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► To cite this version:

Alberto Luini, Joel Rososchansky, Giovanna Gatti, Stefano Zurrída, Pietro Caldarella, et al.. The surgical margin status after breast-conserving surgery: discussion of an open issue. *Breast Cancer Research and Treatment*, 2008, 113 (2), pp.397-402. 10.1007/s10549-008-9929-0 . hal-00478312

HAL Id: hal-00478312

<https://hal.science/hal-00478312>

Submitted on 30 Apr 2010

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The surgical margin status after breast-conserving surgery: discussion of an open issue

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Published online: 4 April 2008
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Abstract *Hypothesis* The best therapeutic approach to the involved or proximal surgical margins has not been defined yet; surgical margins status can influence the local relapse of disease in breast carcinoma, but the impact on overall survival has not been clearly demonstrated. Purpose of this work is to find in the available literature further evidence to guide the therapeutic behaviour in patients with close margins by invasive carcinoma. *Design* Review of the currently available literature on the evaluation of surgical margins in breast conserving surgery; influence of margin involvement by invasive component or intraductal component. *Patients or other participants* Literature research by PubMed on the topics of breast carcinoma, conservative surgery and margin definition and status; therapeutic approach to involved margins. *Main outcome measure* We reviewed the available literature focusing our

attention to the definition of clear surgical margins and to the value of the close proximity of margins in relation to the local control of disease and the best therapeutic management of different situations. *Results* Further evidence is needed on large numbers of patients to understand how to evaluate surgical margins in invasive breast carcinoma. *Conclusions* There is no consensus on the definition of “clear surgical margins”, and the ideal approach to the close proximity of margins has not been defined. It is not sure whether a new surgical procedure is really needed in every case of close proximity of tumor cells to the margins. Radiation therapy could be a good option in the management of these cases, but further evidence is needed to establish the real impact of clear surgical margins on local control of disease and, furthermore, on survival.

Keywords Breast carcinoma · Surgical margins · Local relapse

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Introduction

Surgical margins definition

No uniform definition of surgical margins has been established in the literature among Institutions. There is general consensus among a series of published studies that a surgical margin is positive if cancer cells are immediately at the edge of resection on an inked histology section according to the investigators from the National Surgical Adjuvant Breast and Bowel Project [1–3]

Other Authors consider a margin positive if cancer cells are present within some arbitrary distance from an inked surface (such as 5 mm) [4] At the European Institute of Oncology we currently consider 1 mm as the minimal

distance to be kept for surgical margins before becoming positive.

This issue is not clear in the literature: the most accepted definition is, however, that starting from a certain distant limit of the tumor, the margin becomes known as “negative”, and the distance between this margin and the tumor becomes “close”.

Some Authors classify these negative distances as greater than 1 mm [5–8], greater than 2 mm [9–14], greater than 3 mm [15] or even greater than 5 mm [16].

To classify the extent of margin involvement, some Authors use the four-tier system based on the number of microscopic low-power fields showing the tumor and/or the number of section containing the tumor. The four possible categories are focal, minimal, moderate, and extensive [17–22].

Therefore, the definition of surgical margin is not clear yet, and it is possible that a consensus will be reached after the results of the ongoing trials.

Surgical margin in invasive breast cancer: review of the literature

The main question is whether or not the surgical margin status can influence the result of breast conserving surgery. As there is no consensus on which is the value of the ideal margin, each Institution adopts a certain value: due to this fact, the comparison of the results can be accomplished only among Institutions with the same definition adopted for surgical margin.

All patients in the available literature were submitted to breast-conserving therapy for unilateral clinical stage I or II breast carcinoma, followed by local irradiation with or without a boost.

Among the Institutions who consider negative margin >1 mm, Gage, who evaluated 340 patients in 1996, concluded that the 5-year rate of ipsilateral breast recurrence (IBR) for all patients with negative margins was 2%; for all patients with positive margins the rate was 16%. Among patients with negative margins, the 5-year rate of IBR was 2% for all patients with close margins (≤ 1 mm) and 3% for those with negative >1 mm [5].

In the same way of Gage, Park et al. [8] concluded that patients with close (<1 mm) and negative margins had similarly low rates of local recurrence (LR), suggesting that patients with negative and close margins are equally good candidates for breast conserving therapy. They also concluded that this indication could not be applied to patients with extensively involved margins (\geq four low-power microscopic fields), who should undergo re-excision.

On the other hand, Anscher et al. [6] and Tafra et al. [7] reported statistically higher local recurrence rates in patients 1 mm or less between tumor cells and inked

margin (9 and 14%, respectively), compared with negative margins (1.5 and 5%, respectively).

When considering “close margin” being ≤ 2 mm and negative margin >2 mm, the literature shows similar results. Patients who were treated with breast-conserving therapy [8] had 8-year actuarial LR rates of 17% (≤ 2 mm) and 9% (>2 mm) ($P = 0.27$) with a median follow-up time of 82 months. Freedman et al. [9] at the Fox Chase Cancer Center had 10-year actuarial LR rates of 14% (≤ 2 mm) and 7% (>2 mm) ($P = 0.04$) with 76-month median follow-up time.

As Freedman, there are other Authors as Wazer et al. in [10] and Smitt et al. in [11] who published studies proving that at 10-years follow-up the breast tumor recurrence rate for patients with close (<2 mm) margins is similar to that in patients with positive margins.

Wazer [23] also published in 1998 that patients with close margins (≤ 2 mm) had the same low risk of LR as those with negative margins within the first 10 years. One year later, Papa et al. [12] published that small and clinically detectable unifocal tumors with close margins (<2 mm) could probably be treated without the need of further excision. The eradication of possible microscopic residual tumor could be done by radiation treatment alone, thus sparing the patient an additional surgical procedure.

In 1999, Peterson et al. [13] made some considerations saying that patients with focally close (one or two foci of tumor ≤ 2 mm) or focally positive microscopic margins can be treated with breast conserving surgery and radiation therapy, with local failure rates similar to those in patients with negative margins.

This classification was suggested by Schnitt et al. [14] dividing the case into negative, close to the margins, focally positive and more than focally positive. There is a clear difference among the four groups regarding the risk of local recurrences.

Some Authors consider negative margin as being >3 mm, as Pittinger et al. [15] who studied 211 patients affected by stage I and II breast cancer treated with BCT: in these patients the local recurrence rate was equivalent by Fisher exact test in patients with negative and close (≤ 3 mm) final margins (3%). In general, numerous reports demonstrate that the margin status influences the risk of recurrence. If the final margins are negative, the 5-years risk of local failure is 2–7%. If the margins are positive, the risk is 0–22%; if the margins are close, it is 2–11%; finally, if the margins are unknown the risk is 7–16% [6, 8–9, 20, 23–27]

The surgical re-excision due to the margin status in invasive breast carcinoma

Submitting a patient to a re-excision after conservative surgery for breast carcinoma has the purpose to reduce the

risk of local recurrence of disease. Freedman et al. [9] published that patients who obtained a final negative margin after a re-excision had the same low risk of LR in 10 years as the patients with the initially negative margin.

Neuschatz et al. [20] showed that re-excision specimens had positive findings in 30, 46, 68 and 85% in cases with focal, minimal, moderate, and extensive margin positivity, respectively. An important factor to be considered is the presence of extensive DCIS as a significant predictor of increased residual disease at re-excision [22]. On the other hand, most patients with close or focally positive margins do not have significant residual cancer in the breast [12].

The main difficulty is to know when the re-excision must be indicated, selecting those patients who could obtain more benefits with this procedure. Each case should be evaluated individually.

DCIS and margins

DCIS represents approximately 25–30% of all newly diagnosed, mammographically detected, breast malignancies.

There is no consensus yet on the minimal surgical margin to be taken in case of DCIS. Negative margins as large as 5 mm and even 10 mm have been suggested by some Authors to obtain good results in terms of LR.

According to Vicini et al. [16], due to the tendency of DCIS to be multifocal, very large surgical margins should be necessary to ensure low rates of LR.

Silverstein et al. [28] published that for DCIS excellent local control can be achieved without radiation therapy when margin widths of at least 10 mm are obtained, regardless of nuclear grade, the presence or absence of comedonecrosis, and tumor size.

It is often difficult to evaluate surgically the limits of DCIS, especially when the clinical aspect is made of diffuse microcalcifications. To decrease the risk of positive margins at the final histological examination, the surgeon should in principle remove a large quadrant to ensure a radical excision.

About the parameters possibly linked to the LR of DCIS, some studies reported the presence of comedo necrosis as specifically associated with LR [29–30], including the NSABP B-17 trial [1–3]. However, others have failed to find this factor as significant, especially with longer follow-up [31–33], suggesting that necrosis may have greater impact on early recurrence.

Radiotherapy

Many Authors suggested that positive resection margins are associated with low rates of LR after conservative surgery and radiation therapy when treated with high doses

of radiation boost. The strategy is to use moderate dose of radiation therapy to eradicate sub-clinical disease [34].

Ryoo et al. [35] reported that the risk of breast recurrence in patients with close or positive margins was 7% with the boost and 30% without the boost.

Heimann et al. [36] found that the 5-year local control for patient with positive resection margins was 91% with the radiotherapy up to a total dose of >60 Gy compared to 76% when doses were ≤60 Gy.

A randomized trial from the European Organization for Research and Treatment of Cancer (EORTC) has been made on 5,318 women with stage I/II breast carcinoma, by giving radiotherapy up to 50 Gy with or without a 16 Gy boost. All surgical margins were microscopically negative; patients with positive margin were randomized using a separate protocol. At a median follow-up of 5.1 year, actuarial rates of local failure decreased from 7.3 to 4.3% with the use of to 16 Gy boost [37].

Higher radiation doses (>65 Gy) are ineffective in overcoming the adverse effect of positive surgical margins on local tumor control [9, 26].

Systemic treatment

Some randomized trials have shown a reduction in LR when both radiation therapy and systemic therapy are used.

One of this papers was published by Park et al. [8] and concluded that among patients with extensively positive margins the rates of local recurrence (LR) were similar (26 and 29%) for the 31 patients treated with systemic therapy and the 35 patients treated without systemic therapy. Patients with close or negative margins had 5 and 8% rates of local failure with or without systemic therapy, respectively. However, among patients with focally positive margins, the 45 patients who received systemic therapy had a 7% LR rate compared with 18% for the patients who did not received systemic therapy.

Disagreeing with Park, Freedman et al. [9] showed that the delay of the recurrence with systemic treatment did not change the relative risk of local recurrence.

The risk of local recurrence

In the attempt of obtaining success in the local control of breast cancer, which may be translated as the absence of the local recurrence, many studies tried to identify which would be the more important factor of risk in this topic.

There is almost unanimity in the published studies that the pathologic margin status is the most important factor to determine the risk of LR after breast-conserving therapy [4, 5, 11, 38, 39].

There are studies that add other risk factors to the surgical margin, as in the publication of Darvishian et al., in

which the conclusion was that tumor size and the extent of linear margin positive directly correlates with local control in breast cancer patients [40].

There are studies analysing each factor in univariate analysis. Two of these studies are particularly significant: the first one by Tartter et al. [27] who examined 674 excision biopsy specimens from patients who were candidates to breast conservation. By univariate analysis, positive biopsy margins were associated with younger patient age, family history of breast cancer, larger tumor size, presence of DCIS, and presence of extensive intraductal component (EIC). By multivariate analysis, only large tumor size was found as a significant factor. The second study was done by Mirza et al. [41]: 1,153 consecutive female patients were evaluated at the M.D. Anderson Cancer Center. By multivariate analysis, in addition to surgical margin status, young age (<50 years), large tumor size, positive lymph nodes, no chemotherapy administered, and no endocrine therapy were significant independent predictors of loco-regional recurrence.

On the contrary, Ohsumi et al. [42] published that the status of the margins was not a significant predictor for local recurrence in a univariate analysis.

There are studies conducted in patients affected by DCIS, which consider the width of tumor-free margin as the most important prognostic factors in BCT [16, 20, 25, 30, 31, 43].

A retrospective analysis of a series from the Memorial Sloan-Kettering Cancer Center has shown age, comedo subtype, grade, margin status, and postoperative radiotherapy as significant predictors of local failure on univariate analysis. On multivariate analysis, however, only margin status remained significant [15].

Discussion

The status of surgical margin after breast conserving surgery in a important issue due to the impact of positive margins on the incidence of local failure.

In case of close surgical margins after conservative surgery more data are needed to support the best approach which could be surgery and/or radiotherapy. This uncertainty is also due to the fact that a uniform definition of “close margin” does not exist yet.

Conservative treatment of early invasive breast carcinoma, mainly by quadrantectomy, sentinel node biopsy and/or axillary dissection and radiotherapy is currently an accepted procedure worldwide. The technique allows oncological safety and better psychological and cosmetic results than radical mastectomy.

Nevertheless, local recurrence in patients submitted to conservative surgery is more common than in patients

treated by mastectomy. The rate of local recurrences following breast-conserving surgery varies in different series between 5 and 10% 1–3%.

The incidence of local recurrence after conservative surgery is higher when surgical margins of the excised tissue are involved, regardless of radiotherapy, mainly in invasive carcinoma but probably also in DCIS. Radiotherapy at the standard dose (50 + 10 Gy) is not able to eradicate macroscopical tumor presence; its value is mainly in the subclinical disease.

Many Authors have pointed out the importance of residual malignant cells as a significant predisposing factor for local recurrence after conservative treatment [44–46]. The concept is that the ideal clear macroscopic margins are at least 1 cm in the lateral limits [47], or 2 cm in the classical quadrantectomy technique described by Veronesi in 1981 [48].

It was very well demonstrated by Holland et al. [49] that with breast conserving surgery residual cancer cells remain on the margins in a significant number of cases. The addition of radiotherapy in these cases has exclusively the aim of acting as a complement of surgery by destroying residual microscopic cells. The width of surgical specimen is critical in influencing the outcome of breast conserving surgery in terms of margin status and risk of local relapse: this was demonstrated in the Milan II trial [50].

Nevertheless, there are other risk factors for local recurrence after breast conserving surgery, such as inadequate dose of radiotherapy (Guys hospital study), tumor multifocality and multicentricity, vascular invasion [51].

Many Authors focused the attention on the effects of the intra-operative pathological evaluation of surgical margins during quadrantectomy; breast cancer may be a multifocal disease, and in a significant number of cases it is multicentric. The problem is that if we look extensively to the margins, it will be quite sure that we find microscopic disease. Radiotherapy has the aim of destroying these microscopic foci.

Possible causes of different results in the literature when dealing with conservative surgery, margin evaluation and local relapse of disease depend on:

- (1) Individual characteristics of the patients and their capability to have different reactions in front of similar situation.
- (2) Technical aspects inherent to the treatment:
 - a. Selection criteria
 - b. Radiological evaluation and intra-mammary staging of the extension of the disease
 - c. Pathological evaluation considering available resources
 - d. Surgeons and their training and technique

- e. Radiotherapy: training, skills, technique and resources
- f. Traduction of the pathology findings in clinical manifestation of the disease in terms of local relapse during the time.

Considering that breast cancer is frequently a multifocal disease, many times multicentric, the finding of positive or negative margins could in principle be a matter of how extensive we looked at the margins. Negative margins do not mean necessarily that we did not leave multifocal tumor in the breast.

When analysing the results of the Milan II trial, there is a big difference in local recurrence in favor of quadrantectomy. This study [50] showed that positive margins were rare in quadrantectomy patients (4%) but frequent in lumpectomy patients (16%). All patients were treated post-operatively with radiotherapy, and of 169 sampled patients with negative margins treated with quadrantectomy, 6 experienced a local recurrence (4.5%) and of 243 patients with negative margins treated with lumpectomy, 21 experienced a local recurrence (8.6%).

We can conclude that sometime cancer cells remain in the breast beyond the negative margin of resection. There are known reasons for this failure: breast specimens are irregular, the evaluation of margins is made by random and not all the surface is examined, and the cancer spread around the tumor is not a continuous process, so areas of discontinuity are found.

At the European Institute of Oncology in Milan our policy after the detection of close surgical margin for invasive breast carcinoma is to treat patient with personalised radiotherapy. We do not perform re-excision, due to the idea that the prognosis is not influenced by close surgical margins in presence of a good radiation treatment.

Acknowledgements We wish to acknowledge Maria Grazia Villardita for the precious contribution to the entire development of this review.

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