MARGINI DI RESEZIONE: IMPATTO SULLA GESTIONE CHIRURGICA E RADIOTERAPICA

S.Giudici

Struttura complessa di Radioterapia

Ospedale di Sanremo

“E’ rimarchevole il fatto che più di 25 anni dopo la dimostrazione che la sopravvivenza dopo chirurgia conservativa della mammella, seguita da radioterapia, è equivalente alla sopravvivenza dopo mastectomia, non ci sia ancora consenso su cosa costituisca un margine negativo adeguato“

N.Houssami, Ann Surg Oncol 2014

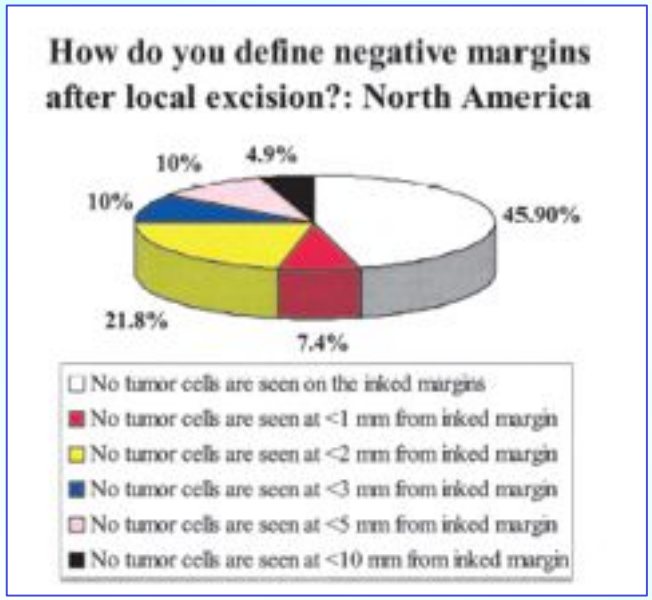
Current Perceptions Regarding Surgical Margin Status After Breast-Conserving Therapy

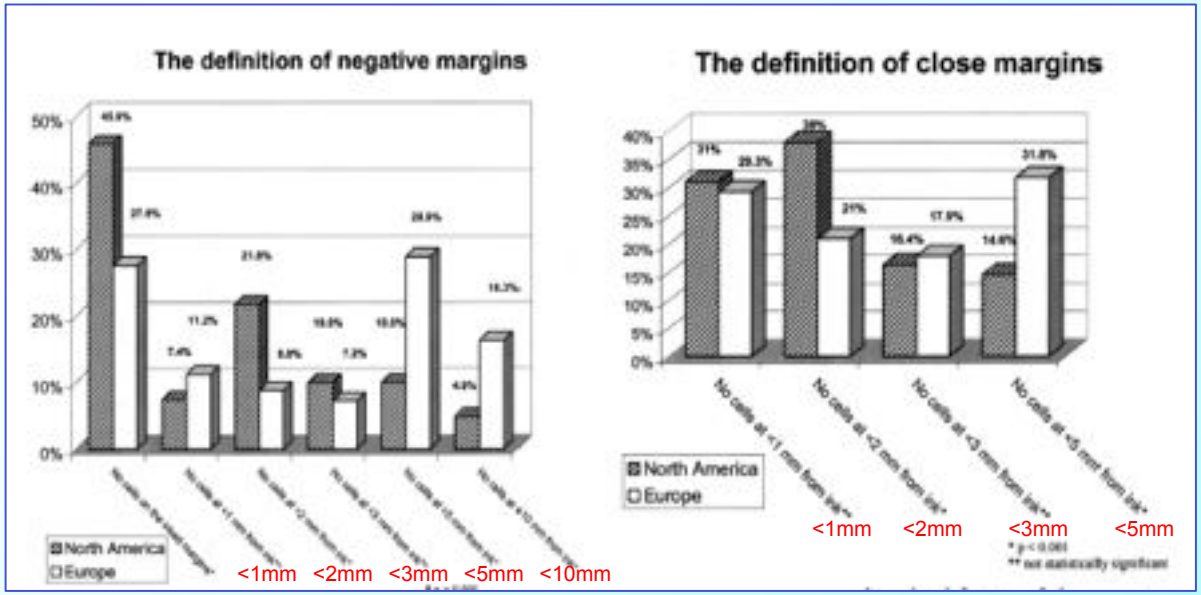
Results of a Survey

Alphonse Taghian, MD, PhD, Majid Mohiuddin, MD, Reshma Jagsi, MD, DPhil, Saveli Goldberg, PhD, Elizabeth Ceilley, MD, and Simon Powell, MD, PhD

Annals of Surgery • Volume 241, Number 4, April 2005

Questionario sottoposto a membri di ESTRO e ASTRO relativamente alla definizione di margini negativi e close





The Breast 21 (2012) 730–734

Contents lists available at SciVerse ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Practice patterns and perceptions of margin status for breast conserving surgery for breast carcinoma: National Survey of Canadian General Surgeons☆

Peter J. Lovrics [a,b,*], Maggie Gordon [a,b], Sylvie D. Cornacchi [a], Forough Farrokhyar [a], Amanda Ramsaroop [a], Nicole Hodgson [a,c], May Lynn Quan [f], Francis Wright [e], Geoffrey Porter [d]

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Questionario sottoposto a 1443 Chirurghi relativamente al concetto di margini negativi e close

NEGATIVI

40%	assenza di cellule tumorali sul margine inchiostrato
14%	1mm
28%	2mm
18%	5mm

CLOSE

59%	assenza di cellule tumorali entro 1mm dal margine inchiostrato
29%	2mm
12%	5mm

“Marging: a status report from the Annual Meeting of the American Society of Breast Surgeons”
Harness J.K. et Al. - AnnSurgOncol 2014

Panel costituito da componenti di:

Society of Surgical Oncology
American Society of Breast Surgeons
ASTRO
ASCO
College of American Pathologists

Ai partecipanti erano sottoposte domande a risposte multiple prima e dopo la descrizione, da parte dei relatori, della metanalisi di Houssami.

“Marging: a status report from the Annual Meeting of the American Society of Breast Surgeons”
Harness J.K. et Al. - AnnSurgOncol 2014

Quale margine può considerarsi adeguato nella chirurgia conservativa del Carcinoma infiltrante della mammella?

	PRIMA	DOPO
>10 mm	2%	
5-10 mm	2%	
1-4 mm	21%	
0.1-1 mm	13%	
No tumor su margine inchiostrato	**62%**	**96%**

Quando non vi è ragione di procedere ad una reescissione?

96% riteneva sufficiente l'assenza di cellule neoplastiche sul margine inchiostrato

PERCENTUALI DI REESCISSIONE

31-46% per DCIS

Meijen P. Ann Surg Oncol 2008

Dillon M.F. Ann Surg Oncol 2008

11-46% per il Ca invasivo

Kurniawan E.D. Ann Surg Oncol 2008

Jeevan R. BJM 2012

McCahill L.E. JAMA 2012

Variability in Reexcision Following Breast Conservation Surgery

Laurence E. McCahill, MD
Richard M. Single, PhD
Erin J. Aiello Bowles, MPH
Heather S. Feigelson, PhD, MPH
Ted A. James, MD
Tom Barney, BS
Jessica M. Engel, MSN
Adedayo A. Onitilo, MD, MSCR

Context Health care reform calls for increasing physician accountability and transparency of outcomes. Partial mastectomy is the most commonly performed procedure for invasive breast cancer and often requires reexcision. Variability in reexcision might be reflective of the quality of care.

Objective To assess hospital and surgeon-specific variation in reexcision rates following partial mastectomy.

Design, Setting, and Patients An observational study of breast surgery performed between 2003 and 2008 intended to evaluate variability in breast cancer surgical care outcomes and evaluate potential quality measures of breast cancer surgery. Women with invasive breast cancer undergoing partial mastectomy from 4 institutions were studied (1 university hospital [University of Vermont] and 3 large health plans [Kaiser Permanente Colorado, Group Health, and Marshfield Clinic]). Data were obtained from electronic medical records and chart abstraction of surgical, pathology, radiology, and outpatient records, including detailed surgical margin status. Logistic regression including surgeon-level random effects was used to identify predictors of reexcision.

Main Outcome Measure Incidence of reexcision.

Results A total of 2206 women with 2220 invasive breast cancers underwent partial mastectomy and 509 patients (22.9%; 95% CI, 21.2%-24.7%) underwent reexcision (454 patients [89.2%; 95% CI, 86.5%-91.9%] had 1 reexcision, 48 [9.4%; 95% CI, 6.9%-12.0%] had 2 reexcisions, and 7 [1.4%; 95% CI, 0.4%-2.4%] had 3 reexcisions). Among all patients undergoing initial partial mastectomy, total mastectomy was performed in 190 patients (8.5%; 95% CI, 7.2%-9.5%). Reexcision rates for margin status following initial surgery were 85.9% (95% CI, 82.0%-89.8%) for initial positive margins, 47.9% (95% CI, 42.0%-53.9%) for less than 1.0 mm margins, 20.2% (95% CI, 15.3%-25.0%) for 1.0 to 1.9 mm margins, and 6.3% (95% CI, 3.2%-9.3%) for 2.0 to 2.9 mm margins. For patients with negative margins, reexcision rates varied widely among surgeons (range, 0%-70%; $P = .003$) and institutions (range, 1.7%-20.9%; $P < .001$). Reexcision rates were not associated with surgeon procedure volume after adjusting for case mix ($P = .92$).

Conclusion Substantial surgeon and institutional variation were observed in reexcision following partial mastectomy in women with invasive breast cancer.

JAMA. 2012;307(5):467-475 www.jama.com

2206 pazienti sottoposte a chirurgia conservativa

% REESCISSIONE

85.9%	nel caso di margini positivi
47.9%	margini < 1mm
20.2%	margini ≥ 1 mm e ≤ 1.9 mm
6.3%	margini ≥ 2 mm e ≤ 2.9 mm

Breast Cancer Res Treat (2013) 140:353–361
DOI 10.1007/s10549-013-2627-6

EPIDEMIOLOGY

Margin status and the risk of local recurrence in patients with early-stage breast cancer treated with breast-conserving therapy

Andrea L. Russo · Nils D. Arvold · Andrzej Niemierko · Nathan Wong · Julia S. Wong · Jennifer R. Bellon · Rinaa S. Punglia · Mehra Golshan · Susan L. Troyan · Jane E. Brock · Jay R. Harris

906 pazienti in Stadio I-II sottoposte a chirurgia conservativa tra il 1998 ed il 2006

CLASSIFICAZIONE DEI MARGINI:

Ampiamente negativi	≥ 2mm
Close	> 0mm e < 2mm
Positivi	presenza di cellule neoplastiche sul margine inchiostrato

Close/positivi ma non passibili di ulteriore allargamento

41.6% sottoposte a reescissione

1.9%	margini iniziali negativi
36.3%	margini iniziali close
55.4%	margini positivi

La reescissione era stata decisa non solo sulla base dello stato dei margini ma anche in base ad ulteriori fattori di rischio legati al T o alla paziente

Nel **63%** dei casi il tessuto asportato con la chirurgia di allargamento **non conteneva** ulteriori foci neoplastici

Lo stato FINALE dei margini era:

729 pz	(80%)	ampiamente negativi
85pz	(9%)	close
92pz	(10%)	close/positivi non ampliabili

Russo et Al.

Breast Cancer Res Treat 2013

90.8%	terapia farmacologica adiuvante:	75.8% OT 42.7% CT
100%	WBRT	
98%	WBRT+Boost	
22%	N+	

L'incidenza cumulativa a 5 anni della LR:

2.3%	se margini negativi
3.5%	se margini close
6.4%	se positivi/close non allargabili

Tempo mediano alla LR: 52.3 mesi

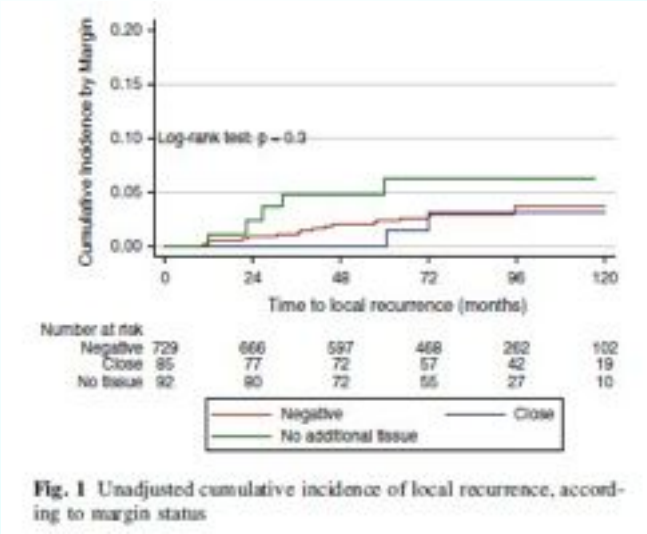

Fig. 1 Unadjusted cumulative incidence of local recurrence, according to margin status

NESSUNA differenza statisticamente significativa tra i 3 gruppi.

Va riconsiderato il concetto che la reescissione sia sempre un parametro di qualità nella chirurgia conservativa del carcinoma mammario

Russo et Al.
Breast Cancer Res Treat 2013

EUROPEAN JOURNAL OF CANCER 46 (2010) 3219–3232

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

ELSEVIER

EJC

Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy ☆

Nehmat Houssami [a,*], *Petra Macaskill* [a], *M. Luke Marinovich* [a], *J. Michael Dixon* [b], *Les Irwig* [a], *Meagan E. Brennan* [a], *Lawrence J. Solin* [c]

21 studi di cui **20** retrospettivi

Gli studi erano considerati elegibili per la valutazione solo se più del 90% delle pazienti presentava carcinoma in forma invasiva in stadio I-II
(< 10% la percentuale di DCIS o stadio III)

FU mediano 104.4 mesi

MARGINI POSITIVI: presenza di tumore (invasivo e/o in situ) sul margine inchiostrato

MARGINI NEGATIVI: assenza di tumore nell'ambito di una specifica distanza espressa in mm

MARGINI COSE: presenza di tumore all'interno di questa distanza ma non sul margine inchiostrato

Alcuni studi codificavano esclusivamente la distanza necessaria per definire il margine negativo vs positivo non contemplando la categoria "close".
Per questo motivo si sono dovuti adottare 2 modelli di analisi:

MODELLO1
(21 studi)

Positive vs Negative

MODELLO 2
(16 studi)

Positive vs Close vs Negative

Houssami N.
EJC 2010

IMPATTO DEI MARGINI SULLA LR

MODELLO1

La probabilità di LR presenta un'associazione statisticamente significativa con lo stato dei margini:

P<0.001 **positivi/close** vs **negativi**.

Non vi è invece associazione con la distanza dei margini (nessuna significatività):

5 mm vs 1 mm P=0.12

2 mm vs 1 mm P=0.58

5 mm VS 2 mm P=0.16

	Model estimates for the effect of margins (unadjusted)			Model estimates adjusted for study-specific median follow-up time (months)		
	Odds of LR (odds ratio)	95% CI	P-value[b] [P for trend]	Odds of LR (odds ratio)	95% CI	P-value[b] [P for trend]
Model 1 – 21 studies with median 8.7 years follow-up (based on study-specific median follow-up time for 16,866 subjects; 14,571 with known margins were included in model estimates)[a]						
Constant	0.09	0.06–0.14		0.027	0.009–0.084	
Margin status			<0.001			<0.001
Negative	1.0	–		1.0	–	
Positive/close	2.03	1.72–2.40		2.02	1.71 – 2.38	
Threshold distance[c] for negative margins			0.019 [0.005]			0.27 [0.11]
1 mm	1.0	–		1.0	–	
2 mm	0.62	0.34–1.14		0.85	0.46–1.56	
5 mm	0.37	0.19–0.72		0.58	0.28–1.17	
Model 2 – 16 studies with median 9.0 years follow-up (based on study-specific median follow-up time for 11,409 subjects; 9,555 with known margins were included in model estimates)						
Constant	0.08	0.05–0.13		0.040	0.01–0.14	
Margin status			<0.001			<0.001
Negative	1.0	–		1.0	–	
Close	1.80	1.44–2.26		1.80	1.43–2.25	
Positive	2.43	1.94–3.04		2.42	1.94–3.02	
Threshold distance[c] for negative margins			0.045 [0.014]			0.23 [0.097]
1 mm	1.0	–		1.0	–	
2 mm	0.59	0.33–1.06		0.75	0.39–1.45	
5 mm	0.39	0.19–0.82		0.51	0.23–1.16	

La probabilità di LR diminuisce lievemente quanto più aumenta la distanza necessaria per considerare i margini negativi, ma non vi è alcuna significatività statistica

Houssami N.
EJC 2010

IMPATTO DEI MARGINI SULLA LR

MODELLO 2

La probabilità di LR presenta un'associazione statisticamente significativa con lo stato dei margini:

P<0.001 positivi vs close vs negativi.

Anche in questo caso la probabilità di LR non è associata alla distanza dei margini:

5 mm vs 1 mm P=0.10
2 mm vs 1 mm P=0.37
5 mm VS 2 mm P=0.21

Sia nel Modello 1 che nel Modello 2 i dati si confermano anche dopo correlazione con tutte le altre variabili

Houssami N.
EJC 2010

1mm rappresenta la minima distanza per dichiarare un margine negativo.

Adottare margini più ampi di 1mm non fornisce vantaggi in termini di riduzione della LR.

Houssami N.
EJC 2010

Ann Surg Oncol (2014) 21:717–730
DOI 10.1245/s10434-014-3480-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY 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]

[1]Screening and Test Evaluation Program (STEP), School of Public Health (A27), Sydney Medical School, University of Sydney, Sydney, Australia; [2]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

33 STUDI contenenti i dati di **28.162** pazienti

In 18 studi 100% stadio I-II

In 15 studi >90% stadio I-II

FU mediano 79.2 mesi

IMPATTO DEI MARGINI SULLA LR

MODELLO 1

Dati relativi a 33 studi

LR in 1506 pz su 28.162

La probabilità di LR è correlata in modo statisticamente significativo alla stato dei margini: positivi vs negativi (P<0.001)

Vi è una debole associazione con l'ampiezza dei margini (P=0.06): il rischio di LR diminuisce quanto più aumenta la distanza stabilita per dichiarare i margini NEGATIVI

Tuttavia, se i dati sovrariportati vengono corretti in relazione al tempo del FU non vi è più alcuna correlazione con l'ampiezza dei margini (P=0.12)

(differenza rispetto al lavoro del 2010)

Houssami N.

Ann Surg Oncol 2014

MODELLO 2

Dati relativi a 19 studi

LR in 753 pz su 13.081

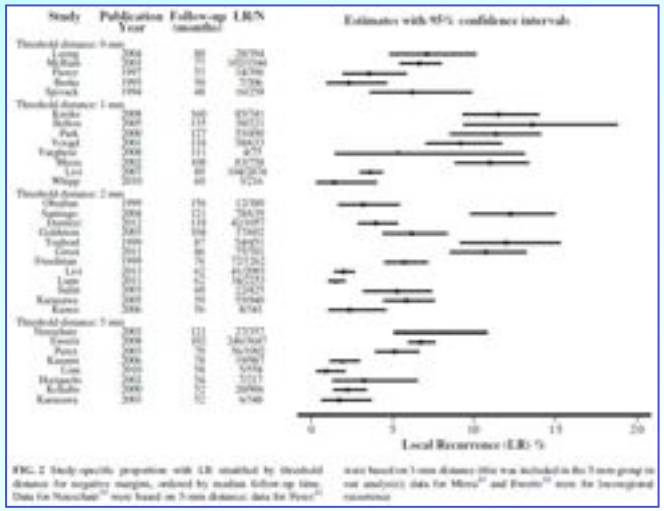

TABLE 2 Models of the effect of surgical margins on LR in early-stage invasive breast cancer

	Number in model		Model estimates adjusted for study-specific median follow-up time		
	Subjects	LR	Odds of LR (odds ratio)	95 % CI	*P* value[a] [*P* for trend]
Model 1 (median study-specific median follow-up time 6.6 years)	28,162	1,506	–	–	
Margin status					<0.001
Negative	21,984	1,005	1.0	–	
Positive/close	6,178	501	1.96	1.72–2.24	
Threshold distance for negative margins[b]					0.12 [0.21[c]]
>0 mm	2,898	167	1.47	0.67–3.20	
1 mm	6,008	422	1.0	–	
2 mm	11,144	530	0.95	0.54–1.67	
5 mm	8,112	386	0.65	0.34–1.26	
Model 2 (median study-specific median follow-up time 8.7 years)	13,081	753	–	–	–
Margin status					<0.001
Negative	9,033	393	1.0	–	
Close	2,407	176	1.74	1.42–2.15	
Positive	1,641	184	2.44	1.97–3.03	
Threshold distance for negative margins[b]					0.90 [0.58]
1 mm	2,376	235	1.0	–	
2 mm	8,350	414	0.91	0.46–1.80	
5 mm	2,355	103	0.77	0.32–1.87	

[a] *P* reports *P* value for association; *P* in square brackets gives *P* for trend and reflects whether there was statistical evidence of a decrease in the odds of LR as the threshold distance for declaring negative margins increased

[b] Threshold distance for negative margins based on >0 mm (5 studies), 1 mm (referent; 8 studies), 2 mm (12 studies), and 5 mm (8 studies) in model 1; and based on 1 mm (referent; 6 studies), 2 mm (10 studies), and 5 mm (3 studies) in model 2

[c] Trend tested excluding studies using >0 mm (test based on 28 studies) for model 1—see "Methods" section

La probabilità di LR è correlata in modo statisticamente significativo alla stato dei margini: positivi vs close vs negativi (P<0.001)

Si riscontra una lieve tendenza all'aumento del rischio di LR al diminuire dell'ampiezza dei margini che tuttavia diviene inconsistente se i dati vengono corretti in base al tempo del FU

Houssami N.

Ann Surg Oncol 2014

Tale tendenza si annulla completamente quando il dato venga corretto considerando l'impiego di OT adiuvante o del boost di Radioterapia:
nessuna differenza tra margine ≥ 5mm e margine = 1mm

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		Margin status (adjusted OR)			Threshold distance for negative margins (adjusted OR)			*P* for association [*P* for trend] for margin distance
		Unadjusted	Adjusted for margins and follow-up time	Negative	Close	Positive	1 mm	2 mm	5 mm	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*	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]

** Indicates OR significantly different to referent at $P < 0.001$

* Odds of LR increased as proportion receiving reexcision increased

Houssami N.

Ann Surg Oncol 2014

Questa, che rappresenta la principale differenza rispetto ai dati del 2010, trova la sua spiegazione nel fatto che i numerosi studi aggiunti in questa metanalisi erano cronologicamente più recenti e prevedevano pertanto l'impiego nella terapia sistemica adiuvante di inibitori dell'aromatasi e di trastuzumab oltre che un più ampio utilizzo di taxani → **RIDUZIONE GLOBALE DELLA LR**

CONCLUSIONI

L'ottenimento di margini negativi rimane fondamentale nella pratica clinica in quanto impatta in modo statisticamente significativo il rischio di LR

Il valore prognostico dello stato dei margini (positivi vs negativi) **NON E'** diminuito dalla globale riduzione delle % di LR determinato negli ultimi anni dagli avanzamenti della terapia adiuvante

L'adozione di distanze più ampie per definire un margine negativo non sembra fornire vantaggi in termini di LR a lungo termine

Houssami N.

Ann Surg Oncol 2014

International Journal of Radiation Oncology biology • physics
www.redjournal.org

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‖‖

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Received Oct 31, 2013. Accepted for publication Nov 6, 2013.

Panel riunitosi a Luglio 2013

Revisione dei dati dei **33** studi presi in considerazione dalla metanalisi di Houssami

MARGINI POSITIVI

Un margine positivo , definito come presenza di Carcinoma invasivo o DCIS sul margine inchiostrato, si associa ad un incremento di IBTR (Ipsilateral Breast Tumor Recurrence) di almeno **2** volte.

Table 4 Summary of selected results of margins meta-analysis (13)

	Relationship between IBTR and margin status				
	No. of Studies	No. of participants	Adjusted OR of IBTR*	95% CI	*P* (association)
Margin category (model 1)		28,162			<.001
Close/positive	33	6178	1.96	1.72-2.24	
Negative	33	21,984	1.0	-	
Margin category (model 2)		13,081			<.001
Positive	19	1641	2.44	1.97-3.03	
Close	19	2407	1.74	1.42-2.15	
Negative	19	9033	1.0	-	-
Threshold distance (model 2)†					.90
1 mm	6	2376	1.0	-	-
2 mm	10	8350	0.91	0.46-1.80	-
5 mm	3	2355	0.77	0.32-1.87	-

Moran M.S.
Int J Radiat Oncol 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

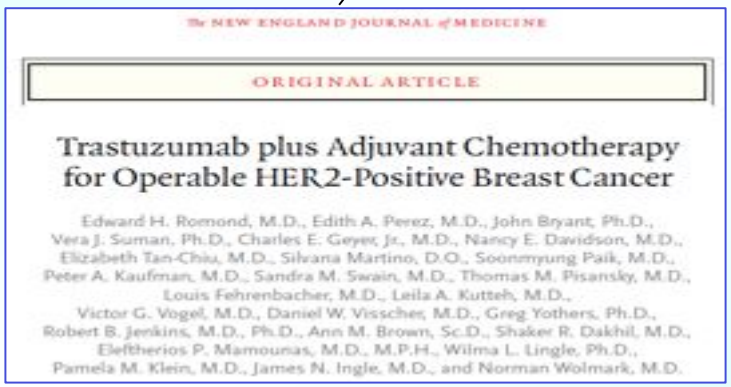
Five Years of Letrozole Compared With Tamoxifen As Initial Adjuvant Therapy for Postmenopausal Women With Endocrine-Responsive Early Breast Cancer: Update of Study BIG 1-98

The NEW ENGLAND JOURNAL of MEDICINE

MARCH 11, 2004

A Randomized Trial of Exemestane after Two to Three Years of Tamoxifen Therapy in Postmenopausal Women with Primary Breast Cancer

RIDUZIONE GLOBALE DELLA LR



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial

VOLUME 25 · NUMBER 22 · AUGUST 1 2007

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Impact of a Higher Radiation Dose on Local Control and Survival in Breast-Conserving Therapy of Early Breast Cancer: 10-Year Results of the Randomized Boost Versus No Boost EORTC 22881-10882 Trial

Harry Bartelink, Jean-Claude Horiot, Philip M. Poortmans, Henk Struikmans, Walter Van den Bogaert, Alain Fourquet, Jo J. Jager, Willem J. Hoogenraad, S. Bing Oei, Carla C. Wárlám-Rodenhuis, Marianne Pierart, and Laurence Collette

Purpose
To investigate the long-term impact of a boost radiation dose of 16 Gy on local control, fibrosis, and overall survival for patients with stage I and II breast cancer who underwent breast-conserving therapy.

Patients and Methods
A total of 5,318 patients with microscopically complete excision followed by whole-breast irradiation of 50 Gy were randomly assigned to receive either a boost dose of 16 Gy (2,661 patients) or no boost dose (2,657 patients), with a median follow-up of 10.8 years.

L'impiego di un boost di 16 Gy sul letto tumorale nel caso di MARGINI NEGATIVI riduce la % di IBTR a 10 anni:

10.2% (no boost) **6.2%** (boost) **P<0.001**

Tuttavia nel caso di MARGINI POSITIVI l'incidenza di IBTR a 10 anni:

17.5% (boost 10Gy) **10.8%** (boost 26Gy)

In caso di margini positivi anche aumentando la dose del boost **NON** si riesce a ridurre la % di IBTR ai valori che si ottengono realizzando un boost a dose totale più bassa in caso di margini negativi

MARGINI POSITIVI

Dei 19 studi che indicavano la profondità dei margini, 15 includevano informazioni dettagliate sullo stato ER:

ER+ margini+ vs **ER+ margini-**

% IBTR significativamente più elevata nel primo gruppo **(P<0.001)**

Le pazienti con margini positivi che presentino fattori biologici favorevoli, quale una forte espressione dei recettori per gli estrogeni, rimangono comunque a più alto rischio di IBTR rispetto alle pazienti con analoghe caratteristiche ma con margini negativi

Moran M.S.
Int J Radiat Oncol 2013

La terapia sistemica adiuvante e la realizzazione di un boost di Radioterapia hanno un impatto positivo sulla riduzione della IBTR, ma NON annullano l'aumento del rischio determinato dalla positività dei margini, anche quando i dati vengono aggiustati in relazione alle altre variabili.

Nemmeno fattori biologici favorevoli sono in grado di annullare tale aumento del rischio.

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MARGINI NEGATIVI

Margini negativi (assenza di tumore sul margine inchiostrato) riducono significativamente il rischio di IBTR.
Margini più ampi di quanto sopra descritto **NON** riducono ulteriormente questo rischio ed un loro ottenimento non è pertanto indicato.

Table 4 Summary of selected results of margins meta-analysis (13)

Relationship between IBTR and margin status					
	No. of Studies	No. of participants	Adjusted OR of IBTR*	95% CI	P (association)
Margin category (model 1)		28,162			<.001
Close/positive	33	6178	1.96	1.72-2.24	
Negative	33	21,984	1.0	-	
Margin category (model 2)		13,081			<.001
Positive	19	1641	2.44	1.97-3.03	
Close	19	2407	1.74	1.42-2.15	
Negative	19	9033	1.0	-	
Threshold distance (model 2)†					.90
1 mm	6	2376	1.0	-	
2 mm	10	8350	0.91	0.46-1.80	
5 mm	3	2355	0.77	0.32-1.87	

Impact of margin width on IBTR adjusted for individual covariates and follow-up†					
		Threshold distance negative margin: adjusted OR (mm)			
Covariate	No. of studies	1	2	5	P (association)
Age	18	1.0	0.53	0.77	.53
Endocrine therapy	16	1.0	0.95	0.90	.95
Radiation boost	18	1.0	0.86	0.92	.86

Abbreviations: CI = confidence interval; IBTR = ipsilateral breast tumor recurrence; OR = odds ratio.
* Adjusted for study-specific median length of follow-up.
† Threshold distance was also tested for significance for trend (reflects whether there was statistical evidence of a decrease in the odds of IBTR as the threshold margin distance increased from 1 mm, 2 mm, and 5 mm). P (trend) = .58.

Moran M.S.
Int J Radiat Oncol 2013

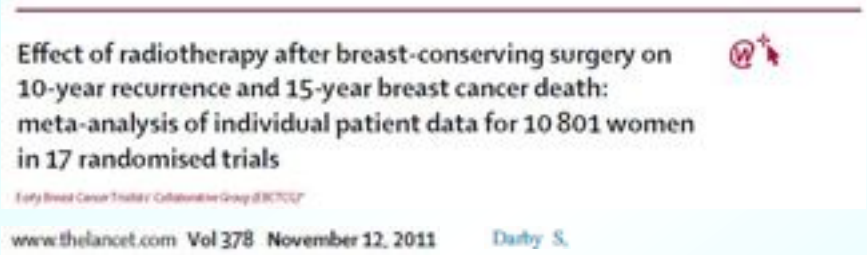
IMPATTO DELLA TERAPIA SISTEMICA

Studio NSABP B14

	TAM	vs	No TAM	in ER+ N0
IBTR	**5%**	vs	**11.6%**	**P<0.001**

Studio NSABP B13

Chemio	vs	No Chemio in N0	
IBTR	**5.4%**	vs	**15.3%**	**P<0.001**



	TAM	vs	No TAM	in	ER+
IBTR a 10 aa	**8.7%**	vs	**18.6%**		

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Edward H. Romond, M.D., Edith A. Perez, M.D., John Bryant, Ph.D., Vera J. Suman, Ph.D., Charles E. Geyer, Jr., M.D., Nancy E. Davidson, M.D., Elizabeth Tan-Chiu, M.D., Silvana Martino, D.O., Soonmyung Paik, M.D., Peter A. Kaufman, M.D., Sandra M. Swain, M.D., Thomas M. Pisansky, M.D., Louis Fehrenbacher, M.D., Leila A. Kutteh, M.D., Victor G. Vogel, M.D., Daniel W. Visscher, M.D., Greg Yothers, Ph.D., Robert B. Jenkins, M.D., Ph.D., Ann M. Brown, Sc.D., Shaker R. Dakhil, M.D., Eleftherios P. Mamounas, M.D., M.P.H., Wilma L. Lingle, Ph.D., Pamela M. Klein, M.D., James N. Ingle, M.D., and Norman Wolmark, M.D.

National Surgical Adjuvant Breast and Bowel Project trial B-31

The North Central Cancer Treatment Group trial N9831

Table 2. Sites of First Events.

Patients	Trial B-31		Trial N9831	
	Control Group	Trastuzumab Group	Control Group	Trastuzumab Group
	number of patients			
All patients with follow-up	872	864	807	808
Patients alive and event-free	701	781	717	758
Patients with any first event	171	83	90	50
Local or regional recurrence	35	15	22	12
Distant recurrence	111	60	63	30
Contralateral breast cancer	6	2	0	1
Other second primary cancer	15	2	3	3
Death with no evidence of disease	4	4	2	4

In entrambi gli studi l'impiego nelle pazienti HER2+ di Trastuzumab in aggiunta alla chemioterapia riduce le percentuali di IBTR in modo **statisticamente significativo**.

IMPATTO DELLA TERAPIA SISTEMICA

Le percentuali di IBTR vengono ridotte dall'impiego della terapia sistemica.
Nel caso in cui la paziente non riceva terapia sistemica, non vi sono evidenze che sia vantaggioso ottenere margini più ampi dell' assenza di tumore sul margine inchiostrato

Moran M.S.
Int J Radiat Oncol 2013

Ann Surg Oncol (2014) 21:1209–1214
DOI 10.1245/s10434-013-3416-5

Annals 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]

[1]Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; [2]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY; [3]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; [4]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

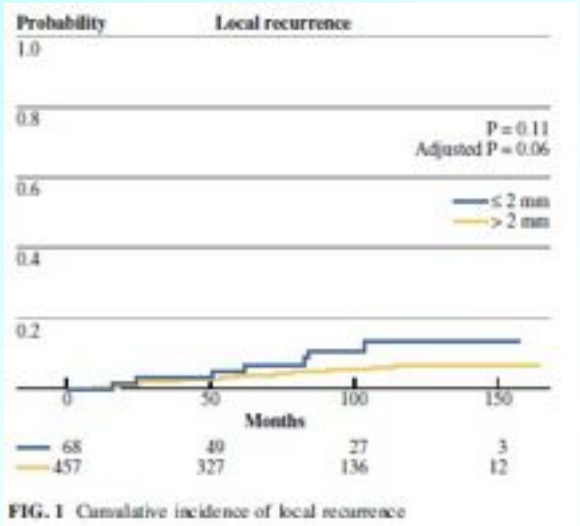


FIG. 1 Cumulative incidence of local recurrence

SOTTOTIPI BIOLOGICI

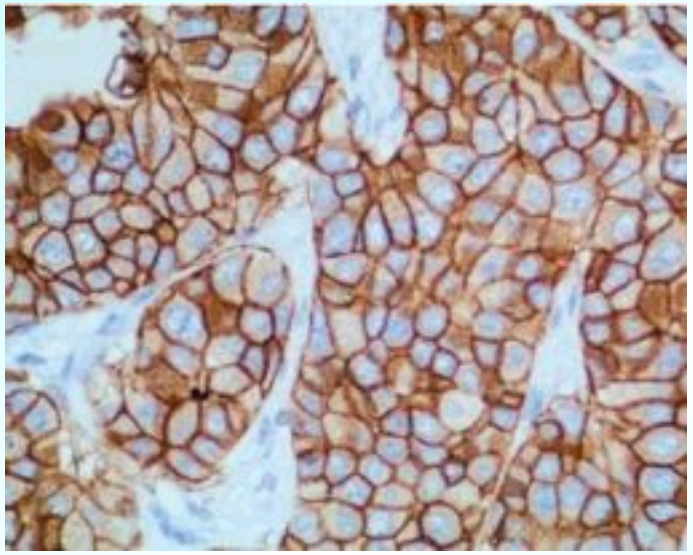
535 pz affette da TNBC

Ad una valutazione a 60 mesi dell'incidenza di IBTR:

Margine ≤ 2mm	Margine > 2mm
7.3%	5.1%

NESSUNA differenza statisticamente significativa

SOTTOTIPI BIOLOGICI



Margini più ampi dell'assenza di tumore sul margine inchiostrato non sono indicati sulla base del sottotipo biologico

Moran M.S.
Int J Radiat Oncol 2013

CARCINOMA LOBULARE INFILTRANTE

Available online at www.sciencedirect.com
SciVerse ScienceDirect
EJSO
the Journal of Cancer Surgery
ELSEVIER
EJSO 39 (2013) 455–460
www.ejso.com

Clinical-pathologic features, long term-outcome and surgical treatment in a large series of patients with invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC)

N. Biglia [a,*], F. Maggiorotto [b], V. Liberale [a], V.E. Bounous [a], L.G. Sgro [a], S. Pecchio [a], M. D'Alonzo [a], R. Ponzone [b]

[a] Academic Division of Gynaecology and Obstetrics, Mauriziano Hospital "Umberto I", University of Turin, Largo Turati 62, Turin, Italy
[b] Division of Gynecological Oncology, Institute for Cancer Research and Treatment (IRCC), Candiolo (TO), Italy

Accepted 1 February 2013
Available online 13 March 2013

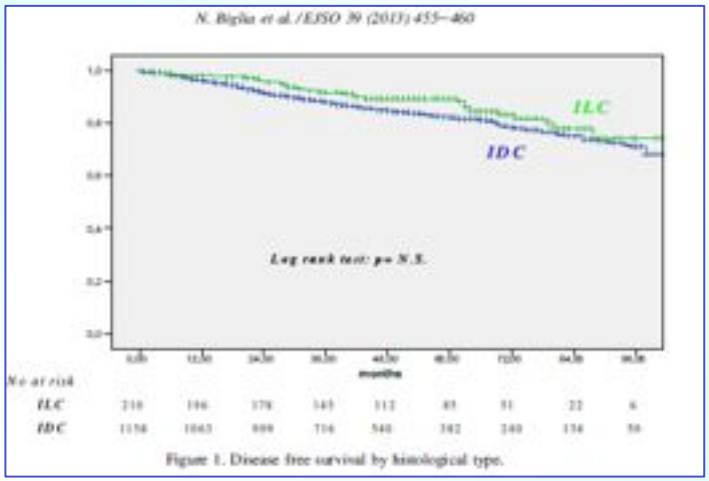


Figure 1. Disease free survival by histological type.

Se margini negativi:

	IDC	e ILC
DFS a 5aa	79%	83%
LRFS a 5aa	94%	96%

ORIGINAL ARTICLE

Influence of Margin Status on Outcomes in Lobular Carcinoma: Experience of the European Institute of Oncology

Viviana Galimberti, MD, Patrick Maisonneuve, Dip.Eng†, Nicole Rotmensz, Msc†, Giuseppe Viale, MD‡§, Claudia Sangalli, PhD*, Manuela Sargenti, MD*, Fabricio Brenelli, MD*, Oreste Gentilini, MD*, Mattia Intra, MD*, Fabio Bassi, MD*, Alberto Luini, MD*, Stefano Zurrida, MD*†§, Paolo Veronesi, MD*†§, Marco Colleoni, MD¶, and Umberto Veronesi, MD**

Annals of Surgery • Volume 253, Number 3, March 2011

TABLE 3. Outcomes in 382 Patients With Primary Lobular Breast Cancer Treated With Conservative Surgery at the European Institute of Oncology Between 1994 and 2001 According to Margin Status

	All Patients	≥10 mm Margins*	<10 mm Margins	P Logrank	Margins <10 mm			
					In-situ	1–9 mm	<1 mm	Involved
All patients	382	295	87		34	5	16	32
Median follow-up (inter quartile range)	8.4 (2.9)	8.4 (2.8)	8.2 (3.4)		8.2 (3.0)	9.3 (0.1)	8.2 (3.7)	8.3 (4.7)
Patient-years	3193	2485	708		269	45	124	270
Total breast-related events†	66 (17.2%)	49	17	0.53	6	0	4	7
Locoregional relapse†	27 (7%)	22 **7%**	5 **6%**	0.60	1	0	2	2
Local relapse in the same quadrant	15 (3.9%)	11	4	0.70	1	0	2	1
Ipsilateral breast cancer	7 (1.8%)	7	0	0.14	0	0	0	0
Axillary/regional node relapse	5 (1.3%)	4	1	0.89	0	0	0	1
Distant metastasis†	30 (7.8%)	20	10	0.14	3	0	2	5
Contralateral breast cancer†	11 (2.9%)	9	2	0.74	2	0	0	0
Other primary cancer	18 (4.7%)	14	4	0.97	1	0	0	3
Deaths‡	28 (7.3%)	22	6	0.93	2	0	1	3
Breast cancer	17 (4.5%)	12	5	0.47	2	0	0	3
Other cause	8 (2.1%)	7	1	0.51	0	0	1	0
Unknown cause	3 (0.8%)	3	0	0.36	0	0	0	0
Total number of unfavorable events	90 (23.6%)	68	22	0.66	7	0	5	10

Non vi sono differenze statisticamente significative in termini di LR nel caso dell'ottenimento di margini > 1cm o < 1cm

CARCINOMA LOBULARE INFILTRANTE

Il Carcinoma lobulare infiltrante non necessita di margini più ampi dell'assenza di tumore sul margine inchiostrato

Moran M.S.
Int J Radiat Oncol 2013

ETA'

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

Lancet 2011; 378: 1707–16

La giovane età alla diagnosi (<40 aa) si associa sia ad un incremento di IBTR dopo BCT sia a quello di recidiva di parete dopo mastectomia.
Non ci sono evidenze che un aumento dell'ampiezza dei margini riesca ad annullare questo aumentato rischio.

Moran M.S.
Int J Radiat Oncol 2013

RADIOTERAPIA

5318 pz sottoposte a BCS

VOLUME 25 · NUMBER 22 · AUGUST 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of a Higher Radiation Dose on Local Control and Survival in Breast-Conserving Therapy of Early Breast Cancer: 10-Year Results of the Randomized Boost Versus No Boost EORTC 22881-10882 Trial

Harry Bartelink, Jean-Claude Horiot, Philip M. Poortmans, Henk Struikmans, Walter Van den Bogaert, Alain Fourquet, Jos J. Jager, Willem J. Hoogenraad, S. Bing Oei, Carla C. Wárlám-Rodenhuis, Marianne Pierart, and Laurence Collette

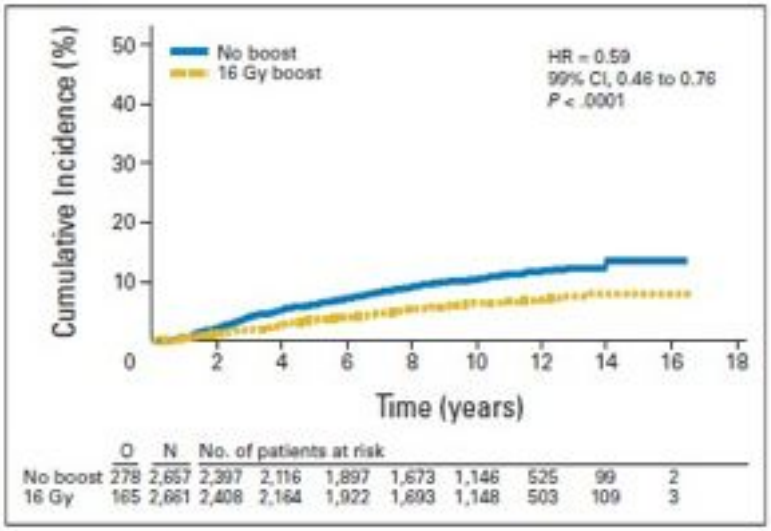


Fig 2. Cumulative incidence of recurrence of tumor as first event in the ipsilateral breast after 50 Gy whole-breast irradiation or 50 Gy whole-breast irradiation and a boost of 16 Gy. HR, hazard ratio; O, occurrences; N, number of patients at risk.

In questo, come in altri studi atti a valutare l'efficacia dell'aggiunta del boost alla WBRT, erano reclutate solo le pazienti con margini negativi e per margine negativo si intendeva l'assenza di tumore sul margine inchiostrato.

I risultati a 10 anni hanno mostrato una riduzione della LR del 41% (dal 10.2% al 6.2%)

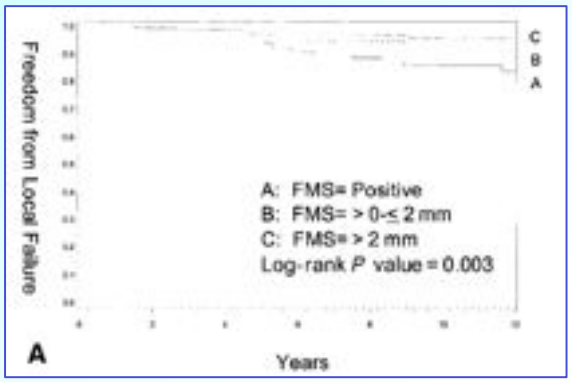
Long-Term Follow-Up of a Prospective Policy of Margin-Directed Radiation Dose Escalation in Breast-Conserving Therapy

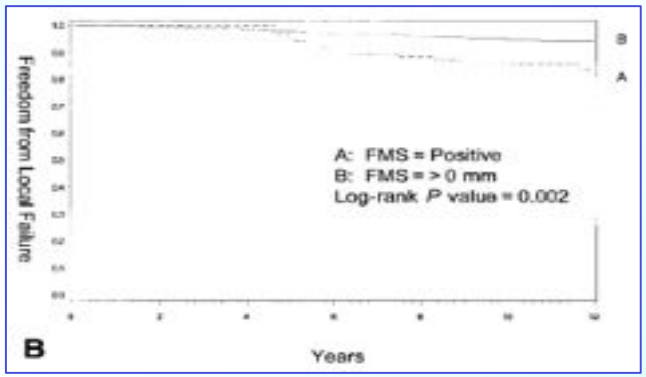
Andrew C. Neuschatz, M.D.[1]
Thomas DiPetrillo, M.D.[1]
Homa Safaii, M.D.[2]
Lori Lyn Price, M.A.S.[3]
Rupert K. Schmidt-Ullrich, M.D.[4]
David E. Wazer, M.D.[1]

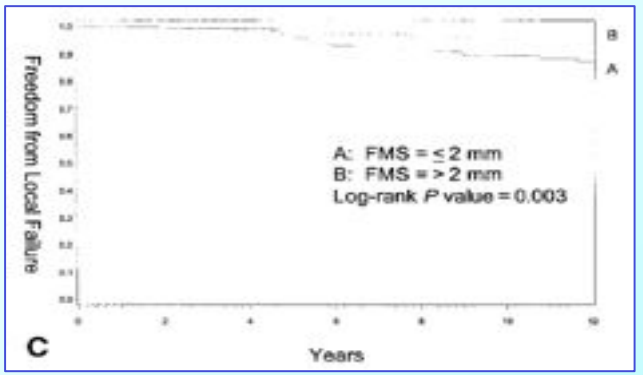
509 pz sottoposte a BCT + WBRT

BOOST

10Gy	FMS>	5mm
14Gy	FMS	2-5mm
20Gy	FMS<	2mm o POSITIVI







Le percentuali di LR a 5 e 10 anni erano complessivamente basse, rispettivamente < 3% ed < 8%. L'escalation di dose del boost non è in grado di compensare adeguatamente l'impatto prognosticamente sfavorevole del FMS.

Il dato della LR in relazione al FMS si conferma anche a 12 anni:

17%	FMS	POSITIVO	
9%	FMS	≤	2mm
5%	FMS	>	2mm
0%	FMS	>	5mm

Inoltre:

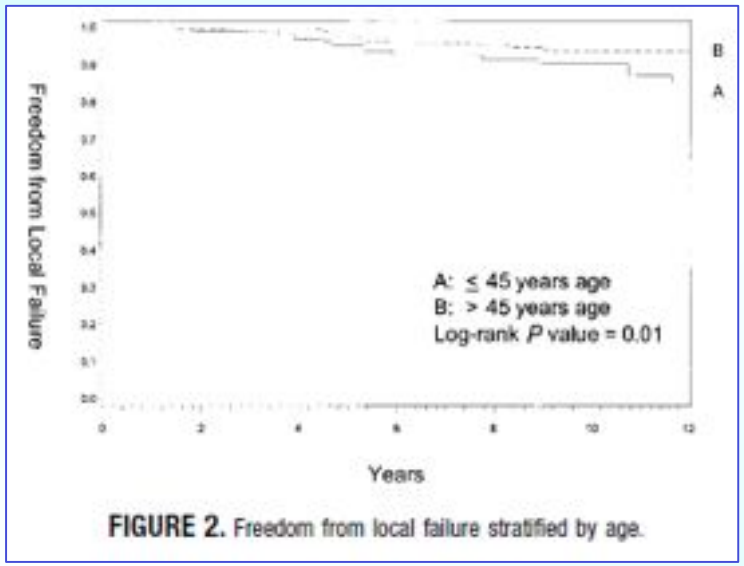


FIGURE 2. Freedom from local failure stratified by age.

L'escalation di dose del boost non è in grado di compensare il valore prognosticamente detrimentale dell'età alla diagnosi.

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Breast cancer radiotherapy

Radiotherapy boost dose-escalation for invasive breast cancer after breast-conserving surgery: 2093 Patients treated with a prospective margin-directed policy

Lorenzo Livi, Icro Meattini, Davide Franceschini, Calogero Saieva, Fiammetta Meacci, Livia Marrazzo, Elena Gerlain, Isacco Desideri, Vieri Scotti, Jacopo Nori, Luis Jose Sanchez, Lorenzo Orzalesi, Pierluigi Bonomo, Daniela Greto, Simonetta Bianchi, Giampaolo Biti

Dati relativi a 2093 pz sottoposte a BCS + WBRT (50Gy/25 fraz.)

MARGINI POSITIVI: presenza di tumore invasivo su 1 o più margini

MARGINI CLOSE: ≤ 2mm

MARGINI NEGATIVI: > 2mm

La dose del boost veniva stabilita sulla base dello stato finale dei margini (FMS):

10 Gy	FMS	>	5mm
16 Gy	FMS		2-5 mm
20 Gy	FMS	<	2mm*

* o nel caso di margini POSITIVI non passibili di reescissione

Table 2
Disease-Free Survival (DFS) analysis of 2093 BC cases in relation to local recurrence (LR) occurrence according to selected parameters: patients at start, LR, p-value from log rank test, Hazard Ratio (HR) and 95% Confidence Intervals (95% CI) from Cox regression univariate analysis.

Feature	Patients at start	LR	p-Value	HR (95% CI)
FSM status				
>5 mm	1655	30		
2–5 mm	352	9		
<2 mm/positive	86	2	0.46	

Ad un FU mediano di 5.2 anni le % di LR:

2.3% FMS < 2mm

2.6% FMS 2-5mm

1.8% FMS > 5mm

P= 0.46

Lo stato finale dei margini non ha un impatto significativo sulla LR

Un'escalation di dose del boost sembra ridurre l'impatto del FMS sulla LR

Livi l. et al.
Radiotherapy and Oncology 2013

TUTTAVIA.....

Table 2
Disease-Free Survival (DFS) analysis of 2093 BC cases in relation to local recurrence (LR) occurrence according to selected parameters: patients at start, LR, *p*-value from log rank test, Hazard Ratio (HR) and 95% Confidence Intervals (95% CI) from Cox regression univariate analysis.

Feature	Patients at start	LR	*p*-Value		HR (95% CI)
Nuclear grade					
1–2	1434	19			1
3	598	21	**0.0004**	**S**	**2.95 (1.58–5.50)**
Tumor stage (pTNM)					
T1	1721	26			1
T2	372	15	**0.005**	**S**	**2.45 (1.28–4.68)**
Age at diagnosis					
<45	265	10			1
⩾45	1828	31	**0.027**	**S**	**0.45 (0.2–0.93)**
BC subtype[a]					
Luminal A	883	10			1
Luminal B	113	1			0.60 (0.08–4.71)
HER2 overexpressing	186	5			2.43 (0.83–7.12)
Triple negative	81	6	**0.002**	**S**	**5.46 (1.97–15.2)**

.....non è in grado di superare l'impatto sfavorevole determinato dall'**età** alla diagnosi, da un **G elevato**, da **stadio T alto** e dal **TNBC.**

In questi sottogruppi di pazienti, il riscontro di margini **POSITIVI** o < 2 mm renderebbe **OPPORTUNA** la reescissione

Livi l. et al.
Radiotherapy and Oncology 2013

Radiotherapy and Oncology 90 (2009) 80–85

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

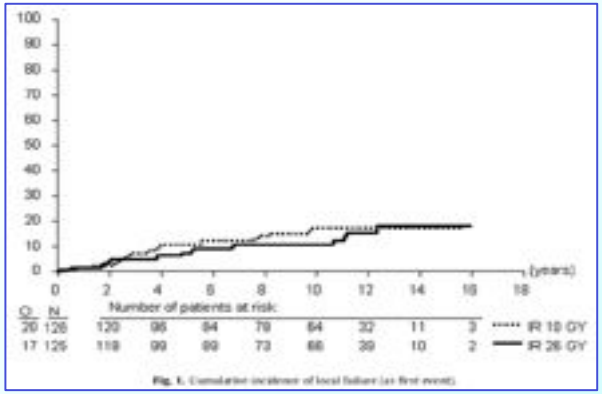
Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial

Philip M. Poortmans [a,*], Laurence Collette [b], Jean-Claude Horiot [c], Walter F. Van den Bogaert [d], Alain Fourquet [e], Abraham Kuten [f], Evert M. Noordijk [g], Willem Hoogenraad [h], René-Olivier Mirimanoff [i], Marianne Pierart [b], Erik Van Limbergen [d], Harry Bartelink [j], On behalf of the EORTC Radiation Oncology and Breast Cancer Groups

1725 pz sottoposte a BCT + WBRT

251 pz presentavano resezione incompleta e sono state randomizzate a ricevere boost di:

10 Gy vs 26 Gy



LR a 10 anni **17.5%** vs **10.8%**

P>0.1 Nessuna differenza statisticamente significativa

Il confronto a 10 anni tra il gruppo a margini negativi e le 251 pz a resezione incompleta evidenzia che queste ultime hanno un rischio doppio LR (**15%** vs **8%**).
La positività dei margini **rappresenta un indubitabile fattore prognostico negativo**.

RADIOTERAPIA

La scelta delle tecniche di realizzazione della WBRT, il frazionamento e la dose del boost non dovrebbero dipendere dall'ampiezza dei margini

Moran M.S.
Int J Radiat Oncol 2013

VOLUME 32 · NUMBER 14 · MAY 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stage I and II Invasive Breast Cancer: American Society of Clinical Oncology Endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology Consensus Guideline

Thomas A. Buchholz, Mark R. Somerfield, Jennifer J. Griggs, Souzan El-Eid, M. Elizabeth H. Hammond, Gary H. Lyman, Ginny Mauro, and Lisa A. Newman

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

Abbreviations: ASTRO, American Society for Radiation Oncology; BCT, breast-conserving therapy; DCIS, ductal carcinoma in situ; EIC, extensive intraductal component; IBTR, ipsilateral breast tumor recurrence; LCIS, lobular carcinoma in situ; SSO, Society of Surgical Oncology; WBRT, whole-breast radiation therapy.

Conclusion

The ASCO review panel endorses the SSO/ASTRO recommendations with qualifications, as follows. The 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.

CONCLUSIONI

Secondo le LINEE GUIDA di SSO, ASTRO L'OTTENIMENTO DI MARGINI NEGATIVI, INTESI COME ASSENZA DI TUMORE SUL MARGINE INCHIOSTRATO, E' L'UNICO OBIETTIVO CHE DEBBA ESSERE PERSEGUITO NELL'INTENTO DI RIDURRE LE PERCENTUALI DI IBTR.

LA TERAPIA SISTEMICA ADIUVANTE

(ORMONOTERAPIA, CHEMIOTERAPIA, ANTICORPI MONOCLONALI) MIGLIORA IL CONTROLLO GLOBALE DI MALATTIA MA

RIDUCE ANCHE LE % DI IBTR

LA RADIOTERAPIA, SPECIE SE REALIZZATA CON BOOST SU LETTO TUMORALE, RIDUCE IN MODO SIGNIFICATIVO IL RISCHIO DI IBTR

TUTTAVIA…….

CONCLUSIONI

Età ≤ 40 anni

G elevato

T alto

Her2+

TNBC

Si associano a più alte % di IBTR

L'ASCO pur avvallando le linee guida di ASTRO ed SSO ne raccomanda l'applicazione con "flessibilità" per un periodo adeguato a verificarne l'outcome

PERTANTO:

In presenza di tali fattori di rischio
dovrebbe essere considerata l'opportunità
di ottenere margini più ampi.

Grazie