Review Article

Pathology and resection margins following mastectomy prior to immediate breast reconstruction

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Abstract: Risk of local recurrence (LR) (and even distant disease-free survival) after mastectomy is associated with margin status. Furthermore, the vast majority of LR are located at the anterior (superficial) margin. Margins in mastectomy are considered anatomical borders and not true resection margins; such a conception may erroneously lead to underestimation of the risk of LR after mastectomy. If dissection is accurate along the fascia, only skin, subcutaneous tissue and minimal residual breast gland tissue (rBGT) are expected to remain in the patient. However, the subcutaneous fascia is an inconsistent anatomical structure that may be absent in almost half of patients. Studies and routine clinical practice suggest that resection may frequently, though often focally, be within the breast glandular tissue leaving various amounts of rBGT. Such areas may be nidus for subsequent de novo or recurrent premalignant or malignant disease. There is no consensus on handling of close/positive margins and intervention is extrapolated from studies on breast conserving surgery with subsequent radiotherapy. Handling of a close/positive margin is complicated by poor correlation between the *ex vivo* findings on the specimen and the attempt to relocate the area of concern in a patient with reconstructed breasts. In this clinical practice review, we strongly advocate for reporting of the lesion-to-margin distance in mastectomies to collect further evidence on the association between LR and margin status.

Keywords: Pathology; breast; mastectomy; reconstruction; superficial margin

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Introduction

The challenge of histopathological examination is to bring complex, three-dimensional biological structures into a two-dimensional understanding. Though constantly striving to describe and quantify all parameters meticulously, histopathology cannot capture the comprehensive picture of multifaceted tumor biology. Instead, it provides the best possible estimation of the tumor's true biology. Current

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treatments are nevertheless based on these estimates, which is also true for handling of close/positive margins based on evidence regarding associations on local recurrence (LR) rates and lesion-to-margin distances.

Skin sparing (SSM) and nipple sparing mastectomies (NSM) aim to surgically remove all breast gland tissue via dissection at the subcutaneous fascia level. The superficial/anterior margin is, therefore, considered an anatomic boundary, and not a true resection margin and the flap is expected to hold only skin and subcutaneous fat and minimal amounts of residual breast gland tissue (rBGT). As such, the nipple base in NSM is considered the only true resection margin. There is no consensus on the appropriate intervention in the case of a close/positive superficial margin in mastectomies and handling varies from no intervention, to intervention strategies based on extrapolating level III evidence on breast conserving surgery (BCS) followed by radiotherapy (RT) (1,2). In addition, the superficial/anterior margins in case of mastectomy may not be reported regardless of the surgical procedure (3,4).

In this review, we emphasize the importance of reporting the status of the superficial/anterior margin and the lesion-margin distance to collect evidence regarding the risk of LRs associated with the superficial margin status, and provide guidelines for management of patients with positive superficial margins. Furthermore, we encourage a multidisciplinary effort for better orientation/marking of specimens to correlate *in vivo*/*ex vivo* findings thereby securing re-excision of the right area of positive/close margins after mastectomy.

Anatomy

The breast gland is suspended in a three-dimensional fascia system; the anatomy of which has been described through autopsy studies all the way back to Vesalius (5,6). The superficial fascia parts into a dorsal and a ventral sheet that fuses in the periphery of the breast as the circum-mammary ligament (6). The dorsal sheet constitutes a continuous and well-defined layer separating the breast glandular tissue from the pectoral muscle. The ventral sheet of the superficial fascia (= subcutaneous fascia) is, on the contrary, a delicate and discontinuous structure. Based on a study of breast resection specimens, the ventral sheet is an inconsistent anatomical structure and may be absent in almost half of the patients (7). Both sheets of the fascia are separated from the breast glandular tissue by a layer of fatty tissue of varying thickness. The subcutaneous fascia is further separated from the skin by varying layers of subcutaneous fat (median thickness of subcutis 10 mm; range, 0–29 mm) (8,9). In a study by Beer *et al.* (7), the minimal distance from breast glandular tissue (beneath the fascia) to the dermis was 0.4 mm in patients where the subcutaneous fascia could be found; a distance from dermis to breast tissue of >5 mm was only encountered in 17% of specimens. This distance shows inter- and intra-personal variation. The extension of the breast tissue may be highly imprecise and breast glands may be found in close proximity to skin adnexal structures in some areas and with larger distance in others. In some women a clear distinction can on the other hand be seen between the compact fibroglandular tissue and the overlying fatty tissue (beneath the subcutaneous fascia). The posterior sheet of the fascia is connected to the ventral sheet of the fascia through vertical suspensory ligaments (Cooper's ligaments) traversing the glandular tissue posteriorly-anteriorly and anchoring the breast gland to the dermis (10). Accordingly, Cooper's ligaments may be found below and above the subcutaneous fascia level. Isolated glands or lobules may be present in Cooper's ligaments and have been documented in the subcutaneous fascia in almost half of patients (7). Lobules may also be present in the papilla in 9% to 17% of nipples (9,11). Removal of the whole breast during mastectomy will therefore inevitably leave small amounts of breast glands in patients, and a small risk of subsequent *de novo* premalignant or malignant lesions persists.

Pathological evaluation of margins

Histopathological examination of margins in BCS as well as in mastectomies begins with clinical information. The quality of the examination depends on availability of information regarding e.g., size of the lesion, if the lesion is well-defined or not, potential satellite foci and distribution of calcifications as determined by imaging. Unambiguous orientation of the specimen by the surgeon is also crucial for the pathologist. Skin-sparing mastectomies and especially NSM have no unique characteristics or features. It is therefore imperative to highlight e.g., two sutures in the cranial and lateral fields to ensure reliable assessment of margins. *Figure 1A-1C* shows macroscopical pictures of a nipple-sparing mastectomy as it appears when received fresh and unfixated. The base of the nipple in NSM is often not clearly identifiable after a short period of ischemia and drying of the fresh specimen (*Figure 1A*), so this also needs marking by the surgeon. The nipple base may also not be clearly visible upon sectioning and formalin fixation

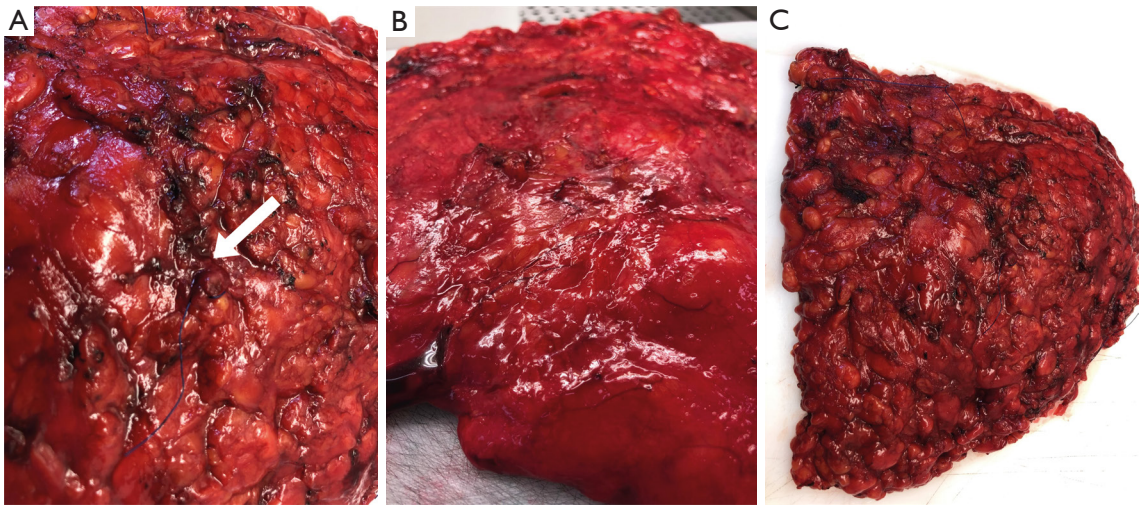

Figure 1 Nipple-sparing mastectomy. (A) Nipple base marked by one suture (arrow). (B) Dorsal sheet of the superficial fascia. (C) Varying amounts of fat covering the superficial/anterior margin (specimen marked with short suture cranial, long suture lateral).

Figure 2 Skin-sparing mastectomy with artefacts from fixation.

further compromises the evaluation. Most optimally, the marking of the base of the nipple is done with 4 sutures. Specific information on the surgical procedure is essential for accurate pathological examination, e.g., if the dorsal sheet of the fascia is present on the specimen. If additional tissue has been resected (after initial mastectomy) in the same procedure, the pathologist needs to know the location of this tissue, if it is not stitched to the mastectomy. Any prior sectioning of the specimen, cautery artefacts and fragmentation before the pathological assessment limits the ability to evaluate the margins.

The macroscopical examination is a combination of inspection and palpation. Optimal evaluation of margins begins by inspection of the fresh specimen, though varying national and local guidelines and logistics do not allow for evaluation of fresh specimens in all institutions. Inspecting the fresh specimen, nevertheless, leaves the pathologist with the best impression of the "*in vivo*" appearance of the breast and the natural boundaries/fascia's are easier to appreciate. Subsequent fixation creates artefacts due to shrinkage, retraction and deformation (*Figure 2*). Following mastectomy, the dorsal sheet can easily be visualized macroscopically on the posterior side of the fresh specimen (*Figure 1B*) and may also be visible microscopically. However, the subcutaneous fascia (ventral sheet) is rarely visible macroscopically; mainly due to varying amounts of subcutaneous fatty tissue covering the surface of the specimen (*Figure 1C*). Microscopically, the subcutaneous fascia is difficult to appreciate due to the fascia being very thin (often less than 10 µm) and discontinuous (*Figure 3A,3B*). Often, the fascia cannot be verified microscopically. The impression of the fascia on the *ex vivo* specimen may contrast with the surgical impression of an avascular plan separating the subcutaneous fat and the breast tissue. During macroscopical evaluation and grossing, the superficial margin of the specimen may be inked, sometimes in several different colors to maintain the orientation (*Figure 4A-4D*), but margins can also be identified by submitting them into specific cassettes (*Figure 5A-5C*). Hereafter, the mastectomy is sectioned following national and/or local guidelines, based on fresh or fixated specimens. In Denmark, the Danish Breast Cancer Group (DBCG) have guidelines for imaging, pathology, surgery and RT for patients with breast cancer and ductal carcinoma in situ (DCIS) and non-classical

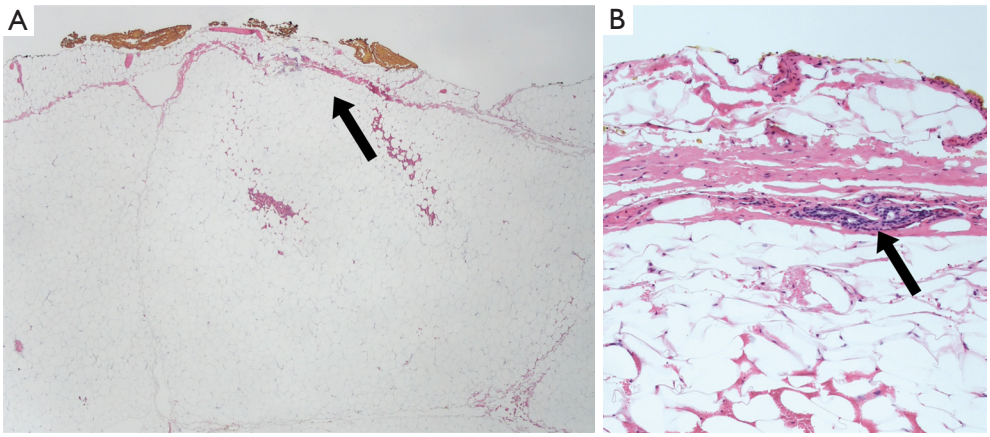

Figure 3 Microscopical sections from a skin-sparing mastectomy stained with hematoxylin-eosin stain. (A) Microscopical picture showing example of the subcutaneous fascia (arrow) below a yellow-inked superficial margin (original magnification ×2). (B) Isolated glands in subcutaneous fascia (arrow) (original magnification ×10).

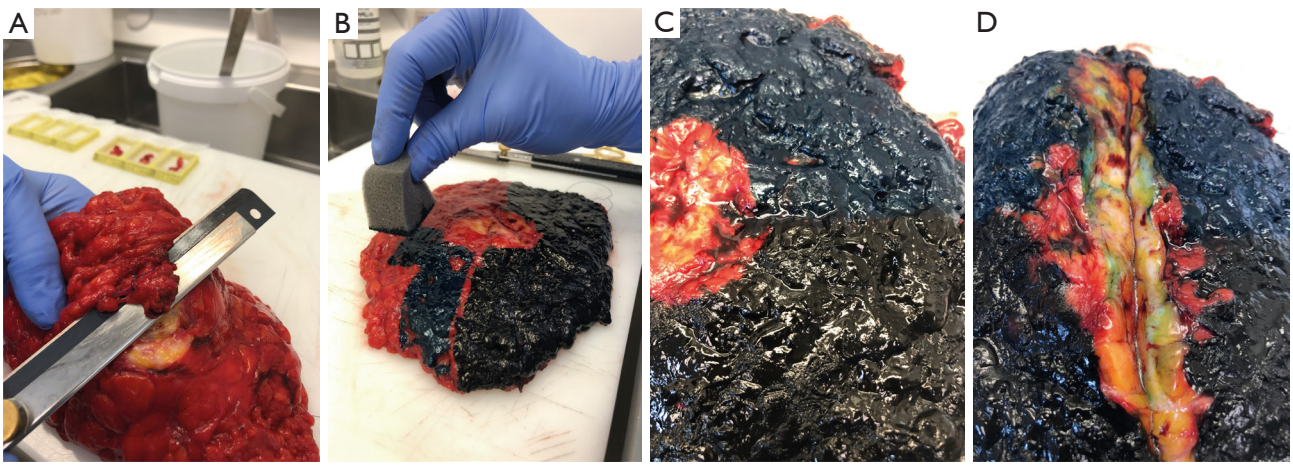

Figure 4 Macroscopical handling of the anterior/superficial margin of a nipple-sparing mastectomy. (A) Tangential sections from the resection margin corresponding to the suture-marked nipple base is taken. (B,C) Inking of the anterior/superficial margin in two colors (upper quadrants: green; lower quadrants: black) (nipple base not inked). (D) Perpendicular section on the anterior/superficial margin.

lobular carcinoma in situ (LCIS). There is a high adherence to the national guidelines across Denmark. Institutional and personal preferences may, however, lead to varying grossing procedures similar to variations due to surgeon preference and surgical technique. In general, the whole mastectomy will be sectioned in thin slices for examination. Smaller sections from the lesion will be secured for microscopic analysis as well as any additional areas that are macroscopically and/or palpably distinct from normal breast tissue. These sections also include areas representing the macroscopically closest lesion-to-margin distance.

Sampling from margins can be performed using either tangential sections or perpendicular sections (*Figures 4A*,*4D*,*5A*,*5B*). The tangential approach is comparable to peeling an orange, which allows for examination of a large area of the surface of the margin. Due to the uneven surface of the mastectomy, the sections chosen for microscopy may, however, vary in thickness (from 2–3 mm). As such, using the tangential approach can lead to misclassification of the exact distance from lesion to the inked margin. Estimation of distance to margin (e.g., "on ink", <1 mm, >2 mm) can, however, be obtained through

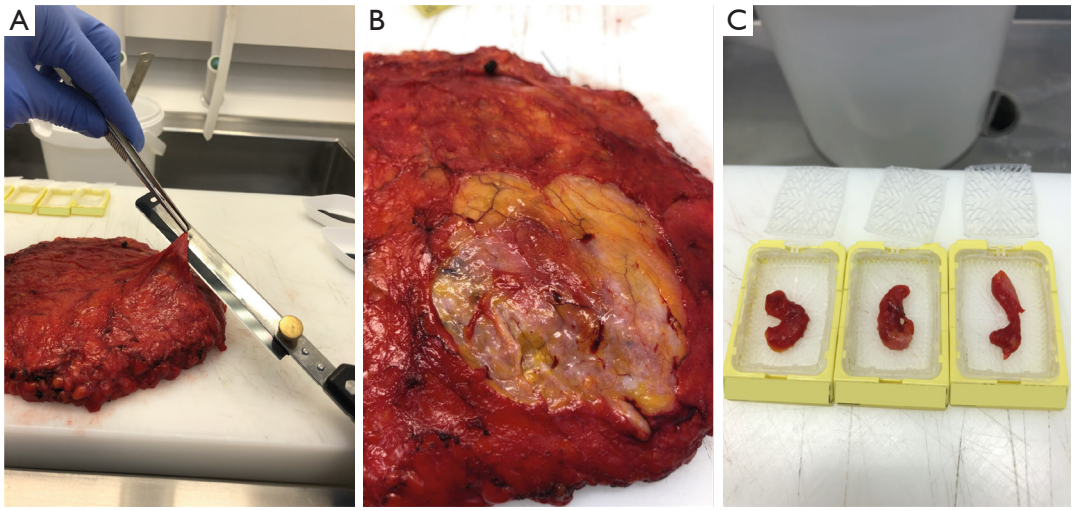

Figure 5 Macroscopical handling of the posterior/deep margin of a skin-sparing mastectomy. (A) Removal of the dorsal sheet of the superficial fascia with tangential sections. (B) After removal of the fascia over the lesion. (C) The sections of the fascia placed in three cassettes.

deep level sectioning. On the other hand, the perpendicular approach allows measurement of the exact lesion-to-margin distance. However, this approach relies on visualization of smaller, representative areas of the margin of interest and <1% of the margin is expected to be examined (12). The choice of approach varies between pathologists and between specimens. and may be combined if preferred, and it is in general not regulated by guidelines. A survey among Danish breast pathologists, showed that it is primarily perpendicular sections that are taken in areas of interest. Studies of BCS have shown a higher proportion of reported positive margins with the tangential approach, which may partly be due to its limited ability to discriminate close and involved margins (13,14). Similarly, the guidelines may not state how many sections should be sampled, and if sections should be taken from (potentially unaffected) tissue, which is not in the vicinity of the lesion (e.g., from all 4 quadrants) (15). The use of whole mount/large section slides may assist in creating a better view of the lesion, the 3D-architecture and relation to margins (12).

The microscopic analysis relies on the representative sections sampled during grossing. Danish guidelines recommend verification of the margins if they are macroscopically estimated to be less than 15 mm (16). Microscopically, the appearance of breast glandular tissue can easily be distinguished from sporadic glands present in Coopers ligaments. However, the pathologist should be careful not to regard grooves in the uneven fatty tissue as the true surface, when measuring distances from lesions to the superficial margin. Focal resection in the actual breast glandular tissue is not an infrequent finding in SSM/NSM specimens; a finding easily distinguishable from the presence of focal diminutive glands in e.g., Coopers ligaments or subcutaneous fascia (*Figure 3B*). The distance to closest margin is routinely reported, but in some institutions, the distance to the deep and/or superficial margins may not be reported. Most national guidelines do not provide specific guidance on handling of the superior/anterior margin of mastectomies (4,15-19). In the College of American Pathologists (CAP) guidelines and guidelines of The Royal College of Pathologists (4,19), the synoptic report is recommended to include distance to margin including specification of which margin, also including the deep/posterior and superficial/anterior margins. In the Danish DBCG surgical guidelines, the surgical procedure is, however, considered radical even if there is "tumor on ink" at the superficial margin as long as the surgeon has reported dissection along the superficial fascia (16).

The CAP guidelines recommend including the extent of involvement defined as unifocal (1 focal area of carcinoma at the margin), multifocal (2 or more foci of carcinoma at the margin) or extensive [carcinoma present at the margin over a broad front (>5 mm)] (4), but there is no evidence for these arbitrary categories.

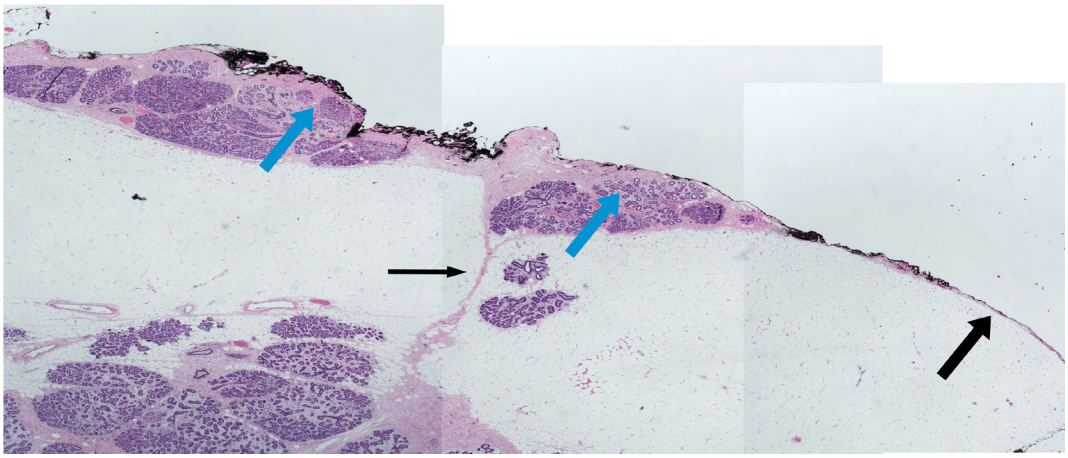

Figure 6 Surgical resection below the subcutaneous fascia (fat black arrow: subcutaneous fascia on ink; thin black arrow: Coopers ligament below the subcutaneous fascia level; blue arrows: resection in normal fibroglandular tissue below the fascia level) (hematoxylin-eosin stain, original magnification ×2).

Risk of leaving residual breast tissue

In general, the studies attempting to measure rBGT are limited in number and characterized by using highly varying methodology.

Recent postoperative magnetic resonance imaging (MRI) based studies have shown a higher risk of leaving rBGT in SSM/NSM as compared with simple mastectomy (20,21) with higher likelihood in risk-reducing mastectomies compared with therapeutic procedures. In the study by Woitek *et al.*, rBGT was found in 20% of patients (2.8% after total mastectomy, 13.2% after SSM and 51% after NSM). The finding of rBGT was significantly higher in NSM than in SSM (P=0.003), but with no difference in regard to the location of rBGT (P=0.305). The risk of leaving residual breast glandular tissue has, in general, been described as greatest in the subareolar area and in the upper outer quadrant (20,22). Based on histopathological findings, several earlier studies have described an association between flap thickness and the presence of rBGT (23-25). In the MRI studies, a mean flap thickness of 13.2±9.2 mm (range, 2–39 mm) (20) and 12.1 mm (range, 0–73 mm) (21) was found. The flap thickness was thinnest in the central areas (9.6 mm) and thickest in the periphery (23.2 mm) (20). In support of the histological studies, an association with flap thickness and rBGT was reported on MRI by Giannotti (21), whereas such an association could not be found by Woitek (20).

In the prospective SKINNI trial, systematic biopsies after SSM and NSM were taken from 14 locations in the flap, followed by histological verification of the presence of rBGT in 1,844 biopsies from 160 patients. rBGT was found in 51.3% of skin-flaps and was found to be significantly associated with type of surgery (68.9% NSM *vs.* 40.4% SSM, P<0.001). The amount of rBGT depended on patient anatomy and a varying distance from breast tissue to margin was found within the same breast (range, 0–10 mm), when measured by the pathologists (26). The presence of rBGT was also dependent on the individual surgeon (P<0.001); all of whom were skilled surgeons with high surgical volumes (>50 surgeries/year). These findings contrast to those observed by Woitek *et al.*, who did not find an association with the individual surgeon (20). Neither Woitek, nor Papassotiropoulos could confirm the assumption that body mass index (BMI) was associated with increased rBGT (20,26). Limited view during surgery in relation to incision type has also been assumed to influence the risk of leaving rBGT. Nonetheless, while a periareolar incision was almost exclusively used in SSM, an association with rBGT and incision type was not found in the SKINNI trial (26).

Based on the current data, mastectomy type and indication influences the risk of rGBT. Factors such as varying thickness of subcutaneous fat layer within the same breast, surgical experience and younger patient age may contribute to a resection that may—at least focally—be below the fascia level and in the actual glandular tissue (*Figure 6*). Since a larger surface is left in SSM/NSM than in simple mastectomies, there is likely to be more residual breast tissue. The importance of rBGT in terms of risk of

developing a subsequent malignancy and the impact of age-dependent involution on this risk are unknown.

Risk of LR after mastectomy and spatial location of recurrences

The risk of loco-regional recurrence (LRR) after mastectomy is low, 2–5% at 10 years, though earlier studies have shown higher LRR risks (up to 20%), e.g., in patients with DCIS. In a recent systematic review of 21 studies (including 6,901 patients) treated with mastectomy (cancer or DCIS), risk of LR was found to be 3.5% with a median time to LR of 26 months (range, 1–169 months) (27).

In a systematic review of 34 studies including 34,833 patients treated with mastectomy for cancer or DCIS, a positive (tumor on ink) or close (<2 mm) margin was in multivariate analysis (MVA) associated with a greater risk of LR [hazard ratio (HR) =2.29 (1.35–3.89) (on ink) and HR =2.96 (2.20–3.98) (<2 mm), respectively] (1). The risk was even more pronounced in SSM in subgroup analysis with an adjusted HR of 3.40 (1.90–6.20) for LR, if there was positive margin with tumor on ink. The review further proved an association between distant disease-free survival and positive margins after mastectomy in MVA [HR =1.53 (1.03–2.25) (on ink)]. In the included studies reporting on multivariate models', the factors considered included molecular subtype and use of adjuvant therapy (RT and chemotherapy), but information on e.g., BMI or preoperative breast volume was not reported. In addition, a study by Bernstein-Molho and colleagues, investigated rates of LR in BReast CAncer Gene (BRCA) mutation carriers with breast cancer according to the type of surgical procedure (28). They found that those with early stage tumors (T1–2, N0) who underwent immediate breast reconstruction (IBR), without postmastectomy RT (no indication for RT) had higher rates of LR compared with BRCA carriers, who had more advanced disease stage and underwent breast conserving therapy (BCS with RT) or IBR and postmastectomy RT. The cumulative LR rate was 11.8% in the IBR non-RT cohort compared with 0 of IBR-RT group (P=0.01) and 4.7% in the BCS-RT group (P=0.06). As many of the LR occurred within the first 2 years of follow-up, the authors suggested that residual tumour foci and not only rBGT might be responsible for high LR rates in this population.

The spatial location of LR after mastectomy has been studied in a systemic review of the literature by Kaidar-Person *et al.* (27). The authors concluded that 82% of LR were located in the skin/subcutis and only 18% at the pre-pectoral area. In studies reporting relation between the tumor bed location and LR, 80% of LR were found to be located near the primary tumor bed. After SSM/NSM, LR were exclusively found to be located in the skin/subcutis. These findings suggests that residual tissue/disease has been left at time of surgery. Since superficial margin status in SSM/NSM may not be acted upon and hence not reported, the risk of LR may be underestimated. These results, nevertheless, emphasize the importance of the anterior/superficial margin status and the need to report these margins.

Considerations on how to report and handle a positive margin

After surgery, if a positive margin is reported, the specific area may be difficult to locate during histopathological examination of the specimen, but even more difficult to relocate in the patient; now having a reconstructed breast. Use of photo-documentation during grossing may help pinpoint the area of interest in the case of close margins, but may not help identify the corresponding area in a patient subsequently. Similarly, the insertion of a clip in the patient to indicate areas of concern may not help the pathologist, and so resecting more tissue from these areas during primary surgery is recommended instead. Performing frozen sections from areas of concern during surgery may be used to guide the decision of resecting further tissue in the area. This approach is used in some institutions including Federal University of Goias and the Araújo Jorge Hospital, from Goiás Anticancer Association, in Brazil (personal communication with breast surgeon Ruffo Freitas-Junior). The advantage of this perioperative evaluation is, however, also time consuming, and from a technical perspective, it should be emphasized that the morphology on frozen sections may be suboptimal, and may compromise the distinction between DCIS and e.g., simple ductal hyperplasia.

If the surgeon is uncertain of the location of the positive margin, this may impede further surgery and treatments. Importantly, radiation planning may be hampered as well, as it will be impossible to assure good coverage to the high-risk region. This may result in the need for an additional boost dose to the location of the positive margin. In addition, postmastectomy radiation after IBR leads to significant complications, especially in case of an implant base reconstructions (29). A bolus (tissue equivalent) may be needed to assure coverage of the superficial volumes

of the reconstructed breast (30-32), and an additional radiation boost to increase local control (33). These additional treatments are associated with increased acute and late radiation-related toxicities, leading to implant/reconstruction loss without significant improvement of LRs or disease control. A radiation boost has been associated with postoperative infections, skin necrosis, and implant exposure. In case of implant reconstruction patients, the boost was independently associated with increased risk of implant failure (33). Therefore, preoperative planning of appropriate surgery is mandatory to avoid that positive/close margins are the only indication for radiation in these patients.

Handling of a close/involved margin in SSM/NSM demands a well-functioning multidisciplinary communication, but it is equally important for the surgeons and pathologists to constantly communicate on the quality of the individual procedures—even in patients with negative margins. This involves quality control and an honest communication on whether the resection is in fact in the level between the subcutaneous fat and the breast glandular tissue. It is of great importance that the pathologists respect that the subcutaneous fascia may be easily appreciated by the surgeons during surgery, though not easily seen during grossing. It is equally important, that the surgeons acknowledge that microscopically verified breast tissue on the ink, not related to isolated glandular structures in Coopers ligaments or sporadically present in the fatty tissue, unequivocally indicate a resection below the fascia level. We, therefore, suggest that surgeons and pathologists work in tandem to consult on the presence of glands in the different quadrants, periareolar area etc., thereby optimizing the quality of their surgical technique.

In the study by Al-Himdani *et al.* (3) of 577 breast cancer patients undergoing mastectomy at a single institution, the authors concluded that failure to re-excise in cases of margins with a distance below 1 mm led to an unacceptably high LR rate [adj. HR =2.83; 95% confidence interval (CI): 1.7–4.73)] after SSM. The authors further stated that they, based on these results, prospectively changed their institutional practice to obtain negative margins by re-excision "despite the embarrassment to the surgeon at explaining the issues to the patient".

Conclusions

Current evidence shows that risk of LR after mastectomy is associated with margin status and that the vast majority of LR are located at the anterior/superficial margin especially in SSM and NSM. Anatomical and histopathological studies have shown the subcutaneous fascia to be very thin, discontinuous and absent in almost half of patients. As such, the subcutaneous fascia may not always be a reliable plane for distinguishing subcutaneous fat and breast tissue. Unwaveringly considering the superficial margin on mastectomies as anatomical boundaries is, therefore, a conception that erroneously may lead to underestimation of the risk of LR after mastectomy.

Based on the current data, we strongly advocate for the continuous reporting of the status of the superficial/anterior margin with exact measurement of lesion to margin distance, and preferably including information on extent of involvement. We further recommend that the pathologist include a note whenever presence of normal fibroglandular tissue is observed at the inked margin for continuous quality assurance for the surgeon.

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Footnote

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