israel Deaconess Medical Center, Harvard Medical
School, UCLA Medical School, Radiation Oncology

Methods

- Systematic literature review (1995-2016)
- Inclusion criteria:
 - Minimum follow-up: 50 months
 - Explicit pathologic definition of margin status
 - Local recurrence reported in relation to margin status
- 38 studies with 55,302 patients identified, including 31 of the 33 studies from the previous meta-analysis (**>20,000 additional patients**)
 - 1 updated study
 - 1 follow-up <50 months (eliminated)
- Median follow up 7.2 years

Methods

- Margin definitions similar to previous analysis
- "Positive" = invasive cancer or DCIS at the surgical margin
- "Negative" = no tumor within specified distance from margin
- "Close" = no tumor on ink but there was tumor less than specified distance from the margin
- Series of models developed based on cut-point desired

Population

	# of studies	Median	(Range)
Number of subjects	38	826	48-11900
Follow-up (years)	38	7.15	4.2-13.3
Age (years)	33	55	40-63
T1	31	74.1%	43.4-100.0%
T2+	31	23.5%	0.0-56.6%
Other	31	0.0%	0.0-5.5%
N0	30	71.7%	58.2-100.0%
N+/Unknown	30	28.3%	0.0-41.8%
Re-excision rate	19	41.6%	6.1-68.4%
WBI Dose (Gy)	37	47.7	40-60
Boost Dose (Gy)	33	13	0-21.25
Endocrine Therapy	30	39.1%	0.0-79.7%
Chemotherapy	29	24.4%	0.0-100.0%

Covariate	Follow-up time adjusted model p-values- Model 1			
	Margin = 0	Margin = 1	Margin = 2	Margin = 5
Median study year	0.193	0.246	0.130	0.002
Median patient age	0.048	0.040	0.051	0.086
Median follow-up	N/A	N/A	N/A	N/A
100% stage 1/2+	0.898	0.973	0.638	0.413
Negative Nodes	0.386	0.365	0.405	0.930
Re-excision rate	0.099	0.575	0.301	0.078
WBI median dose	0.769	0.914	0.912	0.998
Median boost dose	0.361	0.335	0.295	0.129
Endocrine Therapy	0.001	0.002	<0.001	<0.001
Chemotherapy	0.989	0.655	0.829	0.651

Methods

- 3 Models in Present Analysis:

- Model 1: similar to previous analysis (Model 1) of negative vs. close/positive

- Model 2: performed to assess impact of margin width range rather than a set margin width

- 0-2 mm, 2-5 mm, >5 mm

- Not included in previous analysis

- Model 3: similar to previous meta-analysis of negative, close, positive margins (1, 2 e 5mm)

Results- Model 1

Odds ratios for local recurrence for negative vs. close/positive margins

- >0 mm: 0.46 (0.40-0.53, $p < 0.001$)
- >1 mm: 0.43 (0.36-0.51, $p < 0.001$)
- >2 mm: 0.49 (0.42-0.55, $p < 0.001$)
- >5 mm: 0.53 (0.43-0.66, $p < 0.001$)

- Best odds ratio for 1 mm margin, as compared to close/positive margin
- Similar results to previous meta-analysis
- Odds ratios are very similar: unable to say what's the optimal margin

Results- Model 3

When modeling as negative, close, or positive margins, reduced rates seen with negative margins with lowest rates seen at 2 and 5 mm

MVA confirmed margin status and width as factors associated with local recurrence. Last two bullet points below are the difference from previous work

– Negative/Close/Positive Margins

- 1 mm: 8.0%/13.0%/14.0%
- 2 mm: 3.6%/5.5%/9.5%
- 5 mm: 2.9%/4.1%/12.8%

– Odds Ratio for Local Recurrence by Margin Status

- Close vs. Negative: 1.58 (1.32-1.89)
- Positive vs. Negative: 2.49 (2.10—2.96)
- **2 mm vs. 1 mm: 0.50 (0.42-0.59)**
- **5 mm vs. 1 mm: 0.40 (0.33-0.48)**

Model 2

- All patients within a given margin range were compared against all patients within other margin ranges
- 4 groups included 66% of all cases

Range	Margin range classifications
≤ 0 mm	≤ 0
0-2 mm	0-1, 1-2, 0-2
2-5 mm	2-5
>5 mm	>5

Results –Model 2

- Looking at range of margins, a wider margin further reduced local recurrence and was validated on MVA
- Margin range (negative/close) vs. Positive Margin
 - >0-2 mm: 7.2%, OR: 0.56 (0.49-0.63, $p < 0.001$)
 - 2-5 mm: 3.6%, OR: 0.44 (0.35-0.56, $p < 0.001$)
 - >5 mm: 3.2%, OR: 0.32 (0.26-0.41, $p < 0.001$)
- Multivariate Analysis: margin width only significant variable (larger margin, lower recurrence)

Conclusions

- Limitations of meta-analysis preclude definitive conclusion regarding appropriate margins
- However: data suggest having a margin width beyond no tumor on ink may further reduce rates of local recurrence
 - Consistent with DCIS margin analysis: 2 mm
- Further prospective studies required to validate appropriate margin width
- Question- Should we achieve a 1-2 mm margin (as compared to no tumor on ink)?
 - Potential local control benefit vs. morbidity, time, cost?
 - Which patients with 'no tumor on ink' need more surgery?



Main Interpretation Model 2

0-2 (7.2%)

2-5 (3.6%)

>5 (3.2%)



> 0-1

Referent



≤ 0

Crude Local Recurrence- Model 1

Negative vs close/positive

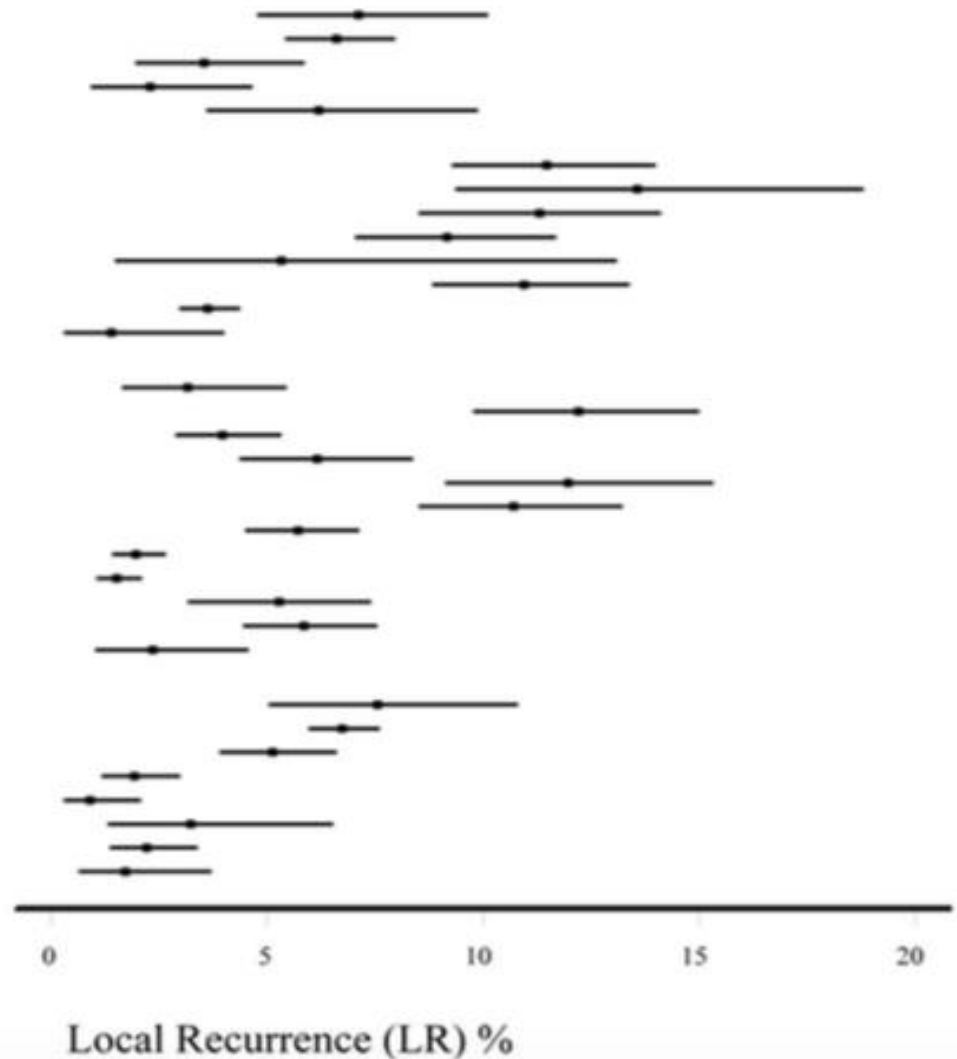
Margin (mm) and status	Number of studies providing data	Total number of observations	Total number of events	LR %
≤ 0	28	2988	352	10.3
> 0	38	33565	1758	3.8
≤ 1	29	5978	405	10.2
> 1	27	31757	1161	3.5
≤ 2	8	9781	519	8.7
> 2	38	19059	1053	3.3
≤ 3	8	659	659	6.7
> 3	8	19059	604	3.2

Major Methodological Problem

...to wider margins observed with greatest difference (benefit) seen at 1 mm (10.2%), but similar rates of recurrence with all negative margin definitions (3.2-3.8%)

Estimates with 95% confidence intervals

Study	Publication Year	Follow-up (months)	LR/N
Threshold distance: 0 mm			
Leong	2004	80	28/394
McBain	2003	77	102/1544
Pierce	1997	53	14/396
Burke	1995	50	7/306
Spivaack	1994	48	16/258
Threshold distance: 1 mm			
Kreike	2008	160	85/741
Bellon	2005	135	30/221
Park	2000	127	55/490
Voogd	2001	118	58/633
Varghese	2008	111	4/75
Mirza	2002	108	83/758
Livi	2007	89	104/2874
Whipp	2010	60	3/216
Threshold distance: 2 mm			
Obedian	1999	156	12/380
Santiago	2004	121	78/639
Demirci	2012	118	42/1057
Goldstein	2003	104	37/602
Touboul	1999	87	54/451
Groot	2011	86	75/701
Freedman	1999	76	72/1262
Livi	2013	62	41/2093
Lupe	2011	62	34/2253
Smitt	2003	60	22/425
Karasawa	2005	59	55/940
Kunos	2006	56	8/341
Threshold distance: 5 mm			
Neuschatz	2003	121	27/357
Ewertz	2008	102	246/3647
Perez	2003	79	56/1092
Kasumi	2006	78	19/987
Liau	2010	58	5/558
Horiguchi	2002	54	7/217
Kokubo	2000	52	20/906
Karasawa	2003	52	6/348



Probably, did not capture the full effect of improvements in systemic therapy

**Systemic Therapy
24%(CT) and 39% (ET)**

**Status HER2 ?
Molecular Subtype ?**

Better Systemic Therapy

Treatment	Relative risk of LRR
Tamoxifen ×5 years versus placebo	0.47
Anastrozole versus tamoxifen	0.83
Tamoxifen ×2 \Rightarrow anastrozole versus tamoxifen ×5	0.50
Chemotherapy versus none (<50 years)	0.63
Trastuzumab versus none	0.47

Biology

**Endocrine
Therapy**

**Target
Therapy**

Chemo

Radiation



Meta-analysis

Thank you

