Tumor margin after conservative breast cancer surgery for early disease: an issue or not?

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Summary

Conservative breast surgery (CBS), i.e. tumorectomy (TUM), has replaced more radical surgical approaches such as mastectomy (MAST) and quadrantectomy (QUAD). The aim of surgeons is to avoid recurrence and still obtain a good cosmetic result. After CBS for early disease, adjuvant radiation consisting of whole breast irradiation followed by a boost dose on the surgical bed is standard of care. However, the question is whether this approach is able to consolidate local control irrespective of the extent of the surgical margin. No consensus exists in the literature concerning what should be considered as a minimal and hence a safe margin. This review will summarize the published data in order to try to define a pragmatic treatment approach.

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Mastectomy (MAST) has progressively been replaced by more conservative approaches. There is enough evidence obtained in randomized controlled trials to suggest to patients to choose for a CBS, provided the tumor diameter allows an acceptable cosmetic result after curative surgery. Quadrantectomy (QUAD) tested in the Milan trials is an alternative surgical approach to MAST resulting in excellent local control.[1] Tumorectomy has been proposed as an alternative to QUAD. Provided external adjuvant radiation therapy is offered to patients submitted to less than MAST, the long term local control rates are similar to more radical surgical approaches and the cosmetic results are considered good to excellent both by physicians and patients. Interestingly, in the Milan experience the local recurrence rate in the group of patients submitted to QUAD, axillary dissection without adjuvant radiotherapy is similar to the rate observed in the subgroup of patients treated with TUM, axillary dissection and radiotherapy. One could potentially conclude from these data that a more radical surgery such as QUAD gives the opportunity to avoid radiotherapy in node negative patients. However, the best local control rate is observed after QUAD, axillary dissection and radiotherapy with a recurrence rate not exceeding the one observed after MAST. This difference between TUM and QUAD is especially evident for patients with an extensive intraductal component (EIC). One explanation may be related to the amount of residual disease after TUM especially in case of an EIC, which in the Milan trials was not eliminated by the adjuvant radiotherapy.[2,3] Based on these data, one could consider there is an optimal margin after resection of the primary tumor. If this margin is obtained, residual tumor burden is probably that low that an optimal effect of adjuvant radiotherapy can be expected. The incidence of residual carcinoma depends on margin status as illustrated in *Table 1*.

Definition of a tumor-free margin

It is difficult to compare the published data for several reasons. The very first question is obviously how to adequately define the resection margin. One should not forget that the assessment of the margin status is a sampling procedure prone to error. It has been shown that at least more than 3,000

Table 1. residual carcinoma after CBS depends on margin status (Modified from *Wazer et al.*)[2,3]

Margin assessment	Residual carcinoma
Tumor at inked margin	46 – 67 %
Margins "close" to the tumor	23 – 32 %
Margins negative	12 – 26 %
Presence of an EIC	31 – 88 %

EIC = extensive intra-ductal component.

histological sections would be required to fully examine the surface of a spherical specimen only 2cm in diameter.[4] On the other hand, the interpretation of the data on margins is particularly hazardous as local and distant failure are very often considered as independent events during the statistical interpretation of clinical data. Hence censoring patients with distant metastases when analysing local control may heavily bias the results. Therefore, one can assume that the reported incidence of local recurrence in most published data is extremely variable and is only an underestimate of the true recurrence rate (*Table 2*). A methodology based on competing risks is therefore more appropriate. Using this statistical approach patients developing distant metastases are not censored but considered as success provided there is no indication for a local recurrence. Moreover, as shown in the overview by *Singletary et al*, the adverse effect of positive margins on local recurrence (LR) is influenced significantly by follow-up duration (*Table 2*). In case of negative margins there is no significant change in LR rates at follow-up times ranging from 36 to 120 (r = -0.31, p = NS) months whereas in case of positive margins, the LR rates increases significantly (r = 0.75, p = 0.008).[5]

Moreover, there are various techniques described for margin assessment such as frozen section analysis and touch preparation analysis. One should not only estimate whether the resection margin is positive or "close", but also try to estimate quantitatively the extent of positive margins.[2,6] It seems important to define not only the clearance around the tumor in mm but also the number of positive margins (*Table 3*).[6] There is currently no consensus in the literature on the definition of a "close" and negative margin.[5,7] There is a remarkable difference between North America (US) and Europe (EU): nearly 50% of health care professionals involved in breast cancer treatment are considering that the absence of cells at the inked margin can be considered as a negative margin in the US, whereas in the EU we are mostly considering a negative margin when there is a minimal clearance of 2mm.[7] This is obviously not without consequences on the burden of residual tumor potentially left after CBS (*Table 1*). It is particularly difficult to compare the efficacy of radiation therapy in this context. In most of the randomized trials, selected in the nineties to define the National Institute of Health (NIH) consensus statement, there's an enormous variability in the definition of a negative margin (*Table 4*).[7] Consequently this yields a wide variation of guidelines and treatment policies in different institutions. Some are considering that the absence of tumor cells at the inked margin as defined in the NSABP trials is adequate whereas others require a margin of at least 1 to 3cm.[7-9] The former state that local control can be obtained with a more aggressive post-CBS approach, whereas the latter claim that close or positive margins predispose to ipsi-lateral breast tumor recurrence leading to a reduction of disease free and overall survival (*Table 3*).[10]

Prognostic factors in case of close margins

Close margins do not always have the same prognostic value. *Holland et al* have described the residual tumor cell burden as a function of the distance in millimetres from the resection margin to the primary tumor.[11,12] Not all histological subtypes of breast cancer carry the same risk. It has clearly been demonstrated that infiltrating lobular carcinoma (ILC) is much more prone to harbour positive margins than infiltrating ductal carcinoma (IDC). This is easily explained by the typical infiltration pattern of ILC. The incidence of positive margins for ILC ranges from ± 20% to ± 50% (*Table 5*).[13-17]

The type of tumor is not the only factor leading to an increased risk of a positive margin. The negative impact of an EIC was illustrated in the Milan trial. In the work of *Holland et al* the incidence of residual cells at a distance of ≥ 2cm and ≥ 4cm highly depends on the presence of an EIC in the pathological

Table 2: Impact of positive (2a) or close (2b) margins on local recurrence rate (LRR). The first column relates to the definition of the margin as published. The data are tabulated according to the definition of the margin and are given in median and ranges. N relates to the number of studies. The last three lines of Table 2a relate to studies with a follow-up exceeding 100 months (numbers in bold) (Modified from *Singletary E*).[5]

Table 2a	N° patients (range)	FU (months) Median (range)	Margin Neg. Median LRR%	Margin Pos. Median LRR%
+ vs – N = 12	44 – 869	75 (50 – 120)	4 (3 – 13)	15 (6 – 31)
Neg > 1mm N = 5	134 – 533	60 (57 – 127)	3 (0 – 7)	19 (3 – 22)
Neg > 2mm N = 11	210 – 1021	86 (36 – 120)	5 (2 – 10)	10 (0 – 22)
Neg > 3mm	183	54	3	25
Neg > 5mm N = 2	108 – 161	47 – 60	0 - 1	0 - 11
Microscopic N = 3	258 – 723	66 (48 – 72)	2 (2 – 4)	16 (9 – 18)
+ vs – N = 4	518 – 704	**120** > 100	**8** (4 – 13)	**16** (10 – 31)
Neg > 1mm N = 2	343 – 533	**> 100**	**3 – 7**	**16 - 19**
Neg > 2mm N = 4	303 - 984	**120** > 100	**2** (2 – 6)	**17** (14 – 22)

Table 2b	N (range)	FU (range)	LRR in %
> 1mm N = 3	Neg: 69 - 204 Close: 28 - 94 Pos: 37 - 188	45 – 53	Neg: 3 – 7 **Close: 2 – 11** Pos: 16 - 22
> 2mm N = 3	Neg: 157 - 968 Close: 17 - 142 Pos: 13 - 152	76 – 120	Neg: 2 – 7 **Close: 6 – 24** Pos: 8 - 22
> 3mm	Neg: 122 Close: 35 Pos: 4	54	Neg: 3 **Close: 3** Pos: 25
> 1 microscopic field	Neg: 333 Close: 108 Pos: 65	66	Neg: 2 **Close 6** Pos: 16
Not defined N = 2	Neg: 283 - 454 Close: 30 - 87 Pos: 23 - 24	68 – 76	Neg: 3 – 6 **Close: 8** Pos: 10 - 13

specimen (*Table 6*).[11,12]

It has been reported several times that age is predicting a worse outcome in breast cancer.[18-22] The question is why do young patients fail? *Wazer et al* highlight several reasons; one of these reasons is the presence of an EIC which is known to be associated with an increased risk of positive or close margins.[21] Together with other factors such as a poor histological grade, presence of lympho-vascular invasion, multi-centricity, negative oestrogen receptor status, presence of necrosis, the risk of recurrence is increased as compared to an older patient population. The same author demonstrates a near linear relationship between risk of tumor residuum and

Table 3. Local control (LC) at 5 and 10 years as a function of number of positive margins. It is noteworthy that in this set of patients there is no difference in LC between patients with an R0 resection and patients with a single positive margin (Modified from *DiBiase et al*).[6]

	5-years local control	10-years local control
1 positive margin	91%	74%
> 1 positive margin	77%	63%

Table 4. Definition of tumor margin in randomized controlled trials (used for the NIH consensus statement) (Modified from *Taghian et al*).[7]

Trial	Years	Margin definition
NSABP	1976 – 1984	No tumor cells at inked margin
NCI	1979 – 1987	No margin requirements
EORTC	1980 – 1986	Requiring a macroscopic margin of 1cm
DBCSG	1983 – 1989	Requiring < R2 resection (R0 and R1 eligible)
IGR	1972 -1980	Requiring a 2 cm margin
Milan	1973 - 1980	QUAD with 2-3 cm margin

NSABP: National Surgical Adjuvant Breast and Bowel Project; NCI: National Cancer institute; EORTC: European Organization for Research and Treatment of Cancer; DBCSG: Danish Breast Cancer Study Group; IGR: Institut Gustave Roussy.

margin status but the risk is considerably higher in patients younger than 45 years.[21] However, in this same cohort of patients the risk of residual tumor becomes independent of age and tumor margin in case of EIC. This latter observation clearly illustrates the complex relationship between tumor- and host-related factors, and the necessity to rely on large patient cohort data to make any meaningful conclusion on independent prognostic and predictive value of these various factors.

Does more intensive treatment solve the problem?

On can argue that tumor margin does not really matter provided no cells are found at the resection margin. The argument holds true if one can propose a tailored treatment to annihilate the risk of residual tumor after CBS. The philosophy behind this approach is easily understandable as one aims to obtain the best cosmetic result in case of CBS.[9] However, is there any published evidence around to claim that a more aggressive local postoperative treatment is able to control the disease without hampering cosmetic outcome later on?

Boosting the tumor bed is traditionally used in radiotherapy after CBS.[23] This approach is based on evidence issued from randomized trials. In the *EORTC trial*, the amplitude of the impact of the boost is age dependent.[24] Although one cannot distinguish a patient population which does not benefit from the boost, the therapeutic efficacy is larger in younger patients. Does that mean that the boost dose is sufficient to compensate in case of close margins? There is no real evidence in the current literature to support such a statement. On the contrary, there are data available showing that even a boost-dose tailored to the margin extent does not compensate for the increased risk of local recurrence. *Leong et al* for example, have increased the boost dose in function of the margin extent, raising the total dose up to 81Gy.[19] Notwithstanding this rather high total dose, the local recurrence rate remains unacceptable especially in younger patients (< 35 years). The ipsilateral breast tumor recurrence (IBTR) is 50%, 33% and 20% in case of positive, indeterminate and negative margins respectively. Similar data have been published by *Neuschatz et al*.[25] The boost dose after a 50 Gy whole breast irradiation in their series varies from 0 Gy in case of negative margins to 20 Gy if a positive margin is described after CBS. In between, the boost dose is tailored to the clearance in mm. Again, the incremental dose is not able to completely eliminate the risk of an IBTR. The 12

Table 5. Different rates of positive margin (in %) can be explained by tumor histology i.e. infiltrating lobular carcinoma (ILC) versus infiltrating ductal carcinoma (IDC).

Author / reference	ILC	IDC	p
Mai et al [13]	52%	26%	NR
Moore et al [14]	51%	15%	< 0.05
Silverstein et al [15]	59%	43%	< 0.003
White et al [17]	63%	60%	NS
Yeatman et al [16]	17.5%	6.9%	0.018

NR: not reported; NS: not significant.

Table 6. Residual carcinoma at a distance of 2 and 4 cm depends on the presence of an extensive intraductal component (EIC) (Modified from *Holland et al*).[11,12]

EIC	Positive	Negative
Residual tumor at > 2cm	59%	29%
Residual tumor at > 4cm	32%	12%

year actuarial local failure after a 20 Gy boost is still 17% in case of a positive margin. In contrast, the corresponding number after a 10 Gy boost dose is 0% in case of a clearance exceeding 5mm. For a clearance larger than 0 and up to 2 millimetres the local failure rate is still 9% after a boost dose of 20 Gy. One should realize that in most radiotherapy departments, based on the data from the *EORTC* and the *Lyon-trial*, the boost dose generally does not exceed 16Gy.[23,26]

Moreover, in the context of a revival of hypo-fractionation, a treatment schedule often used to reduce the treatment burden on the patients and to save machine time in busy departments, the role of the boost dose has still to be redefined making the estimation of the exact risk of an IBTR in case of close margins even more problematic.[27]

Partial breast irradiation instead of whole breast followed by a boost is currently under investigation.[28] The approach potentially allows the conception of a margin dependent intensive dose escalation. However, this approach is still to be considered experimental and must be tested in well designed randomized trials with an extensive quality control for the analysis of the pathological specimen and the assessment of the margin extent. Long-term data are mandatory to assess impact on cosmetic outcome. Moreover, experimental models vlearly illustrate that in case of breast cancer, the stem cells, known to be more resistant to treatment, are located at the periphery of the tumor exactly with-in the region potentially left behind after limited surgery. The latter may not be adequately covered when using certain surgical and radiation therapy techniques as the one suggested by authors using partial breast irradiation.

One should also realize that breast remodelling often performed during CBS greatly complicates the definition of the target volume at risk for the boost dose. There are two ways to deal with this problem: the first one is to cover larger volumes but this harbours the risk of increased long term toxicity and a worse cosmetic outcome, the second one is leaving the cavity as it is but this again might be deleterious for the final cosmetic aspect. Anyway, we strongly suggest surgeons to clip the surgical tumor bed but even that can be misleading for the definition of the target volume for the boost especially when breast remodelling has been performed.

One can argue that for patients requiring a systemic treatment, the local recurrence risk will be reduced adequately if patients are submitted to adjuvant chemotherapy. There are no randomized trials available which are sufficiently powered to definitely settle the question about the optimal sequence when chemotherapy and radiotherapy have to be combined in the adjuvant setting.[29,30] The concomitant use of doxorubicin-based regimens and radiotherapy is not feasible regarding the potentially powerful interactions and hence toxicity. Delaying local adjuvant radiotherapy after systemic therapy may therefore harbour an intrinsic risk of an incre-

Key messages for clinical practice

1. The evaluation of the margin in BCS must be considered a sampling procedure.
2. There is no consensus on what should be considered a safe margin.
3. The association of a close margin with age and EIC harbours a significant increased risk of local recurrence not really counterbalanced by radiotherapy.
4. Chemotherapy (anthracycline-based and intensified with taxanes) yields increased local control, but the delay to start radiation therapy may be deleterious especially in patients with close, positive or unknown margins.
5. Re-intervention, whether conservative or mastectomy, should be considered especially in young patients with a tumor harbouring EIC.

ased local recurrence, especially in case the resection margin is "close" to the tumor. Therefore, one should be cautious with these particular patients and *Bellon et al* states that obtaining "clear" margins by re-excision seems prudent before starting chemotherapy.[29] In a randomized trials published by *Recht et al*, the importance of the status of the tumor margin is highlighted. If the margin is close, positive or unknown, the incidence of local recurrence is higher in the chemotherapy first arm (CMF-P regimen) and the higher incidence of distant metastases in the radiotherapy-first arm group persists.[30] In the era of anthracycline-based chemotherapy, an abstract by *Bellon et al* reports a local recurrence rate of 32% in the chemotherapy-first arm as compared to 4% in the radiotherapy-first arm in their updated results of a randomized trial designed to evaluate the impact of the sequence in the adjuvant setting.[31]

The evidence concerning the possibility to reduce the risk by increasing the intensity of the adjuvant approach is not yet available. In the retrospective analysis of prospective randomized controlled trials runned by the *Cancer and Leukemia Group B* (*CALGB 9344*), *Sartor et al* claim that adding paclitaxel to doxorubicin and cyclophosphamide in node positive breast cancer patients, further reduces the risk of loco-regional recurrence at 5 years despite the further delay in the initiation of radiotherapy post-lumpectomy or in selected cases after mastectomy.[32] This author also states that margin status clearly influences the risk of local recurrence but quantitative data on how close the margins were are not available.

Conclusions

Being as conservative as possible is certainly a "laudable" approach especially - but not only - in young patients. However, this philosophy should not predominate over the risk of a local recurrence which yields demonstrable survival deficits. One should be aware that, especially in young patients and in case of EIC, radiotherapy is not able to reduce the risk of local recurrence to reasonably acceptable numbers. Increasing the dose to higher levels, does not really seem to help in tackling the local problem. Increasing the intensity of the adjuvant chemotherapy does improve local control but harbours the risk of delaying radiotherapy in patients, especially in those at risk of a local recurrence. One should therefore be particularly cautious with close margins and evaluate the possibility of a surgical re-intervention, eventually consider mastectomy and reconstruction, especially in young patients and patients with an EIC.

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