IV ZOOM Journal Club 2014

Gruppo di Studio per la Patologia Mammaria

Bologna, 20 Febbraio 2015
Hotel NH De La Gare

I margini di resezione:

Impatto sulla gestione radioterapica

Rapporteur

Lorenza Marino

2.8.1 - Cenni di Anatomia Patologica

Poiché lo stato dei margini può influenzare la scelta terapeutica, ne è richiesta una precisa valutazione e una descrizione inequivocabile nella refertazione istologica:

2.8.1.1 Esame macroscopico

L'esame macroscopico deve produrre una descrizione, il più possibile dettagliata, del campione chirurgico pervenuto e delle modalità con cui viene campionato.

2.8.1.2 Valutazione microscopica

Margine positivo è indicato dalla presenza di china sulla lesione neoplastica invasiva e/o eventuale componente duttale in situ. Deve essere specificato:

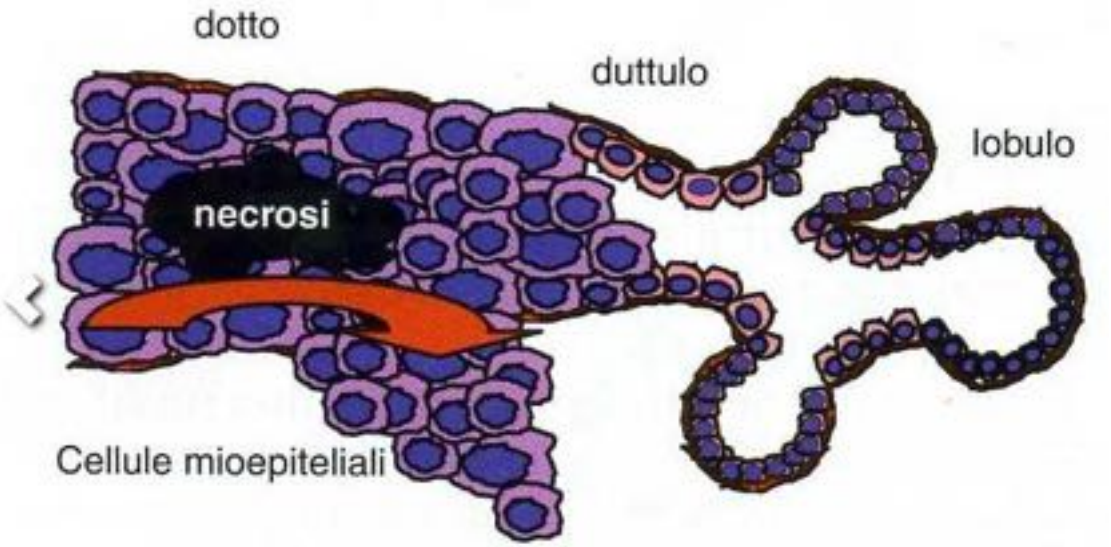
- di quale margine/i si tratta;
- se si tratta di un focolaio unico o multiplo di invasione;
- la dimensione dell'estensione lineare del coinvolgimento del margine/i espressa in mm;
- l'eventuale presenza di componente in situ sul margine.

?

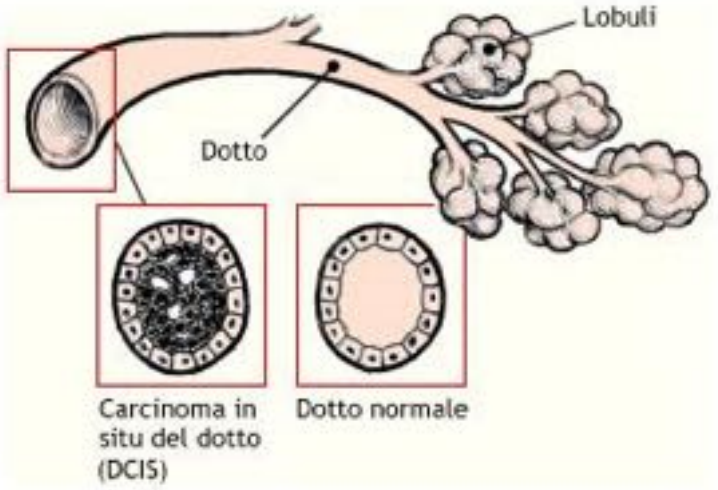
Margine/i indenne/i non si osserva china sulla lesione neoplastica invasiva e/o eventuale componente duttale in situ. Deve essere specificata la misura della distanza della lesione dai margini campionati macroscopicamente a meno di 1 cm (compresa la distanza dall'eventuale componente in situ).

I Margini……

Carcinoma Duttale Infiltrante/ Lobulare Infiltrante

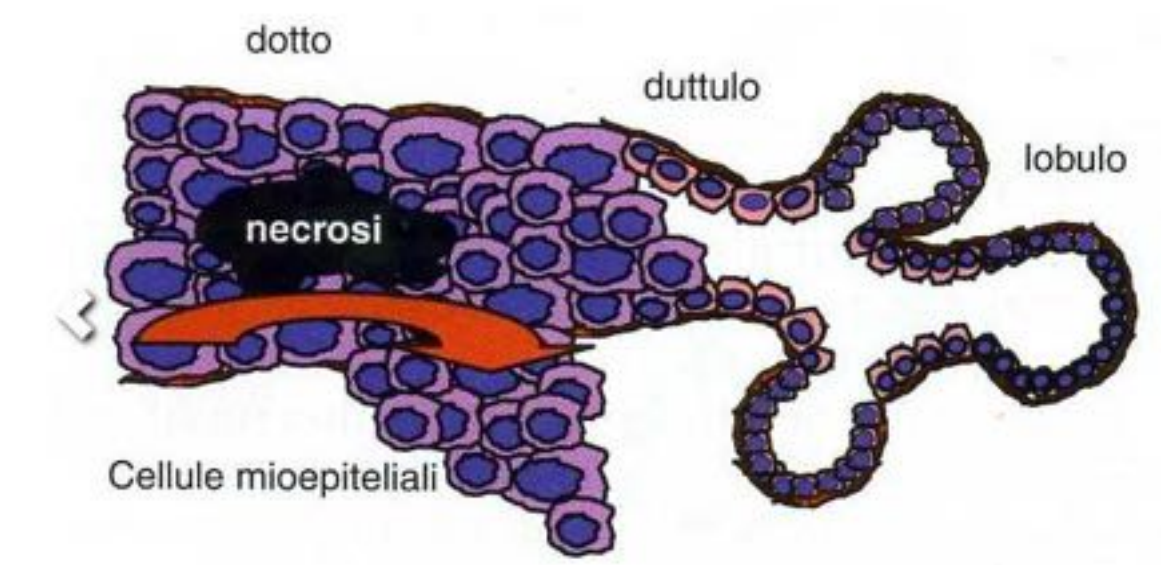


il **carcinoma duttale** in situ



I Margini……

Carcinoma Duttale Infiltrante/Lobulare Infiltrante



MARGIN STATUS IN INFILTRATING CARCINOMA

The use of breast-conserving therapy is predicated on achieving a pathologically negative margin of resection. Cases where there is a positive margin should generally undergo further surgery, either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible to allow for breast-conserving therapy, this can be done with resection of the involved margin guided by the orientation of the initial resection specimen or re-excision of the entire original excision cavity.

It may be reasonable to treat selected cases with breast-conserving therapy with a microscopically focally positive margin in the absence of an extensive intraductal component (EIC).[1] For these patients, the use of a higher radiation boost dose to the tumor bed should be considered.

Margins should be evaluated on all surgical specimens from breast-conserving surgery. Requirements for optimal margin evaluation include:

- Orientation of the surgical specimens
- Description of the gross and microscopic margin status
- Reporting of the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin

REVIEW ARTICLES

Journal of Surgical Oncology 2014;110:2–7

Margins in Breast Conservation: A Clinician's Perspective and What the Literature Tells Us

NEHMAT HOUSSAMI, MBBS, PhD[1,2] AND MONICA MORROW, MD[3,4]*

WHAT DOES A NEGATIVE MARGIN REALLY MEAN?

HOW REPRODUCIBLE IS MARGIN MEASUREMENT?

There is no standard method of margin evaluation. The method of evaluation used is often not specified in studies addressing the importance of margin width.

IS THERE A RELATIONSHIP BETWEEN MARGIN WIDTH AND LOCAL RECURRENCE?

Threshold distance (mm)	# of studies	# Subjects/# LR	OR, 95% CI
1	6	2376/235	1.0
2	10	8350/414	0.91, 0.46–1.80
5	3	2355/103	0.77, 0.32–1.88

from Houssami et al.Ann.Surg Onc 2014

REVIEW ARTICLES

Journal of Surgical Oncology 2014;110:2–7

Margins in Breast Conservation: A Clinician's Perspective and What the Literature Tells Us

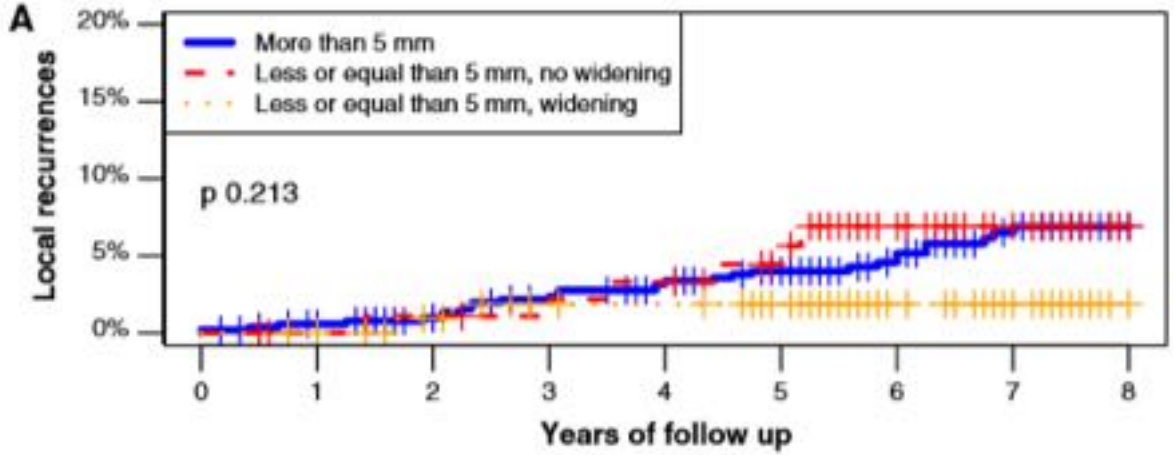
NEHMAT HOUSSAMI, MBBS, PhD[1,2] AND MONICA MORROW, MD[3,4]*

EFFECT OF SYSTEMIC THERAPY ON LOCAL RECURRENCE

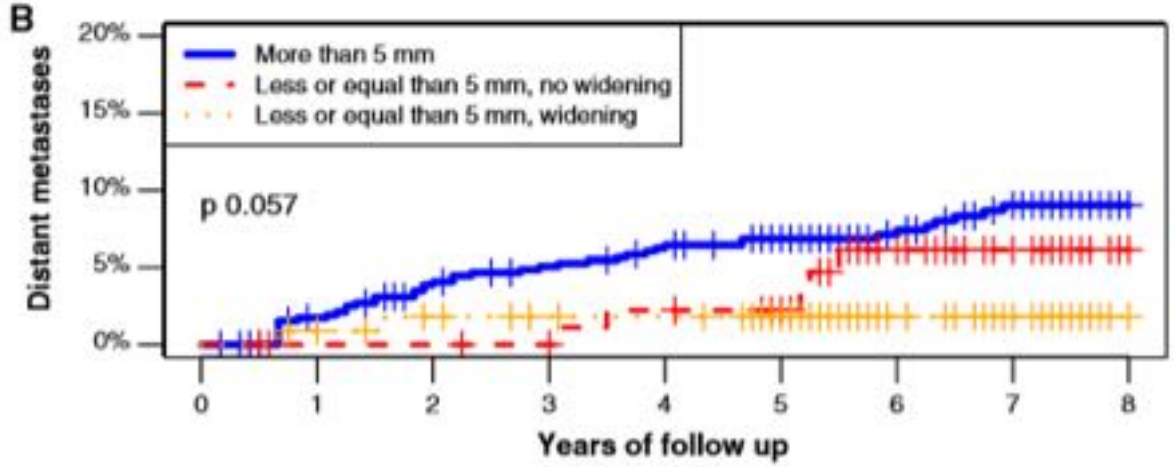
- ✓ the 10-year rate of LR was 8.7% with TAM *vs* 18.6% no TAM *(Lancet 2011;378:1707–1716)*
- ✓ IA or prolonged durations of TAM + IA: 20% to 50% reduction in the risk of LR compared to treatment with TAM alone (*Radiother Oncol 2009; 90:14–22.)*
- ✓ The use of anthracycline-based chemotherapy or CMF reduces the RR of LR 30% to 40% compared to no systemic therapy, and the addition of taxanes to anthracyclines results in a further reduction in LR . *(Lancet 2011;378:1707–1716; Radiother Oncol 2009; 90:14–22)*
- ✓ The use of adjuvant trastuzumab has a substantial impact on the risk of LR. *(Cancer 2012; 118:1982–1988; J Clin Oncol 2013;31:(suppl 26; abstr 61))*

World J Surg (2014) 38:2279–2287
DOI 10.1007/s00268-014-2596-x

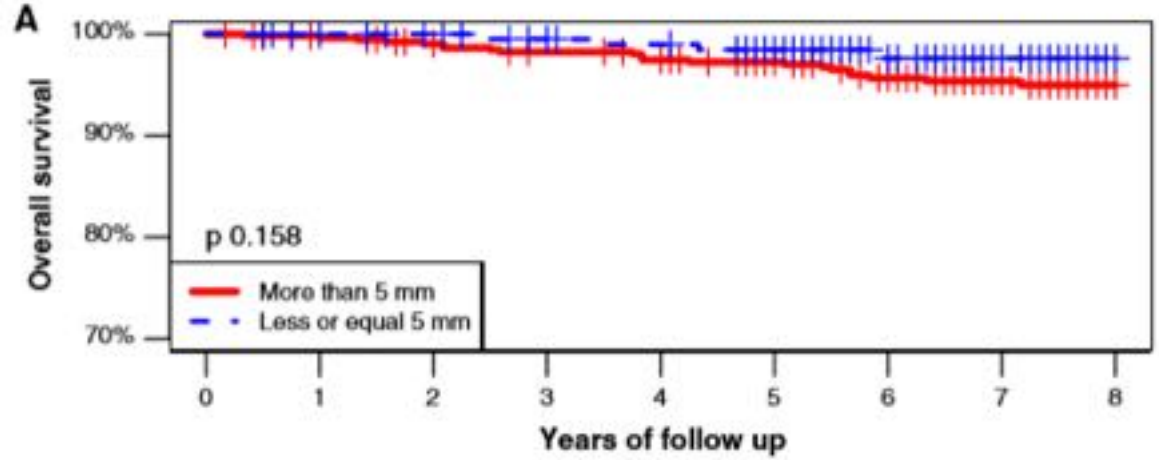
World Journal of Surgery



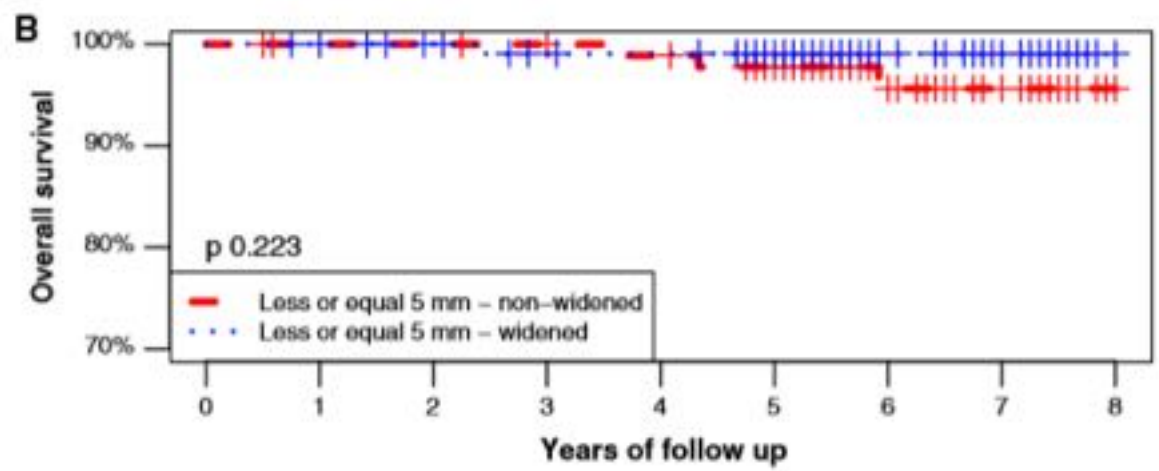
More than 5 mm	525	513	500	487	472	427	323	242	171
<5 mm, no widening	94	92	91	90	86	80	43	30	11
<5 mm, widening	112	111	106	101	100	92	68	56	39



More than 5 mm	525	508	490	479	465	425	328	246	175
<5 mm, no widening	94	92	92	91	88	84	45	31	12
<5 mm, widening	112	110	105	102	101	93	69	57	40



More than 5 mm	525	515	504	495	483	442	338	260	185
ss or equal 5 mm	206	203	199	194	191	177	114	88	52



Non-widened	94	92	92	91	89	83	45	31	12
Widened	112	111	107	103	102	94	69	57	40

	A, Total population		B, Patients without re-operation	
	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
Grading (G3)	2.32 (0.89–6.04)	0.085	2.09 (0.8–5.49)	0.135
Ki-67/Mib-1 >20	7.08 (2.08–24.07)	<0.05	6.96 (2.02–24.01)	<0.05
Triple negative cancer	1.88 (0.69–5.13)	0.219	1.9 (0.68–5.28)	0.219
Comedo-like necrosis	18.51 (3.34–102.6)	<0.05	15.89 (2.58–97.82)	<0.05
Multifocality	5.18 (1.53–17.58)	<0.05	5.8 (1.71–19.73)	<0.05
Extensive intra-ductal component	0.52 (0.15–1.84)	0.314	0.59 (0.16–2.16)	0.429
Peritumoral inflammation	2.17 (0.51–9.31)	0.297	2.49 (0.61–10.21)	0.205
Tumor size >2 cm	1.27 (0.47–3.46)	0.635	1.43 (0.51–3.98)	0.497
Axillary lymph node positivity	0.74 (0.27–2.02)	0.553	0.74 (0.26–2.05)	0.559
Non-axillary lymph node positivity	10.57 (2.24–49.9)	<0.05	5.61 (0.94–33.65)	0.059
Extracapsular invasion of lymph node metastasis	1.46 (0.28–7.59)	0.649	2.1 (0.39–11.37)	0.387
Margin status				
Positive margin	Reference	1.000	Reference	1.000
Free margin between 0 and ≤2 mm	0.88 (0.06–12.55)	0.928	0.55 (0.01–24.26)	0.759
Free margin between 2 and ≤5 mm	5.11 (0.59–44.54)	0.140	3.3 (0.1–104.62)	0.498
Free margin >5 mm	3.35 (0.59–18.99)	0.172	1.28 (0.06–29.05)	0.879

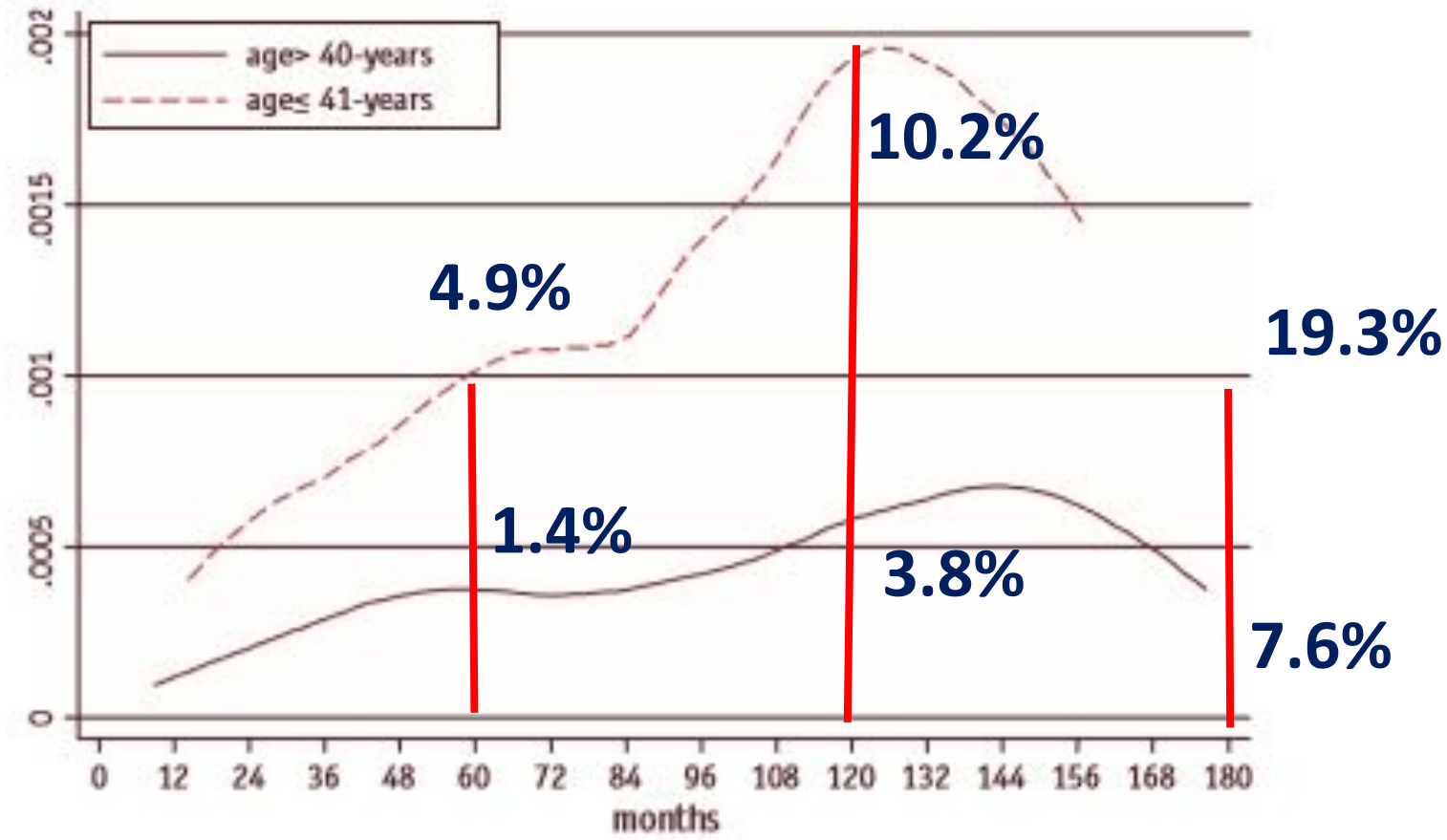
In summary, our findings showed that the status of resection margins and the management of infiltrated or narrow margins had no significant influence on local recurrence rate or on patient survival. Instead, factors linked to **the biological aggressiveness** of the tumor play the most important role in breast cancer prognosis, independent of the surgical radicality. In conclusion, our findings highlight a need for randomized clinical trials, where widening of the margin can be randomly performed to assess how they impact local recurrence.

Int J Radiation Oncol Biol Phys, Vol. 89, No. 5, pp. 1006e1014, 2014

Clinical Investigation

Pattern of Ipsilateral Breast Tumor Recurrence After Breast-Conserving Therapy

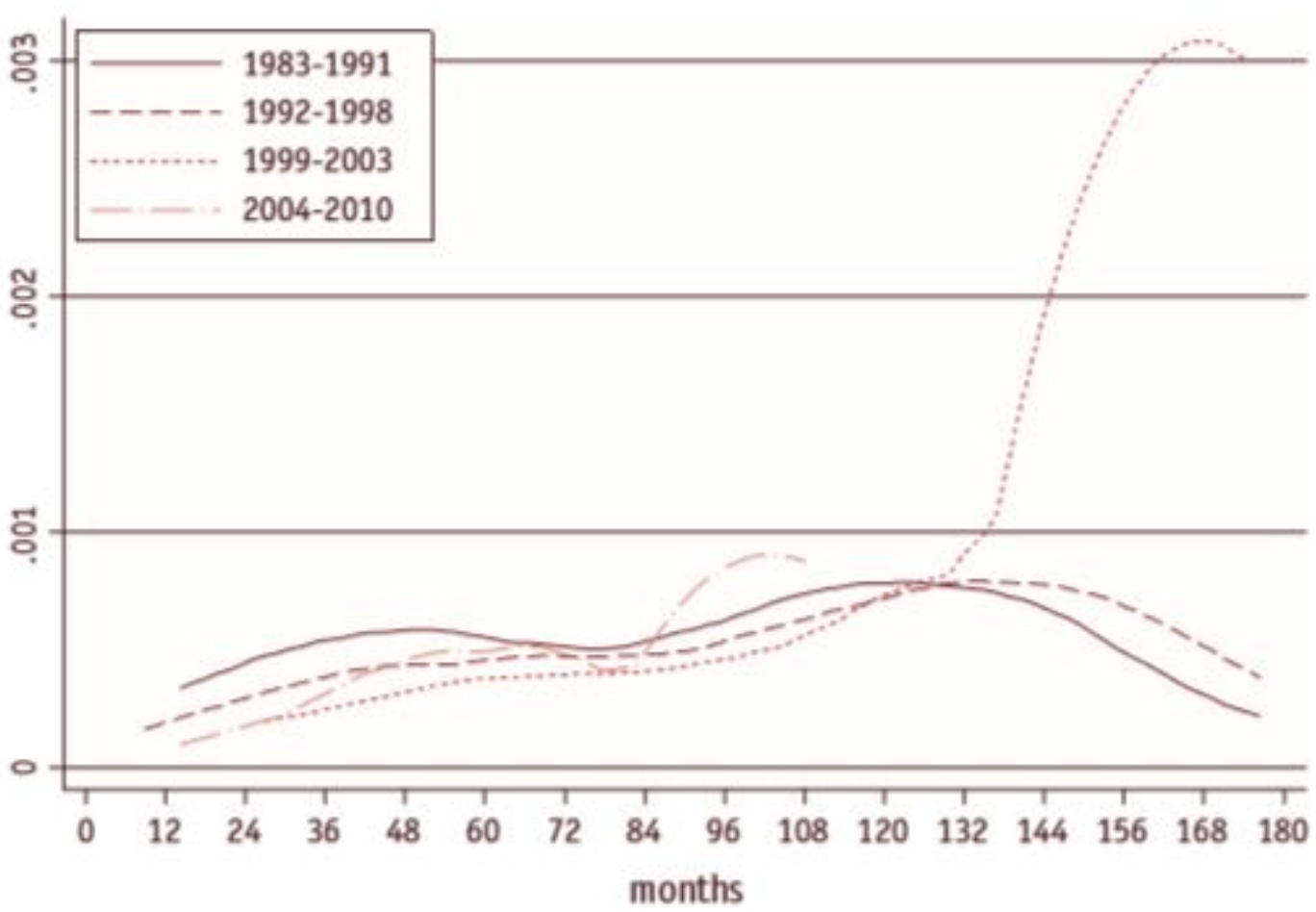
Jan Jobsen, PhD,* Job van der Palen, PhD,†,‡ Sietske Riemersma, PhD,§ Harald Heijmans, MD,‖ Francisca Ong, PhD,* and Henk Struikmans, PhD¶,#



Variable	Stratified by age		Stratified by age + negative margins	
	≤40 years old HR (95% CI)	>40 years old HR (95% CI)	≤40 years old HR (95% CI)	>40 years old HR (95% CI)
Lymph vascular space invasion				
Negative	1	1	1	1
Positive	2.4 (0.9-6.0)	2.1 (1.4-3.4)	3.1 (1.1-8.4)	2.4 (1.5-4.0)
Margin Status				
Negative	1			
Positive IC	5.0 (1.3-18.7)			
Positive DCIS				
Positive IC + DCIS				
Presence of CIS				
None		1		1
LCIS		2.2 (1.3-3.7)		2.4 (1.4-4.0)
DCIS				
Adjuvant systemic therapy				
None	1		1	
Yes	0.4 (0.2-0.8)		0.3 (0.1-0.7)	

Characteristic	1984-1991 (n=484) (%)	1992-1998 (n=1014) (%)	1999-2003 (n=975)	2004-2010 (n=1490)	*P* value*
Age (y)					
5 anni	**97%**	**98.6%**	**98.6%**	**98.4%**	
10 anni	**93.4%**	**96.5%**	**96.3%**	**94.2%**	
2	57 (11.8)	314 (			
3	97 (20.0)	192 (			
Unknown	294 (60.7)	350 (			
Lymph vascular space invasion					
Positive	41 (8.4)	116 (			
Negative	431 (89.1)	894 (			
Unknown	12 (2.5)	4 (			
Presence of CIS					
DCIS	122 (25.2)	241 (			
LCIS	17 (3.5)	60 (			
None	345 (71.3)	713 (			
Hormone receptor					
ERPR-positive	269 (55.6)	544 (			
ERPR-negative	55 (11.4)	164 (			
ER positive and PR negative	64 (13.2)	116 (			
ER negative and PR positive	11 (2.3)	37 (			
Unknown	85 (17.6)	153 (			
Margin Status					
Negative	427 (88.2)	860 (			
Positive IC	34 (7.0)	87 (			
Positive DCIS	13 (2.3)	50 (			
Positive IC + DCIS	10 (2.1)	17 (			

LRFS



Journal of Breast Cancer
J Breast Cancer 2014 December; 17(4): 301-307 http://dx.doi.org/10.4048/jbc.2014.17.4.301
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REVIEW ARTICLE

Unique Features of Young Age Breast Cancer and Its Management

Han-Byoel Lee[1], Wonshik Han[1,2]

US: 11.000 women < 40 years/ann.
Western: <4% breast cancer < 35 years

The relative risk of locoregional recurrence was found to increase 7% for every 1-year decrease in age.

Younger patients with resection margins ≤2 mm had a local failure rate of 19%, whereas those with wider margins had a local failure rate of 7%.

IBTR after BCT is significantly more frequent. Although total mastectomy is not mandatory, securing a sufficiently wide resection margin is required for lumpectomy, and boost radiotherapy should be considered in local treatment of YABC.

Considerations	Unique features
Biological characteristics	Higher proliferation rates (Ki-67), more grades 3/4 & higher ER negativity [9-13] More BRCA1/2 mutations [22-32]
Diagnostic delay	More advanced stage at presentation [33-35]
Prognosis	Worse in ER-positive breast cancer [14,40-42] 5% increased risk of death/1-year reduction in age [7]
Local therapy	More IBTR [43-47] Higher importance of sufficient resection margins [52] Boost radiotherapy should be considered [47]
Adjuvant chemotherapy	Less chemotherapy-induced amenorrhea [41-42] Greater benefits from chemotherapy [58-59]
Adjuvant hormonal therapy	Tamoxifen resistance [14]
Others	Premature ovarian failure and infertility [66-69] More emotional distress and poorer quality of life [72,73]

Int J Radiation Oncol Biol Phys, Vol. 88, No. 1, pp. 57e64, 2014

Is Biological Subtype Prognostic of Locoregional Recurrence Risk in Women With pT1-2N0 Breast Cancer Treated With Mastectomy?

Pauline T. Truong, MDCM,*,† Betro T. Sadek, MD,† Maria F. Lesperance, BSc,* Cheryl S. Alexander, CHIM,† Mina Shenouda, MD,† Rita Abi Raad, MD,† and Alphonse G. Taghian, MD, PhD†

Characteristic	Hazard ratio	95% Confidence interval	P
Institution (BCCA vs MGH)	1.19	0.47-3.00	.71
Age at diagnosis (>50 vs ≤50 years)	0.74	0.35-1.60	.45
Histology (lobular/others vs ductal)	3.48	1.51-8.02	.003
Tumor size (>2 cm vs ≤2 cm)	2.57	1.23-5.35	.012
Tumor grade (2-3 vs 1)	1.47	0.17-12.56	.72
Lymphovascular invasion (present vs absent)	1.84	0.77-4.40	.17
Margins (close/positive vs negative)	3.42	1.36-8.55	.009
No. of excised nodes (<10 vs ≥10)	0.83	0.40-1.71	.61
Systemic therapy (no vs yes)	1.51	0.59-3.85	.39
Subtype			.89
(Luminal B vs luminal A)	1.05	0.10-10.63	.97
(Luminal HER 2 vs luminal A)	0.46	0.05-4.37	.50
(HER 2 vs luminal A)	0.94	0.08-10.53	.96
(Triple-negative vs luminal A)	0.86	0.09-8.20	.45

Margins						.78
Negative	1.7 (19)	2.3 (5)	1.1 (1)	2.2 (2)	1.3 (2)	
Close/positive	3.0 (2)	13.4 (2)	6.2 (1)	0	12.5 (1)	
No. of excised nodes						.81
<10	1.9 (13)	2.7 (4)	1.1 (1)	1.7 (1)	0	
≥10	1.8 (8)	3.6 (3)	2.1 (1)	2.3 (1)	4.1 (3)	
Systemic therapy use						.80
Yes	1.9 (19)	2.8 (6)	0.8 (1)	1.3 (1)	1.0 (1)	
No	1.5 (2)	5.9 (1)	5.0 (1)	3.7 (1)	3.5 (2)	

Clinical Investigation: Breast Cancer

Is Biological Subtype Prognostic of Locoregional Recurrence Risk in Women With pT1-2N0 Breast Cancer Treated With Mastectomy?

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Conclusion

The 5-year risk of locoregional recurrence in our current cohort of women with pT1-2N0 breast cancer treated with mastectomy was low, with no significant differences observed between approximated subtypes. Among women with TNBC, the presence of positive or close margins correlated with an increased risk of postmastectomy LRR. Our data suggest that although subtype alone cannot be used as the sole criterion for offering PMRT, it may reasonably considered in conjunction with other clinicopathologic factors such as tumor size, histology and margin status. Larger cohorts and longer follow-up times are needed to define which women with node-negative breast cancer have high postmastectomy LRR risks in contemporary practice.

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DOI 10.1245/s10434-013-3416-5

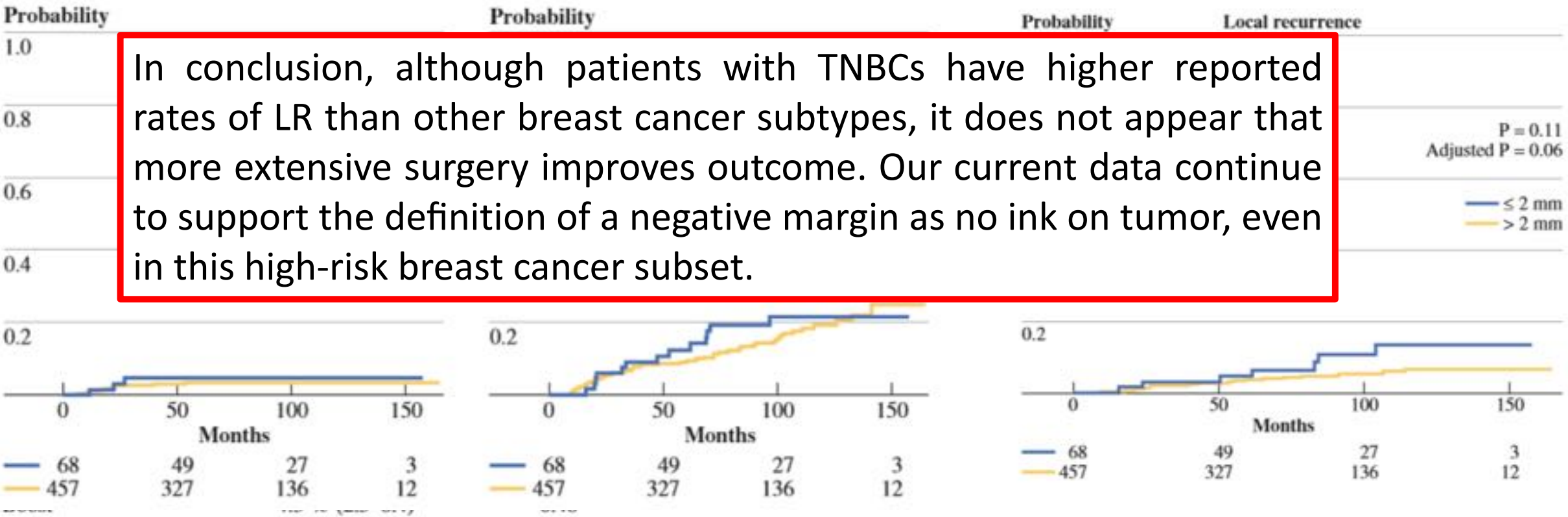
Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Effect of Margin Width on Local Recurrence in Triple-Negative Breast Cancer Patients Treated with Breast-Conserving Therapy

Melissa Pilewskie, MD[1], Alice Ho, MD[2], Emily Orell, BS[1], Michelle Stempel, MPH[1], Yu Chen, BS[3], Anne Eaton, MS[4], Sujata Patil, PhD[4], and Monica Morrow, MD[1]

In conclusion, although patients with TNBCs have higher reported rates of LR than other breast cancer subtypes, it does not appear that more extensive surgery improves outcome. Our current data continue to support the definition of a negative margin as no ink on tumor, even in this high-risk breast cancer subset.



No boost 3.4 % (0–10.2)

Role of re-excision for positive and close resection margins in patients treated with breast-conserving surgery

N. Biglia [a,*], R. Ponzone [b], V.E. Bounous [a], L.L. Mariani [a], F. Maggiorotto [b], C. E
V. Liberale [a], M.C. Ottino [a], P. Sismondi [a]

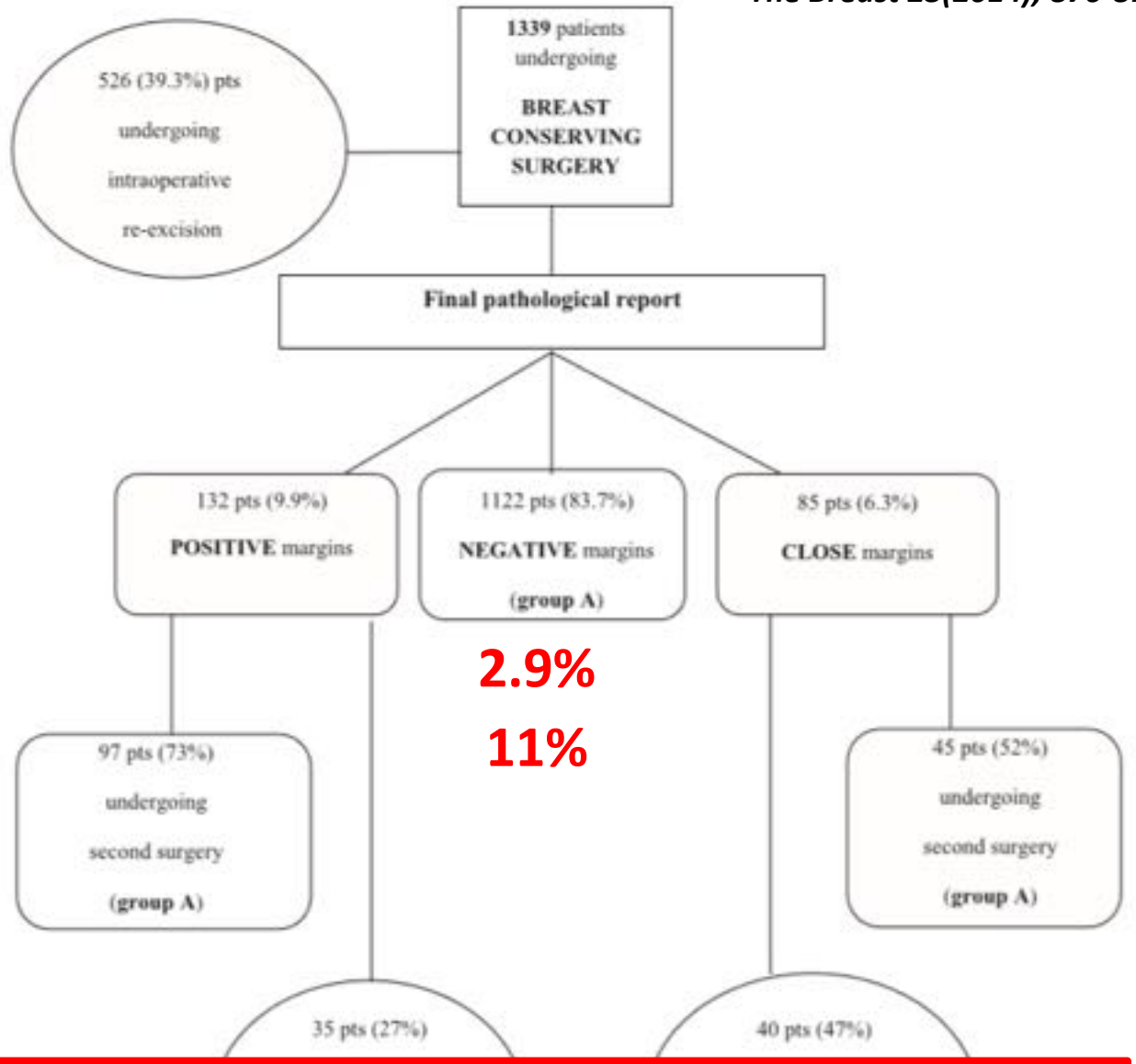
The Breast 23(2014), 870-875

Median LRFS was 10 years / DRFS was 9.14 years

Median LRFS was 7.8 years / DRFS was 7.35 years

Median LRFS was 7.5 years / DRFS was 8 years

After second surgery, residual disease was found in 62.9% of patients with positive margins and in 55.5% of those with close margins.



Conclusions: A significantly higher LR rate was found only among patients with positive margins not receiving additional surgery, but not in those with unresected close margins. Positive margins are a strong predictor for LR and need re-excision that can be avoided for close margins.

Table 1. Summary of SSO/ASTRO Clinical Practice Guideline Recommendations

Clinical Question	Recommendation	Level of Evidence
What is the absolute increase in risk of IBTR with a positive margin? Can the use of radiation boost, systemic therapy, or favorable tumor biology mitigate this increased risk?	A positive margin, defined as ink on invasive cancer or DCIS, is associated with at least a two-fold increase in IBTR; this increased risk in IBTR is not nullified by delivery of a boost, delivery of systemic therapy (endocrine, chemotherapy, biologic therapy), or favorable biology	Meta-analysis, secondary data from prospective trials and retrospective studies
Do margin widths wider than no ink on tumor cells reduce the risk of IBTR?	Negative margins (no ink on tumor) optimize IBTR; wider margin widths do not significantly lower this risk; the routine practice to obtain wider negative margin widths than ink on tumor is not indicated	Meta-analysis, retrospective studies
What are the effects of endocrine or biologically targeted or systemic chemotherapy on IBTR? Should a patient who is not receiving any systemic treatment have wider margin widths?	Rates of IBTR are reduced with the use of systemic therapy; in the uncommon circumstance of a patient not receiving adjuvant systemic therapy, there is no evidence suggesting that margins wider than no ink on tumor are needed	Multiple randomized trials, meta-analysis
Should unfavorable biologic subtypes (such as triple-negative breast cancers) require wider margins (than no ink on tumor)?	Margins wider than no ink on tumor are not indicated based on biologic subtype	Multiple retrospective studies
Should margin width be taken into consideration when determining WBRT delivery techniques?	Choice of WBRT delivery technique, fractionation, and boost dose should not be dependent on the margin width	Retrospective studies
Is the presence of LCIS at the margin an indication for re-excision? Do invasive lobular carcinomas require a wider margin (than no ink on tumor)? What is the significance of pleomorphic LCIS at the margin?	Wider negative margins than no ink on tumor are not indicated for invasive lobular cancer; classic LCIS at the margin is not an indication for re-excision; significance of pleomorphic LCIS at the margin is uncertain	Retrospective studies
Should increased margin widths (wider than no ink on tumor) be considered for patients of young age (< 40 years)?	Young age (≤ 40 years) is associated with both increased IBTR after BCT as well as increased local relapse on the chest wall after mastectomy and is also more frequently associated with adverse biologic and pathologic features; there is no evidence that increased margin width nullifies the increased risk of IBTR in young patients	Secondary data from prospective randomized trials and retrospective studies
What is the significance of an EIC in the tumor specimen, and how does this pertain to margin width?	EIC identifies cases that may have a large residual DCIS burden after lumpectomy; there is no evidence of an association between increased risk of IBTR when margins are negative	Retrospective studies

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DOI 10.1245/s10434-014-3480-5

Annals of SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GUIDELINE AND META-ANALYSIS

The Association of Surgical Margins and Local Recurrence in Women with Early-Stage Invasive Breast Cancer Treated with Breast-Conserving Therapy: A Meta-Analysis

Nehmat Houssami, MD, PhD[1], Petra Macaskill, PhD[1], M. Luke Marinovich, MPH[1], and Monica Morrow, MD[2]

TABLE 3 Model 1—estimating the effect of surgical margins on LR in invasive breast cancer adjusted for covariates (covariates examined in model 1 were selected using criteria described in "Statistical Analysis" section)

Covariate (covariate definition and categories described in "Methods" section)	No. of studies	*P* for association of covariate with LR: Unadjusted	*P* for association of covariate with LR: Adjusted for margins & follow-up time	Margin status (adjusted OR): Negative	Margin status (adjusted OR): Positive/close	Threshold distance for negative margins (adjusted OR): >0 mm	Threshold distance for negative margins (adjusted OR): 1 mm	Threshold distance for negative margins (adjusted OR): 2 mm	Threshold distance for negative margins (adjusted OR): 5 mm	*P* for association [*P* for trend] for margin distance: Adjusted for covariate
Effect of margins (adjusted for follow-up time)	33			1.0	1.96**	1.47	1.0	0.95	0.65	0.12 [0.21]
Age	32	0.11	0.089	1.0	1.91**	1.56	1.0	1.13	0.72	0.12 [0.29]
Median-year of study recruitment	33	<0.0001	0.0086	1.0	1.96**	1.47	1.0	0.95	0.65	0.26 [0.14]
Proportion had endocrine therapy	27	<0.0001	0.0011	1.0	2.07**	1.11	1.0	0.91	0.77	0.19 [0.32]
Proportion ER-positive	24	0.012	0.023	1.0	2.26**	0.87	1.0	0.98	0.56	0.44 [0.25]
Proportion had reexcision[a]	17	0.032	0.088	1.0	2.06**	1.41	1.0	0.82	0.52	0.22 [0.13]
LR type (first vs. any)[b]	33	0.12	0.058	1.0	1.96**	1.11	1.0	0.83	0.51	0.063 [0.074]

TABLE 4 Model 2—estimating the effect of surgical margins on LR in invasive breast cancer adjusted for covariates (covariates examined in model 2 were selected using criteria described in "Statistical Analysis" section)

Covariate (covariate definition and categories described in "Methods" section)	No. of studies	*P* for association of covariate with LR: Unadjusted	*P* for association of covariate with LR: Adjusted for margins and follow-up time	Margin status (adjusted OR): Negative	Margin status (adjusted OR): Close	Margin status (adjusted OR): Positive	Threshold distance for negative margins (adjusted OR): 1 mm	Threshold distance for negative margins (adjusted OR): 2 mm	Threshold distance for negative margins (adjusted OR): 5 mm	*P* for association [*P* for trend] for margin distance: Adjusted for covariate
Effect of margins (adjusted for follow-up time)	19	–	–	1.0	1.74**	2.44**	1.0	0.91	0.77	0.53 [0.58]
Age	18	0.089	0.11	1.0	1.68**	2.35**	1.0	1.12	0.94	0.86 [0.58]
Median-year of study recruitment	19	0.0013	0.0055	1.0	1.76**	2.45**	1.0	0.83	0.57	0.32 [0.14]
Proportion had endocrine therapy	16	0.0003	0.012	1.0	1.77**	2.53**	1.0	0.98	0.90	0.95 [0.75]
Proportion had radiation boost	18	0.015	0.34	1.0	1.75**	2.45**	1.0	0.82	0.92	0.86 [0.75]
Proportion ER-positive	15	0.036	0.078	1.0	1.92**	2.66**	1.0	1.08	0.63	0.67 [0.34]
Proportion had re-excision[a]	11	0.0017	0.0029	1.0	1.97**	2.84**	1.0	0.85	0.69	0.64 [0.34]
LR type (first vs. any)	19	0.46	0.19	1.0	1.74**	2.44**	1.0	0.85	0.65	0.67 [0.34]

We found little to no evidence of association between margin distance and the odds of LR, and there was little to no evidence that the odds of LR decreased as the distance for declaring negative margins across studies increased.

Therefore, we conclude that the prognostic value of the status of surgical margins (positive vs. negative) in BCT is not diminished by temporal declines in LR rates, and obtaining negative margins remains relevant to current oncologic practice.

Impact of margin width on IBTR adjusted for individual covariates and follow-up

Covariate	No. of studies	Threshold distance negative margin: adjusted OR (mm)			*P* (association)
		1	2	5	
Age	18	1.0	0.53	0.77	0.53
Endocrine therapy	16	1.0	0.95	0.90	0.95
Radiation boost	18	1.0	0.86	0.92	0.86

than that seen with negative margins.[16,17] Although various other treatment modalities, including use of a boost dose of radiation and adjuvant systemic therapy with endocrine therapy, chemotherapy, or biologically targeted agents, have all demonstrated a favorable impact on IBTR (see below), adjustment for the covariates of endocrine therapy or use of a boost dose of radiation did not nullify the increased risk of IBTR seen with a positive margin in the meta-analysis. In the 18 studies reporting information

Boost:

- ✓ IBTR con marg+ (OR 2.45; P< 0.001)
- ✓ WBRT+ 16 Gy dopo rimozione completa mic:
  - IBTR a 10 anni *(6.2% vs 10.2%* no boost).*(EORTC; JCO 2007)*
  - IBTR a 10 anni dopo marg+: 17.5% con 10 Gy; 10.8% con 26Gy *(Jones HA, JCO 2009)*

These data suggest that although a boost provides a degree of reduction in IBTR when margins are microscopically positive, the absolute benefit is not sufficient to reduce the rate of IBTR to that seen with negative margins and the use of a boost.

Radiation Therapy Delivery

The choice of WBRT delivery technique, fractionation, and boost dose should not be dependent on margin width.

- ✓ **Hypofractionated**: there is no evidence to suggest that margin width should dictate patient selection for these therapies.
- ✓ There was no clear reduction in IBTR as a result of escalating the radiation dose when margin widths are smaller.

In summary, margin width should not be used to determine the delivery technique or fractionation for WBRT or vice versa. Furthermore, in patients with negative margins (no ink on tumor), the use and dose of a tumor bed boost should be based on a priori estimation of local failure risk and should not be determined, in isolation, by the width of the surgical margin.

THE BOTTOM LINE

ASCO GUIDELINE UPDATE

What Margin Width Minimizes the Risk of Ipsilateral Breast Tumor Recurrence?

Target Population

- Patients with stage I and II breast cancer. The guideline pertains to patients with invasive breast cancer who have undergone whole-breast irradiation.

Target Audience

- Radiation oncologists, pathologists, surgeons, medical oncologists oncology nurses, and patients/caregivers.

Recommendations

- The SSO/ASTRO guideline concluded that the use of no ink on tumor (ie, no cancer cells adjacent to any inked edge/surface of the specimen) as the standard for an adequate margin in invasive cancer in the era of multidisciplinary therapy is associated with low rates of ipsilateral breast tumor recurrence and has the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease health care costs.

Qualifying Statements

- The ASCO panel reinforces and amplifies the guideline authors' call for the monitoring of outcomes of the guideline at the institutional level, as institutions transition to adopting the SSO/ASTRO recommendations; would place greater emphasis on the importance of postlumpectomy mammography for cases involving microcalcifications; and calls for flexibility in the application of the guideline in light of the generally weak evidence supporting the recommendations.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

Ann Surg Oncol (2014) 21:1512–1514
DOI 10.1245/s10434-014-3605-x

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EDITORIAL – BREAST ONCOLOGY

Cost Implications of the SSO-ASTRO Consensus Guideline on Margins for Breast-Conserving Surgery with Whole Breast Irradiation in Stage I and II Invasive Breast Cancer

Rachel A. Greenup, MD, MPH[1], Jeffrey Peppercorn, MD, MPH[2], Mathias Worni, MD, MHS[1], and E. Shelley Hwang, MD, MPH[1]

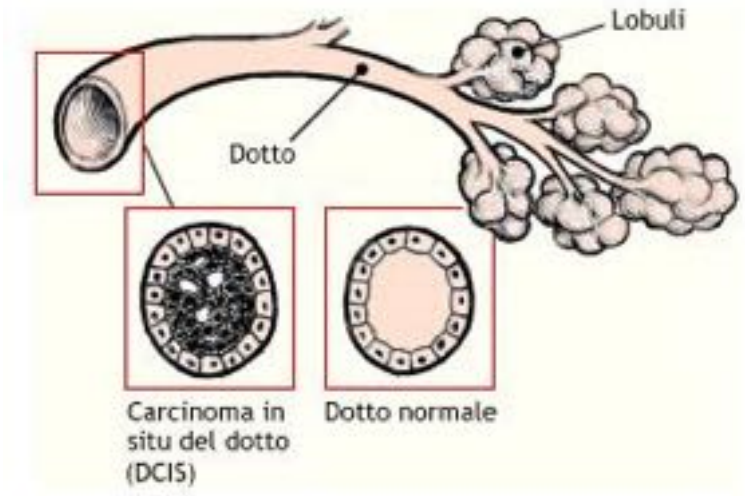
high-quality, evidence-based medicine. Small changes in clinical practice have the potential to yield significant changes in cumulative spending across the wider health care system.[34,35] Certainly, omitting unnecessary surgery without proven benefit is an important and impactful step.

Negative margins
«no tumor on ink»

- ✓ 46% of North American
- ✓ 3% (*Survey of surgeons 2010)*

I Margini……

il **carcinoma duttale** in situ



NCCN Guidelines Version 3.2014
Ductal Carcinoma in Situ

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

MARGIN STATUS IN DCIS

Substantial controversy exists regarding the definition of a negative pathologic margin in DCIS. Controversy arises out of the heterogeneity of the disease, difficulties in distinguishing the spectrum of hyperplastic conditions, anatomic considerations of the location of the margin, and inadequate prospective data on prognostic factors in DCIS.

Margins greater than 10 mm are widely accepted as negative (but may be excessive and may lead to a less optimal cosmetic outcome).

Margins less than 1 mm are considered inadequate.

With pathologic margins between 1-10 mm, wider margins are generally associated with lower local recurrence rates. However, close surgical margins (<1 mm) at the fibroglandular boundary of the breast (chest wall or skin) do not mandate surgical re-excision but can be an indication for higher boost dose radiation to the involved lumpectomy site (category 2B).

Radiotherapy and Oncology 112 (2014) 1–8

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Review

Radiotherapy in DCIS, an underestimated benefit?

Bruno Cutuli [a,*], Jacques Bernier [b], Philip Poortmans [c]

Author	Ref.	Period	*n*	FU [months]	LR %	Invasive LR %	CBC %
Halasz (2011)	[28]	2001–07	246	58	0	0	3
Alvarado (2012)	[14]	1996–07	977	62	2.4	NR	4
Falk (2011)	[29]	1993–07	870	120	3.6	NR	NR
Tunon (2011)	[30]	1971–01	232	120	10.8[1]	NR	NR
Rakovitch (2013)	[25]	1994–03	1895	120	12.3	48	5.1
Vidali (2012)	[31]	1985–00	586	136	10	63	6.8
Shaitelman (2012)	[32]	1980–93	145	228	17.5	76	15

Margins

Solin L., IJROBP 2001	LR negative 9% *vs* 24% positive margin
Cutuli B., IJROBP 2002	LR negative 10% *vs* 25% positive margin
Monteau A., IJROBP 2009	Close margin (< 2 mm): Boost 16 Gy LR 9.3% with 89-month FUP
Dunne C., JCO 2009	LR odd-ratios were 2.56 ($p<0.05$) for a minimally negative margin; 2.89 ($p<0.05$) ≥1mm margin; 1.51 (p=NS) ≥2mm margin
Wang SY, J NatlCancer Inst 2012	Local excision+/-RT showed a progressive reduction of LR with progressive increments in margin width of 2, 5 and 10 mm.

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Boost after WBI

but with a maximum impact in women under 40 [78]. For DCIS, a retrospective multicentric study showed in women under 45 with a 72-month follow-up a 54% LR rate after BCS only, 28% after BCS + WBI, and 16% for WBI with additional boost, respectively [51]. In other retrospective reports, the boost rates were extremely

LR rate at 10 years. In a study from Florence [80], no positive impact of boost was found, but with significantly unfavourable factors (margins < 4 mm and high VNPI) in patients treated with boost. On the contrary, another two recent studies from Boston

Features	No Pts at diagnosis	No LR	*p*-value	HR (95% CI)
Surgical margins, mm				
≥10	298	21		1
1–9	71	2		0.45 (0.10–1.95)
<1	20	3	**<0.0001**	**12.1 (3.49–42.14)**

Facts Views Vis Obgyn, 2014, 6 (4): 210-218

Review

Current view on ductal carcinoma in situ and importance of the margin thresholds: A review

A. Van Cleef[1], S. Altintas[2], M. Huizing[2], K. Papadimitriou[2], P. Van Dam[2], W. Tjalma[2]

The margin status seems to be the most important factor to predict ipsilateral recurrence. There is no consensus about the optimal surgical margin in patients receiving breast conserving surgery with or without postoperative radiation therapy.

Treatment	Positive margin, mean (95% CI)	Margin threshold			
		0 mm, mean (95% CI)	2 mm, mean (95% CI)	5 mm, mean (95% CI)	10 mm, mean (95% CI)
BCS plus RT	20% (16 to 24), N = 698	10% (8 to 13), N = 2057	9% (6 to 11), N = 742	11% (1 to 20), N = 23	4% (3 to 6), N = 86
BCS alone	35% (29 to 41), N = 423	20% (16 to 23), N = 1262	17% (12 to 22), N = 163	20% (3 to 36), N = 10	9% (5 to 12), N = 421

Wang, J Natl Cancer Inst 2012;104:507–516

The effect of re-excision vs radiation therapy on margin width and thus local recurrence

- ✓ When margins are positive or narrow, a re-excision that results in wider margins can theoretically decrease the risk of ipsilateral recurrence.
- ✓ From a critical point of view inadequate surgery cannot be replaced by radiotherapy

Close margins after mastectomy

- ✓ The incidence of local recurrence in patients with close margins is clearly elevated
- ✓ Excision and radiotherapy is successful in 90% of the patients developing local recurrence after being treated with mastectomy for DCIS (Kim et al., 2006).

FACTS VIEWS VIS OBGYN, 2014, 6 (4): 210-218

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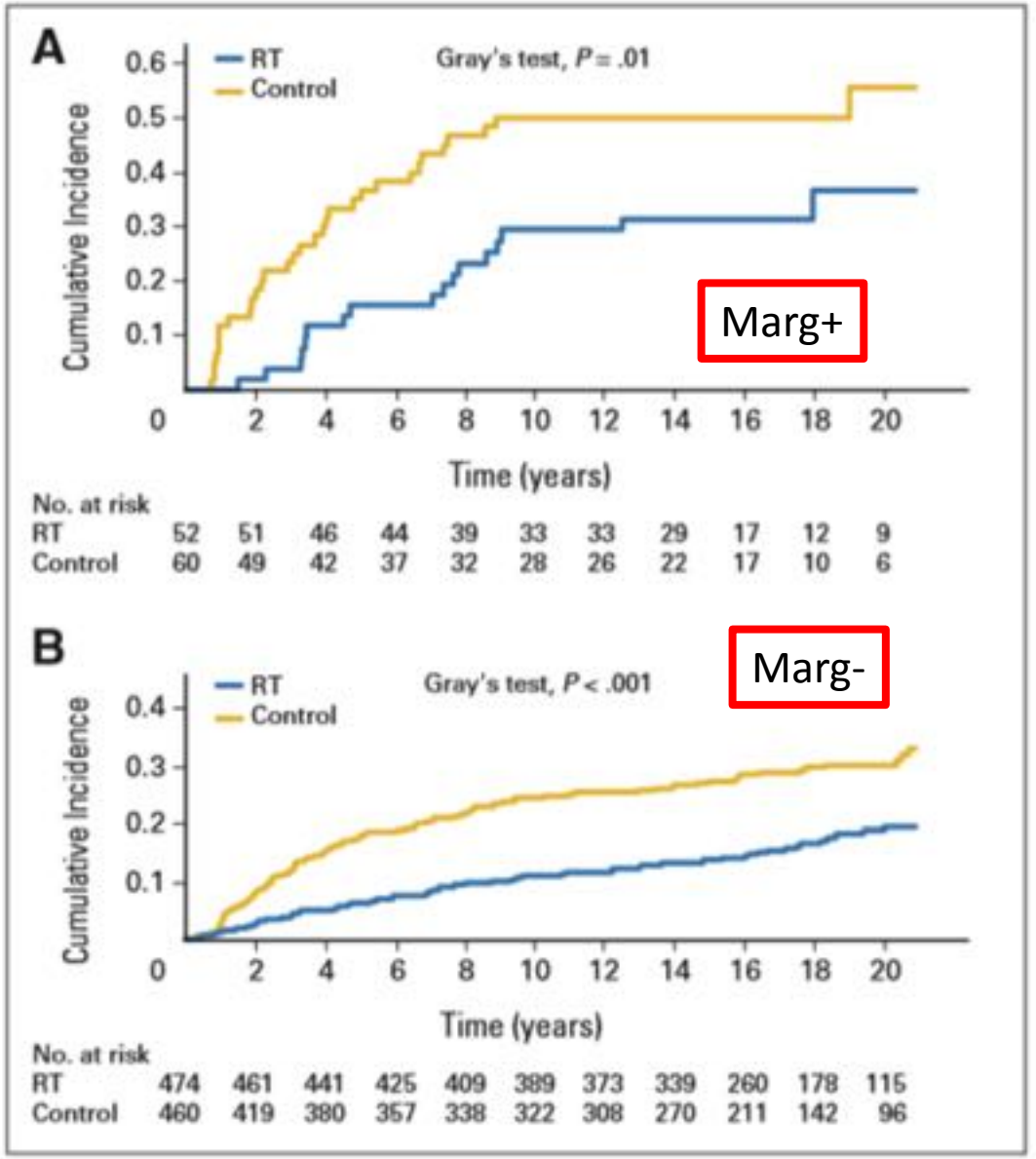
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Effect of Radiotherapy After Breast-Conserving Surgery for Ductal Carcinoma in Situ: 20 Years Follow-Up in the Randomized SweDCIS Trial

Fredrik Wärnberg, Hans Garmo, Stefan Emdin, Veronica Hedberg, Linda Adwall, Kerstin Sandelin, Anita Ringberg, Per Karlsson, Lars-Gunnar Arnesson, Harald Anderson, Karin Jirström, and Lars Holmberg

Characteristic	BCS Plus RT Arm (n = 526) No.	%	Control Arm (n = 520) No.	%
Follow-up time, years				
Median	17.4		17.5	
25th to 75th percentile	14.7-20.5		14.7-20.5	
Clear margins				
Yes	426	81.0	414	79.6
No	52	9.9	60	11.5
Unknown/missing	48	9.1	46	8.8



Clear margins were statistically significantly related to better prognosis regarding IBEs; this was true for both in situ and invasive IBEs. Also, the effect of RT was similar in women with clear margins and those without. BCSD and OS were not affected by margin status in either the RT or control arm.

Attenzione a tirare la coperta…
lasciamola agganciata a dei punti ben saldi

GRAZIE