

Surgical margins in breast-conserving therapy Current trends and future prospects



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Surgical margins in breast conserving therapy: current trends and future prospects

Inadequate surgical margins represent a high risk for adverse clinical outcome in breast-conserving therapy (BCT) for early-stage breast cancer. The majority of studies report positive resection margins in 20% to 40% of the patients who underwent BCT. This may result in an increased local recurrence (LR) rate or additional surgery and, consequently, adverse effects on cosmesis, psychological distress, and health costs. In the literature, various risk factors are reported to be associated with positive margin status after lumpectomy, which may allow the surgeon to distinguish those patients with a higher "a priori" risk for re-excision. However, most risk factors are related to tumor biology and patient characteristics, which cannot be modified as such. Therefore, efforts to reduce the number of positive margins should focus on optimizing the surgical procedure itself, because the surgeon lacks real time intraoperative information on the presence of positive resection margins during breast-conserving surgery. This review presents the status of pre- and intraoperative modalities currently used in BCT. Furthermore, innovative intraoperative approaches, such as positron emission tomography, radio-guided occult lesion localization, and near-infrared fluorescence optical imaging, are addressed, which have to prove their potential value in improving surgical outcome and reducing the need for re-excision in BCT.

KEY WORDS: Breast conserving therapy, New intraoperative modalities, Re-excision

Introduction

Breast cancer is the most common form of cancer and second leading cause of death in women in Europe and the United States^{1,2}. During the last 30 years, widespread mammographic screening and technological developments have led to a rapid increase in the diagnosis of

small, non-palpable breast cancer^{3,4}. Breast-conserving therapy (BCT), consisting of lumpectomy and irradiation therapy, has become the standard treatment for T1-T2 breast tumors and is regarded generally sufficient in appropriately selected patients^{5,6}. Large, randomized, clinical trials (RCTs) have reported no significant difference in disease-free and overall survival between BCT and traditional mastectomy^{7,9}. BCT is considered to be associated with a diminished psychological burden compared with mastectomy, offers better cosmetic results, and reduces wound infection risk¹⁰. The most important disadvantage of BCT is the lifelong risk for local recurrence (LR), in which case additional surgery is necessary¹¹. Large clinical trials have reported LR rates between 6% and 16%^{12,14}. Accurate localization is essential for

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adequate surgical removal of breast tumors, in which an optimal balance between good cosmetic results and preservation of resection margins is the primary goal. Obtaining tumor-free surgical margins decreases the incidence of LR of the primary tumor^{11,15,16}. However, previous studies have shown that the number of patients exposed to BCT in whom tumor cells were present at or near the cut edge of the surgical specimen after resection of the primary tumor ranged from 5% to 82%, with the majority of studies indicating positive margins in 20% to 40% of patients^{10,17,21}. To obtain tumor-free margins, mutilating additional surgical procedures have to be performed. Alternatively, intraoperative radiation therapy can be applied as a boost to the tumor bed or, postoperatively, to the biopsy scar^{22,23}. Boost radiation, as an additive to standard whole-breast radiation therapy, reduces the LR rate; the absolute effect of radiation therapy is of greatest benefit to women with higher risk of LR ($p < 0.0001$)^{23,27}. Adverse effects associated with boost radiation include decreased cosmetic outcome, delayed wound healing,^{27,30} and altered postoperative mammographic and ultra-sonographic findings at the original tumor site in case of detection of recurrent disease^{28,30}. BCT still has limitations in achieving an acceptable therapeutic outcome¹⁰. This review paper outlines the major challenges currently encountered intraoperatively and demarcates risk factors for positive resection margins and LR. In addition, current imaging modalities and future directions in achieving the highest feasible percentage of negative surgical margins in BCT are addressed.

Effects of positive margins

To assess strategies to decrease LR rates after BCT, several RCTs were performed and revealed numerous and varying risk factors that might be associated with LR (Table I). A large meta-analysis of 72 trials, containing information on 42,000 patients, assessed that local surgical control at 5 years showed a significant improvement in disease-free survival and overall mortality at 15 years follow-up²⁴. The influence of "close" margins, usually defined as tumor cells being present within 0 and B2 mm from the cut edge, is still controversial⁴. Several studies reported close margins to be a significant risk for increased rates of LR, as well as the apparent quantity of cancerous cells approaching the cut edge^{31,34}. In a recent trial conducted by Zavagno et al., 431V patients who underwent re-excision due to margin involvement were evaluated from a total of 1,520 patients who underwent BCT³⁵. The authors found LR rates after positive margins and close margins to be 51.8% and 34.1%, respectively ($p = 0.001$). However, no correlation was found between the distance of the tumor from the cut edge (range: 0.08-3 mm) and LR rate³⁵. These findings are consistent with the results of most of the stud-

ies performed on the correlation between margin width and LR rate, as reviewed by Singletary⁴. Margin closeness is therefore currently not seen as an indication for re-excision. Zavagno et al. suggest that residual disease in close margin involvement may be largely due to the existence of multiple cancerous foci and not to margin closeness by itself³⁵. Breast tumors are shown to grow multifocally in 59%, of which 71% grow at a distance 2 cm from the reference tumor³⁶. Therefore, margin status as such may be considered an important judgment factor in planning re excision, but cannot be seen as an indicator for the presence of residual tumor in the surrounding tissue³⁵. Adequate perioperative imaging of cancerous foci may be of great value to the surgeon. Singletary reviewed 34 studies on margin status and LR, in which a total of 15,000 patients were assessed.⁴ In 30 of 34 reviewed studies, persistent microscopic inadequate (R1) or macroscopic inadequate (R2) surgical margins were highly significant for LR compared with negative margins ($p = 0.0001$), depicting the relevance of margin status on the outcome of BCT. In a study by Jobsen et al. of approximately 2,300 patients, the LR rate was found to be related to positive margin status and young age³⁷. The authors found the 10-year LR-free survival rate for young women (≤ 40 years) with positive margins to be significantly lower compared with negative margins (34.6% vs. 84.4%, respectively; $p = 0.008$). The effect of positive margin status for invasive carcinoma seems to be limited to young women and is not only restricted to local control, but also to distant metastasis and survival³⁷. Because positive margin status is found to be an important risk factor for LR, substantial efforts have been made to understand the causes of the relatively high percentage of positive margins after BCT. A number of risk factors for positive margin status have been identified over the years (Table II). Again, young age is reported to be a strong risk factor for positive margin status^{20,37,41}. Vrieling et al. reported that the tumor was significantly larger in young patients (≤ 40 years) compared with older patients ($p = 0.001$)³⁸. Furthermore, re-excisions occurred more often in younger patients (34-35% vs. 20-28%; $p = 0.001$), which was probably related to a more frequent incomplete excision at the first attempt (24-26% vs. 14-21%; $p = 0.001$). Vicini et al. suggested that a lesser extent of the excision, for cosmetic reasons, might be the cause of less optimal margin resection in younger patients³⁴. When adequate negative margins were obtained, no difference in LR was seen in different age groups³⁴. Other reported risk factors for positive margin status are large tumor size, multifocality, and lobular histological type^{17,20,39,43}. Furthermore, the number of positive lymph nodes (N-status) is reported to be a risk factor⁴⁴. However, it should be noted that there is a strong variability in the reported findings of these studies. An explanation for the high rate of positive margins reported in literature might be the restricted visibility of the tumor

and coexisting ductal carcinoma in situ (DCIS) during surgery. To give an adequate perspective on the problems surrounding the pre- and intraoperative visibility of the tumor, the techniques currently used are summarized in the following sections and judged on their merits.

Radiological diagnosis of breast cancer

Approximately one third of all diagnosed breast cancers is clinically occult. As a consequence, additional techniques have to be used to localize the tumor adequately. By current standards, the tumor is visualized with X-ray mammography or ultrasonography before the surgical procedure. However, during the lumpectomy procedure, the surgeon relies mostly on palpation of the tumor⁴⁵. Palpation of the tumor alone is considered inadequate for optimal lumpectomy due to a few basic shortcomings: difficulty detecting occult or multicentric disease and difficulty differentiating between malignant tissue and fibrosis. Furthermore, tumors in younger women are harder to detect because of the firmer nature of the breast tissue⁴². Therefore, most institutions use additional intraoperative techniques to evaluate surgical margins, which may assist in obtaining margin negativity. Because none of these techniques fully guarantee the detection of a negative margins status, preoperative imaging is an absolute necessity for adequate BCT.

PREOPERATIVE MAMMOGRAPHY

Due to widespread mammographic screening programs, radiographic X-ray mammography is currently the common way of detecting breast malignancy. Mammography gives an accurate assessment of tumor size and borders. It also provides information on the presence of multicentricity, multifocality, and microcalcification, which is considered to be a sign for the presence of DCIS^{46,47}. In a recent meta-analysis on the efficacy of mammography for the detection of tumors, sensitivity and specificity rates of 94% and 61% were found, respectively⁴⁸. Although mammography is an adequate technique for breast cancer detection, it has a relatively high rate of nonspecific findings⁴⁹. Furthermore, it does not give any functional information nor does it provide any quantitative information on tissue function or composition⁵⁰. Because of the aforementioned shortcomings, ultrasound was introduced as an addition to mammography for preoperative tumor assessment. Whereas radiography provides information on tissue density and microcalcifications, ultrasound gives a more accurate image of tumor size and growth pattern. Although both imaging modalities act complementary, they fail to assess tumor size and growth pattern in a substantial percentage of patients. Deurloo et al. found an underestimation in tumor extent of 23% in patients considered eligible for

BCT, largely due to failure in assessing diffuse and multi-nodular tumors^{51,52}. Especially patients of younger age present difficulties. An earlier study found failure to meet malignancy criteria in 13% of patients assessed preoperatively by ultrasound alone⁵³.

PREOPERATIVE MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is a highly sensitive imaging technique, which is reported to be a substantial improvement in detecting multi-nodular disease and assessment of tumor spread compared with conventional techniques^{54,55}. MRI provides highly sensitive information on ductal carcinoma in situ⁵⁶. In a trial conducted in Belgium, MRI detected intra-ductal extent in 34 out of 50 (68%) patients who were reported to have an intra-ductal component, compared with 48.5% in mammography and 34.2% in ultrasound⁵⁷. Furthermore, MRI has an accurate capability to differentiate between malignant tissue and fibrosis, enabling assessment of breast tissue after irradiation or chemotherapy for the presence of recurrent disease⁵⁸. MRI is equally accurate in distinguishing malignancies in younger women with more extensive fibro glandular tissue. In a meta-analysis of 2,160 patients in 16 studies, Houssami et al. showed that MRI detects additional disease in 16% of patients with breast cancer, leading to conversion of local excision to mastectomy in 1.1% (95% confidence interval (CI), 0.3-3.6) and to otherwise extended surgery in 5.5% (95% CI, 3.1-9.5)⁵⁹. The authors reported a relatively high false-positive ratio (true-positive to false-positive ratio of 1.91 (95% CI, 1.09-3.34), for which further research on its clinical value is necessary. Nevertheless, MRI has been shown to have a profound clinical impact on selection of patients for BCT and is currently regarded as the preferred imaging modality for preoperative assessment and clinical decision making. It should be emphasized that several studies have shown that MRI assessment before surgery fails to improve postoperative margin status and subsequent LR, even compared with conventional imaging modalities^{60,61}. The intraoperative limitation may be due to the limited provision of real-time margin assessment⁶².

PREOPERATIVE TUMOR LOCALIZATION

Because of the limited intraoperative capabilities of the current preoperative imaging techniques, more invasive imaging and surgical guidance techniques have been developed to assess the location of the tumor intra-operatively, which will be addressed in the next section.

Wire-Guided Localization

For more than 20 years, the standard technique for intraoperative tumor localization of clinically occult tumors

has been wire-guided localization (WGL), in which a wire is introduced in the tumor guided by ultrasound, X-ray mammography, or MRI. After resection, the excised lump can be evaluated mammographically for localization of the tumor and microcalcifications. However, the WGL procedure has been criticized for the last 5 years. Burkholder et al. recently analyzed the success rate of WGL in a retrospective study of 511 patients and found positive to close (3 mm) margins in 21.3% of the patients, of which 26.7% had to undergo re-excision⁶³. Similar percentages were found by Schmidt-Ullrich et al.⁶⁴. Two recent studies reported that WGL resulted in positive margins in up to 38% to 43% of the patients who underwent BCT.^{3,65} An important disadvantage of WGL is that the guide-wire does not provide a clear three-dimensional perspective on the various tumor edges and does not influence surgical margins as such. Furthermore, the guide-wire is prone to move before or during surgery and may for this reason lead to inadequate information on tumor localization. The WGL procedure is time consuming and uncomfortable for the patient, resulting in increased levels of stress and arousal.⁶⁶ Because WGL results in an unacceptable high rate of positive margins, other techniques have been developed for intraoperative tumor detection.

Intraoperative Ultrasound-Guided Resection

Current trends in BCT are moving toward the direction of one combined diagnostic and therapeutic procedure, a so-called “theragnostic” procedure, in which effective visualization plays a more prominent role. One of these theragnostic procedures is intraoperative ultrasound (IOUS)-guided excision. In this technique, the patient is examined with ultrasound (US) before and during surgery to improve tumor assessment. After surgery, the excised tissue is examined using US to assess margin status. In case of positive or close margins, the patient’s cavity margins are shaved to remove any residual disease⁶⁷. Several studies investigating the use of IOUS in BCT showed positive margin rates between 3% and 11%^{68,71}. Rahusen et al. compared IOUS to WGL in a prospective study in 48 patients⁷⁰. The authors reported that positive or close margin status (≤ 1 mm) was improved significantly using IOUS compared with WGL (11% vs. 45%, respectively; $p=0.007$). However, Klimberg showed that only half (50%) of the not palpable breast tumors can be visualized by ultrasonography⁷². Another problem of IOUS is the unreliability in detecting DCIS lesions, because ultrasonography is not suitable for the detection of microcalcifications⁷³. Karni et al. reported on a radiofrequency-based intraoperative margin assessment device (Margin Probe TM, Dune Medical Devices Ltd., Israel), which is able to detect malignant tissue within the surgical specimen up to a depth of 1 mm⁷⁴. The Margin Probe TM displays device readings as “negative” or “positive” margin, the latter indicating excision of additional breast tissue. Sensitivity and specificity

rates of the Margin Probe TM were reported to be 71% and 68%, respectively⁷⁴. Recently, Allweis et al. showed re-excision rates to be lower if the surgeon had a Margin Probe TM at his disposal during breast-conserving surgery compared with the control group, although not statistically significant (12.6% vs. 18.6%; $p = 0.098$)⁷⁵. However, this reduction in re-excision rate might, in part, have been due to the excision of larger tissue volumes in the device group compared with the control group (107 cm³ vs. 94 cm³, respectively; $p = 0.066$).

Intraoperative Specimen Radiography

Another technique for evaluation of surgical margins is intraoperative specimen radiography. After excision by the surgeon, the specimen is evaluated by X-ray radiography. If micro calcifications occur close to the edges of the specimen, the surgeon may decide to shave the associated cavity edges to remove any residual malignant disease. However, the use of radiographic X-ray mammography is limited due to limitations in detecting small, not calcified lesions and a high rate of nonspecific findings⁷⁶. Lee and Carter examined post excision specimen radiographs of 125 patients and found a sensitivity, specificity, and overall accuracy for detecting margin positivity of 49%, 77%, and 62%, respectively⁷⁷. They concluded that intraoperative specimen radiography could not be relied on solely but presents a valuable addition to BCT.

Cryoprobe-Assisted Localization

Cryoprobe-assisted localization (CAL) is a technique of particular value in small, not palpable tumors. This technique makes use of an ultrasound-guided cryoprobe, which is inserted into the breast and freezes the tumor, thereby turning the tumor into a small, palpable sphere that can be more easily located and excised. Tafra et al. compared the capability of CAL in achieving negative margins to conventional WGL in a prospective trial in 310 patients⁷⁸. No significant differences were found between the CAL and WGL arms in positive surgical margin status (28% vs. 31%; $p = 0.691$) and re-excision rates (19% vs. 21%; $p = 0.764$). However, it did reduce the amount of healthy surrounding tissue excised and therefore improved cosmetic outcome ($p=0.001$). Furthermore, excision time and ease were significantly improved using the CAL method ($p=0.001$)⁷⁸.

EXTEMPORANEUS HISTOLOGICAL EXAMINATION

Frozen Section Analysis

Frozen section analysis (FSA) is a commonly applied technique for intraoperative pathological margin assessment in many oncologic procedures. The excised specimen is frozen, sliced, and analyzed microscopically⁷⁹. Because of the relative ease and the wide experience gained, this technique has been applied frequently to

assess tumor margins during lumpectomy. The procedure is performed directly after the tumor has been excised. In case FSA indicates residual disease, the wound can be reopened immediately for additional surgical cavity shaving, thus preventing a costly re-excision procedure at a later stage. The FSA procedure takes an average of 30 minutes, which adds significantly to the operating time⁸⁰. Reported sensitivity rates for detecting residual disease ranged between 65% and 78%, whereas specificity rates ranged between 98% and 100%^{40,81,82}. The relatively high variance in sensitivity might be explained by differences in experience between pathologists. Several studies retrospectively analyzed the influence of FSA on BCT outcome and found that 24% to 27% of the patients underwent additional tissue excision based on FSA, whereas 5% to 9% required a second re-excision procedure after definitive histo-pathological examination^{80,82,83}. FSA during BCT did not improve overall LR rates (3.8% and 1.2%, respectively)^{80,83}. Considering the costs of the FSA procedure (the average Medicare charge for FSA is estimated at US\$90), these low re-excision rates clearly indicate the benefits of the procedure compared with permanent pathological evaluation alone. Nevertheless, in evaluating small tumors (diameter < 10 mm) and presence of DCIS, the technique is less reliable^{80,81}. Other disadvantages of FSA are the prolonged duration of operation time and the requirement of a relatively large part of the specimen, which compromises definitive evaluation by the pathologist for histological aspects and tumor staging. In conclusion, although FSA is a relatively safe and cost-effective procedure that reduces the rate of re-excisions significantly, its reliability for negative margin status is questionable due to relatively high variance in diagnostic sensitivity.

Intraoperative Touch Preparation Cytology

Intraoperative touch preparation cytology (IOTPC) or "imprint cytology" is a promising alternative to FSA. The technique is based on the histological characteristics of the cell surface of malignant cells, which stick to glass surfaces, whereas benign mammary fat tissue does not. To assess margin status, a glass slide is brought against the borders of the excised specimen. Next, cells sticking to the glass surface are fixated, stained, and microscopically evaluated⁸⁴. Several studies have concluded that IOTPC is inexpensive, accurate, quick, and saves tissue for permanent sectioning and histopathological examination⁸⁴⁻⁸⁶. Klimberg et al. evaluated IOTPC for accuracy in diagnosis as well as margin assessment during surgery in a prospective trial in 428 patients⁸⁴. They reported a diagnostic sensitivity and specificity of 96% and 100%, respectively, and a margin status sensitivity and specificity of both 100%. Weinberg et al. compared the efficacy of IOTPC to other histopathological assessment techniques, such as definitive histopathological assessment and intraoperative FSA in a database of 1,713 patients⁸⁷. They reported that intraoperative mar-

gin assessment using IOTPC significantly reduced LR rates compared with conventional methods (2.8% vs. 8.8%; $p=0.0001$). Although the overall results seem promising, IOTPC is not as commonly used as might be expected based on reported LR rates and detection rates of positive margins. A possible explanation might be the likelihood of artifacts caused by draught and surface cautery⁴. Also, IOTPC is proven less effective in distinguishing lobular carcinoma⁸⁵. Another important shortcoming of IOTPC is that close margins are not taken into account, because only superficial tumor cells are detected with the technique. Therefore, no information is gathered on margin width, multifocality, and quantity of cancerous cells approaching the cut edge.

STANDARDIZED CAVITY SHAVING

To avoid the earlier-mentioned difficulties in intraoperative cytological or histological techniques, some authors have suggested that standardized surgical cavity shaving could achieve the intended reduction in positive-margin rates⁸⁸. Hereto, all cut edges are shaved systematically after excision of the primary tumor to remove any residual disease. Huston et al. compared the number of systematically shaved cavity edges to the achieved definitive histopathological margin status and found an inverted correlation between the rate of positive margin status and the total volume of breast tissue removed⁸⁹. Similar results were found by Janes et al.⁹⁰. Because cavity shaving requires additional tissue resection, cosmetic outcome, and thereby one of the primary objectives of BCT, is compromised as a consequence^{89,90}. Furthermore, standardized cavity shaving still does not provide certainty in achieving negative margins due to the lack of intraoperative assessment of margin status.

FUTURE DIRECTIONS

In conclusion, because most of the current techniques result in a relatively high rate of positive resection margins together with a clear impact on LR rates and cosmetic results, new innovative surgical approaches and methods for intraoperative margin assessment are needed^{6,10}. In the following section, innovative applications of radio guided surgery and optical imaging are addressed.

Positron Emission Tomography Imaging

18F-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET) imaging is considered a powerful imaging modality for diagnosis, staging, and monitoring of various malignancies, including breast cancer⁹¹. The oncologic applications of PET are still expanding with the development of new positron-emitting radiopharmaceuticals and imaging techniques⁹². Recently, the suit-

ability of 18F-FDG as a tracer for tumors has led to an interest in its use in PET-probe-guided BCT. The radiopharmaceutical 18F-FDG demarcates sites of high glucose metabolic activity, such as tumors, inflammation, and infection⁹³. Because breast tumors frequently over-express the facilitative glucose transporter GLUT1, uptake of the glucose analogue 18F-FDG may be increased in breast cancer cells⁹⁴⁻⁹⁵. Hand-held PET-probes have become available, which allow for the detection of high-energy gamma rays during surgery and may facilitate localization of breast carcinoma by offering the surgeon real-time, intraoperative evaluation of tumor localization and margin status^{96,97}. The use of hand-held probes for the detection of 18F-FDG accumulating tumors has been shown previously for various malignancies^{91,92,97,99}. Sensitivity and specificity of PET are relatively high for 18F-FDG-avid breast tumors^{100,101}. However, because of limited spatial resolution of PET imaging, small tumors (1 cm) are difficult to detect, whereas breast screening programs and technological developments have led to a considerable reduction in the size of breast cancers being detected^{97,102,103}. The same limited spatial resolution is of major concern for the intraoperative detection of positive margins in itself. Also, PET has a limited role in patients with well-differentiated and lobular types of breast cancer¹⁰⁴. Additionally, PET lacks specificity, because normal physiologic uptake of 18F-FDG can be demonstrated to varying degrees in nonmalignant tissues, such as inflammatory tissue⁹¹. Finally, PET has the disadvantage of high costs and radiation exposure to primary operating personnel during the intraoperative 18F-FDG PET procedure is expected to be relatively high^{101,102}. Further development of more specific radiopharmaceuticals may compensate in part for the current limitations associated with 18F-FDG PET imaging. In carefully selected patients, the intraoperative use of a PET-probe may provide a useful tool to improve surgical outcome⁹³. However, its use in BCT warrants further exploration on feasibility and validation and at this stage cannot be considered to compete with the current techniques⁹¹.

Radioguided Occult Lesion Localization

Radio-guided occult lesion localization (ROLL), introduced by Luini et al. in 1996, is an upcoming surgical technique and theragnostic tool for intraoperative localization and simultaneous resection of non-palpable tumors of the breast¹⁰⁵. The technique makes use of a nonspecific radioisotope, which is injected into the tumor under stereotactic or ultrasonographic guidance. The exact position of the primary tumor can be assessed intraoperatively by use of a hand-held gamma probe. After excision of the primary tumor, the probe also can be used to search for any residual areas of high radioactivity¹⁰⁶. The injection of the nonspecific radioisotope into the tumor is a fundamental step in the ROLL procedure and has to be very accurate to minimize false-neg-

ative and false-positive results. Several studies have shown that the radioisotope was correctly positioned in 95% to 100% of patients^{3,65,106,110}. However, spillage of radio-tracer within the mammary gland during the ROLL procedure might decrease accuracy of location of the lesion¹¹¹. Furthermore, the amount of tracer injected needs to correlate with tumor size. Alternatively, a radioactive iodine (125I) seed can be implanted at the tumor, followed by radio-guided localization and excision of the tumor together with the radioactive seed¹¹². Hughes et al. analyzed 383 patients treated with radio-guided seed localization (RSL) compared with 99 patients treated with WGL and considered the technique to be safe, effective, and more patient-friendly compared with WGL¹¹³. Additionally, RSL was reported to reduce the incidence of inadequate surgical margins compared with WGL (26% vs. 57%, respectively; $p=0.02$)¹¹². However, although RSL might prove valuable for BCT in the future, experience with this technique is still limited. Sarlos et al. analyzed the oncologic safety of the ROLL procedure and the effectiveness of tumor localization in a prospective, controlled trial¹¹⁰. In 20% of patients with invasive ductal carcinoma (IDC), the tumor was excised inadequately (margin B1 mm) at the initial surgical procedure¹¹⁰. These results are consistent with margin positivity reported by others, ranging from 11% to 17%^{3,65,114}. The detection rate of non-palpable breast tumors during surgery was found to be 98%. Although the clinical efficacy of ROLL compared with WGL was found to be similar in two prospective RCTs, there were several aspects in which ROLL exceeded the current standard of WGL^{3,107}. Rampaul et al. concluded that ROLL was less painful for the patient and was an easier technique to perform surgically¹⁰⁷. Furthermore, the ROLL procedure could be combined with lymphatic mapping and sentinel lymph node biopsy, which makes it more patient-friendly compared with WGL^{112,115}. ROLL was reported to significantly reduce pre- and intraoperative localization time of non-palpable breast tumors³. However, the total duration of the surgical procedure was not reduced by ROLL^{3,65,107,114}. Regarding costs, WGL is probably exceeded by ROLL, although this effect could be leveled off by the potential net savings that accompany a reduction of re-excision rates³. In conclusion, ROLL seems to be a simple, accurate, and relatively safe technique compared with the current standard of WGL^{106,109}. Further research is needed to elucidate the position of ROLL for the treatment of non-palpable breast tumors. Currently, a large, multicenter, clinical trial is being conducted in the Netherlands, in which ROLL is being compared to WGL regarding the percentage of positive margins, cost-effectiveness, patient comfort, and cosmetic outcome¹¹⁶.

Near-Infrared Fluorescence Optical Imaging

In recent years, significant progress has been made in the development of optical imaging systems and fluorescent contrast agents for clinical applications^{117,119}.

Several animal and clinical studies have shown the potential use of near-infrared fluorescence (NIRF) optical imaging to improve the therapeutic outcome of surgery^{120,126}. It must be emphasized that NIRF imaging on itself is not possible without the use of near-infrared (NIR) fluorescent molecular probes (fluorochromes), for which several groups can be distinguished. One group consists of “targeted fluorochromes,” which are specific for certain biomarkers involved in breast cancer, such as vascular endothelial growth factor (VEGF) receptor, epidermal growth factor (EGF) receptor, or the Her2/neu receptor^{127,132}. Another group is formed by the “activatable probes,” which show virtually no fluorescence activity in their native state, thereby minimizing background signals¹¹⁹. However, after activation by a specific enzyme, the probe emits a bright fluorescence signal when appropriately excited. A number of enzymes that play a role in carcinogenesis and tumor spreading can already be visualized with activatable probes, including proteases, such as cathepsin B, cathepsin D, and matrix metalloproteinase 2 (MMP2)^{121,133,137}. An optical imaging technique commonly used is two-dimensional (2D) fluorescence reflectance imaging (FRI), also known as epi-illumination fluorescence imaging. FRI with a hand-held imaging device could complement BCT by visualizing tumor delineation, remnant disease, and pinpointing suspicious lymph nodes, thereby enabling the surgeon to detect (diagnostic) and excise (therapeutic) malignant tissue and possible residual disease at the same time^{119,121,122,138}. The use of NIRF optical imaging offers additional advantages: the technology is safe, simple to operate, fast, high resolution (as low as 10 μm), relatively inexpensive, and makes use of nonionizing radiation^{119,122,124,139,141}. Besides the aforementioned advantages, NIRF optical imaging does have limitations, which originate from the intrinsic characteristics of light propagation through tissue¹⁴². Especially, besides absorption and scattering of light, auto-fluorescence can reduce detection sensitivity and imaging performance due to absorbance and subsequent emission of light by intrinsic tissue fluorochromes^{143,144}. Although the use of FRI for noninvasive detection of breast cancer is restricted because of limited depth resolution and a nonlinear dependence between the signal detected on the optical properties of tissue and the depth of the activity, the technique is well suited for intraoperative imaging applications^{119,121,122,139}. Clinical applications for NIRF optical imaging are expected to expand rapidly, although further work is needed to overcome the aforementioned limitations of the technique^{117,145}.

Conclusions

Current imaging techniques used in BCT result in positive surgical margins in 20% to 40% of patients who undergo breast-conserving surgery. Risk factors associat-

ed with positive margins are predominantly related to tumor biology factors or patient characteristics and, therefore, cannot be influenced directly to improve surgical outcome. Instead, multidisciplinary research should focus on techniques that provide the surgeon with a so-called “theragnostic” tool, enabling the surgeon to obtain an optimal balance between safe surgical margins and good cosmetic results. Current techniques present significant difficulties in this perspective. New innovative techniques, such as radio-guided and NIRF optical imaging-guided surgery, are emerging. Further studies are being performed to elucidate their potential value in improving surgical outcome and reducing the need for re-excision in BCT.

Riassunto

I margini chirurgici inadeguati nella resezione tumorale conservativa del cancro precoce della mammilla rappresentano un fattore di rischio elevato di risultato clinico sfavorevole. La maggior parte degli studi riferisce dal 20 al 40% di margini positivi nelle pazienti sottoposte a terapia chirurgica conservativa e può comportare un accresciuto rischio di recidiva locale, o la necessità di reinterventi e di conseguenza effetti negativi dal punto di vista cosmetico, disagio psicologico ed elevati costi gestionali. In letteratura si fa riferimento a vari fattori di rischio che si associano con la verifica di margini positivi dopo la tumorectomia, che inducono il chirurgo ad individuare le pazienti già a priori esposte al rischio di un reintervento. Comunque la maggior parte dei fattori sono connessi alla biologia del tumore ed alle caratteristiche della singola paziente, che, come tali, non possono essere modificati. Per queste ragioni gli sforzi per ridurre l'incidenza dell'eventualità di margini positivi dovrebbero concentrarsi nel miglioramento delle procedure chirurgiche perché nel corso di una resezione conservativa il chirurgo non dispone intraoperatoriamente di informazioni in tempo reale circa l'esistenza di margini positivi di resezione. Questa review presenta lo stato delle modalità pre e intraoperatorie correntemente adottate nella terapia conservativa del cancro mammario. Inoltre si fa riferimento ad approcci intraoperatori innovativi, come la PET la localizzazione radio-guidata di lesioni occulte, l'imaging ottico con l'uso della fluorescenza nell'ambito dei vicini infrarossi che debbono dar prova della loro efficacia per migliorare il risultato della chirurgia e ridurre la necessità di successivi reinterventi dopo trattamento conservativo.

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