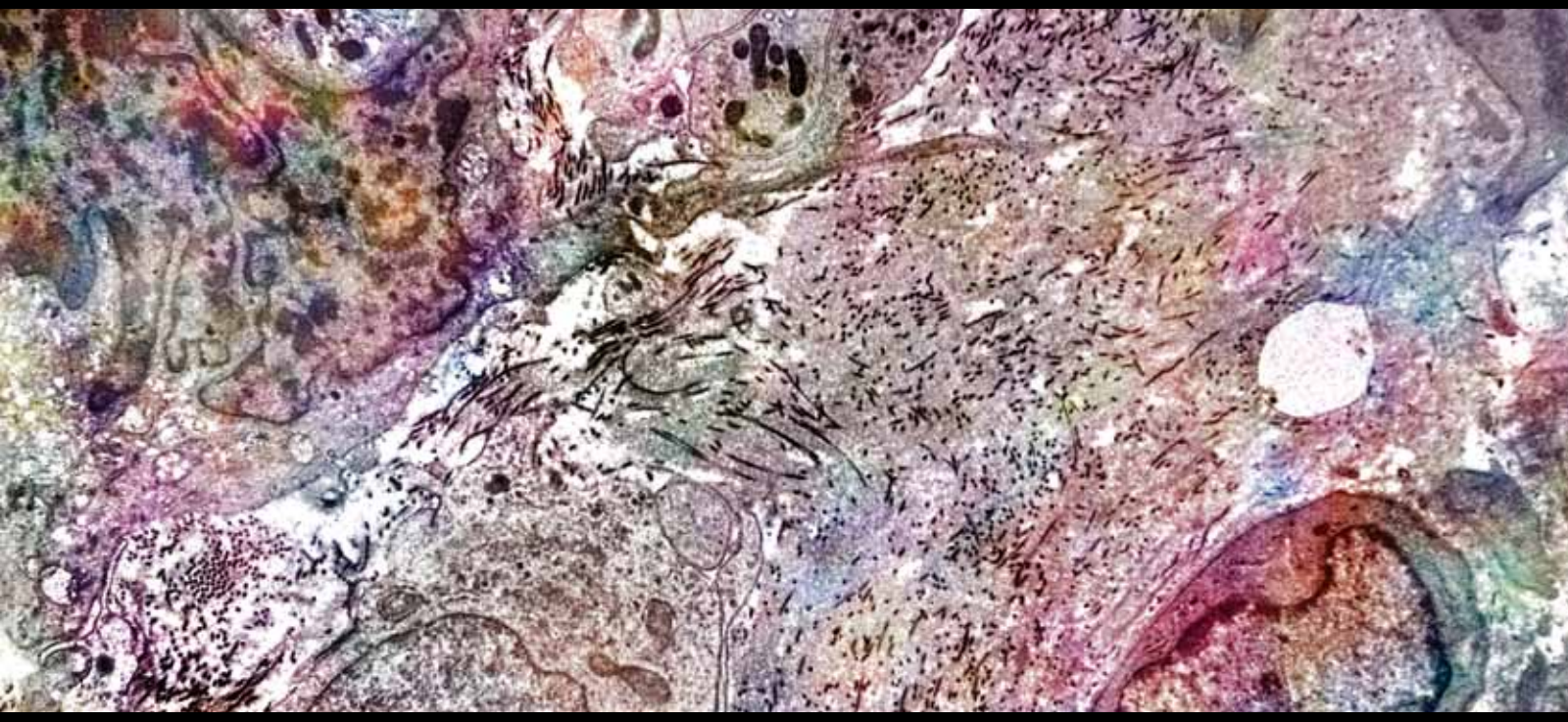
International Journal of Surgical Oncology

Surgical Margins in Breast Conservation

Guest Editors: Sheldon Marc Feldman, Michael Dixon, Joseph P. Crowe, Eisuke Fukuma, and Preya Ananthakrishnan



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Editorial Board

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Editorial

Surgical Margins in Breast Conservation

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Significant progress has been made in the diagnosis and treatment of breast cancer during the past 30 years. The increased availability of screening mammography has resulted in a higher percentage of woman being diagnosed with early stage disease allowing the option of breast conservation therapy to be more widely available. Long-term follow-up studies clearly demonstrate equivalent survival with breast conservation surgery (lumpectomy) and radiotherapy versus total mastectomy [1, 2, 3]. The importance of obtaining clear lumpectomy surgical margins has been well established in minimizing the risk of local recurrence [4]. Unfortunately there is a lack of uniform guidelines in terms of what constitutes an adequately clear lumpectomy margin. Substantial debate about bigger margins being better continues [5]. This has led to wide variations in lumpectomy margin reexcision rates from 15 to 47% [6]. These additional surgical procedures cause significant patient distress, utilize health care resources, and can adversely affect cosmesis. From the patient perspective, they may wonder why we did not get it right the first time. They want their cancer gone while maintaining a normal appearance.

This special issue highlights the areas of controversy and demonstrates current best practices and emerging novel approaches towards optimal breast conservation approach. The goal is to improve our ability to provide breast-conserving approaches for breast cancer while avoiding multiple surgical procedures, minimizing recurrence risk while obtaining excellent cosmesis. We have chosen 6 of 16 submissions to be published in this special issue. Each paper was evaluated by at least two expert reviewers and revised according to review comments.

P. Ananthakrishnan et al. provide an excellent comprehensive review article on all aspects involved in optimizing breast conservation. They include discussion of preoperative breast imaging, lesion localization, impact of tumor biology and systemic therapy, intraoperative lesion identification and margin assessment techniques, the role of margin ablation and oncoplastic techniques. They also discuss the promise of ductal anatomy mapping toward the goal of validating the "Sick lobe hypothesis" [7, 8] which may allow for more accurate identification of breast tissue to be targeted for excision.

R. Emmadi and E. L. Wiley provide an excellent review from the pathology perspective of the different approaches to margin assessment. They explore issues of specimen processing, fixation, cutting techniques, and reporting. They well explain the reasons for the reporting variations between institutions and the need for standardization.

J. L. Baker et al. present a scholarly review of our current understanding of the issue of atypical ductal hyperplasia (ADH) as it relates to surgical margins. They highlight the large interobserver variability among pathologists in differentiating ADH from low-grade ductal carcinoma in situ (DCIS). The issue of whether ADH is a precursor lesion to DCIS is explored.

R. J. Rivera et al. report on a 21-site multicenter clinical trial evaluating the performance of the MarginProbe intraoperative device. This device is based on radiofrequency spectroscopy to assess adequacy of lumpectomy margins. They analyzed volume or resection and reexcision rates in the device group versus usual surgical standard of care (SOC). They demonstrate the reexcision rate of 14.1% in the device group versus 29.9% with SOC. Increased resection volume was 2.6% using the device.

M. M. Chang et al. provide a comprehensive overview of oncoplastic breast reduction. This is a complete review of the

techniques including indication, patient selection, practical pointers, and their experience including a low (3.3%) rate of margin failure. They stress the importance of a coordinated team approach between breast surgical oncology, plastic surgery, breast imaging, and radiation oncology.

Lastly, G. H. T. Au et al. present an exciting research paper on margin assessment using a Quantum-Dot Molecular probe in a mouse model. This employs nanoparticle monoclonal antibodies with molecular imaging. Their concept has a potential advantage over optical imaging and radiofrequency spectroscopy in that it is not affected by tissue heterogeneity. It also can display and differentiate very small (100–200 cells) spots. Timeline of 30 minutes is practical for intraoperative use. This early work is an highly innovative approach to a practical issue.

These papers present a great deal of important information and well explore the current state of the art, controversies and future directions towards the important goal of optimizing breast conservation with particular attention to margin issues.

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Sheldon Marc Feldman

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Clinical Study

Analysis of the Impact of Intraoperative Margin Assessment with Adjunctive Use of MarginProbe versus Standard of Care on Tissue Volume Removed

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Breast conserving surgery has been accepted as the optimal local therapy for women with early breast cancer, emphasizing the necessity to balance oncologic goals with patient satisfaction and cosmetic outcomes. In the move to enhance a surgeon's ability to achieve histologically clear margins intraoperatively at the initial surgery, the MarginProbe (Dune Medical Devices, Caesarea, Israel) has emerged as an effective tool to accomplish that task. Based on previously reported success using the device, we assessed cosmesis and tissue resection volumes among participants in a randomized-controlled trial comparing the standard of care lumpectomy performed with and without the MarginProbe. The use of the MarginProbe device resulted in a 57% reduction in reexcision rates compared to the control group with a small increase in tissue volume removed at the primary lumpectomy. When total tissue volumes removed were analyzed, the device and control groups were still very similar after normalization to bra cup size. We concluded that the MarginProbe is an effective device to assist surgeons in determining margin status intraoperatively while allowing for better patient cosmetic outcomes due to the smaller volumes of tissue resected and the reduction in patient referrals for second surgeries due to positive margins.

1. Introduction

Since the acceptance of breast conserving surgery with radiotherapy as a standard of care for early stage breast cancer [1], the National Comprehensive Cancer Network guidelines for breast cancer treatment recommend the assessment of surgical margins to aide in local control of disease. Any margins deemed positive should be considered for additional surgery according to these guidelines since clear surgical margins have been shown to minimize the risk of local recurrence [2].

The optimal time to identify positive margins is at the time of the initial operation since it affords the opportunity to reexcise positive or questionable margins without subjecting the patient to a second operation. The effort to achieve clear surgical margins intraoperatively is aided by surgeon's judgment, specimen palpation, gross sectioning, imaging [3], wire localization, frozen section, and touch prep analysis [4], among other techniques. In spite of these efforts, up to 40% of women in the USA continue to undergo multiple operations due to initial failure to achieve clear margins.

To further reduce the need for reexcisions, the MarginProbe (Dune Medical Devices, Caesarea, Israel) was developed to provide real-time, intraoperative assessment of the presence of disease at the surgical margins. The MarginProbe is a handheld device that utilizes radiofrequency spectroscopy to detect electromagnetic changes in malignant tissue within 1 mm of the margin surface. A 21-center randomized, controlled trial (Pivotal Trial) was conducted to determine if the adjunctive use of the MarginProbe would

enhance standard of care practices employed by surgeons to reduce the need for reexcision procedures. While the complete results of this study are still awaiting publication, the use of the MarginProbe has been validated in other studies as an effective way to assess margins intraoperatively because of its high sensitivity in identifying malignant tissue and high specificity in distinguishing between normal and malignant tissues [5, 6].

A central question in the Pivotal Trial was whether or not the use of the MarginProbe device would result in the resection of excessively wide margins, thereby producing an adverse effect on cosmesis. Herein, we present the analysis of the cosmetic impact of intraoperative margin assessment using the MarginProbe on the participants in the Pivotal Trial.

2. Materials and Methods

Six hundred and sixty-four (664) women with nonpalpable invasive cancer and/or DCIS undergoing lumpectomy were enrolled in the Pivotal Trial at 21 institutions. Following "standard of care (SOC)" lumpectomy, 596 women were randomized (1 : 1) intraoperatively to MarginProbe device use or control (i.e., SOC only with no device use). The definition of SOC varied by institution, but typically involved wire localization, specimen palpation, specimen radiography, and reexcision of questionable margins. Frozen section, touch prep analysis, and gross sectioning were not permitted to avoid confounding subsequent margin analysis. In women randomized to the device arm, the MarginProbe was used to assess each margin of the resected surgical specimen. The 7 mm sensor footplate at the probe tip was applied to a minimum of 5 sites and a maximum of 8 sites on each margin surface, depending on the area of each margin surface. A vacuum mechanism ensured full contact of the 7 mm sensor with the margin surface (Figure 1). An auditory and visual binary signal (positive/negative) was produced when the MarginProbe detected the presence or absence of malignant tissues within 1 mm of the margin surface at any of the 5–8 examined sites (Figure 2). By protocol requirements, any margin producing a positive reading required the reexcision of the entire affected margin. The thickness of each margin was left to the discretion of the operating surgeon. Skin margins and muscle margins did not require reexcision. Women randomized to the SOC arm underwent no additional margin resection following randomization. Surgeons were discouraged from taking additional shave margins as a safeguard against randomization to the SOC arm. Excision of shave margins following randomization to the SOC arm was considered a protocol violation and resulted in censuring of the data.

All primary and reexcision specimens in both arms were submitted for standard histopathological examination by pathologists who were blinded to the study arm. Device readings were compared per specimen for histological assessment of the initially excised lumpectomy specimens. True positive device readings occurred when invasive breast cancer or DCIS was detected histologically less than 1 mm from original specimen margin. True negative device readings occurred when histopathology of the primary specimen revealed no malignant cells within 1 mm of the corresponding margin surface.

The ability to correctly and intraoperatively identify *all* of the involved margins on the main specimen and reexcise them was defined as a correct Complete Surgical Resection (CSR). Correctness or incorrectness of CSR was defined based on permanent histology data. CSR was defined as correct only when *all* main specimen margins detected as positive by histology were reexcised intraoperatively.

3. Results

The breakdown of tissue volume removed is shown in Table 1. When analyzing the impact of the MarginProbe on reexcision rates, the use of the device resulted in a 57% reduction in reexcision compared to the control group (device: 42/298 (14.1%), Control: 98/298 (29.9%), 57% reduction, $P < 0.0001$). As a result of true positive and false positive device readings, there was a small increase in tissue volume removed at primary lumpectomy (15.6 cc and less than 2 shavings per patient). Among patients requiring reexcision of positive margins at a second operation, less tissue was ultimately removed in the device arm (device: 28.4 cc, control: 49.5 cc, a 43.4% reduction). When analyzing the total tissue volumes removed (all operations combined), resected tissue volume was only slightly greater (8.5 cc) in the device arm (2.6% greater when normalized to bra cup size).

4. Discussion

It is well established that cosmesis after breast conserving surgery is affected by multiple variables. Among the most important are the need for reexcision as well as surgery the amount of tissue removed at the primary and secondary surgeries [7–9]. Accurate intraoperative assessment of surgical margins allows the tumor to be removed in one surgical procedure, thereby sparing patients the burden of a second breast operation. However, standard of care approaches for intraoperative margin assessment (e.g., palpation, gross-sectioning of the specimen, specimen imaging, wire localization, and frozen section or touch prep analysis) continues to be commonly associated with margin reexcision rates of 20–40%. Reexcision has been associated with the risk of postoperative infection, delays in the onset of adjuvant therapy, lower patient satisfaction, lower rates of cosmetic acceptability, increased medical costs, and stress for patients who sometimes needlessly elect mastectomy rather than risk another positive margin [7–11]. Based on the results of the Pivotal Trial, breast reexcisions can be significantly reduced with the use of the MarginProbe device which should, in turn, significantly improve the safety and feasibility of breast conserving surgery.

In spite of its benefits in reducing breast reexcisions, concerns have been expressed that the adjunctive use of the MarginProbe might compromise breast cosmesis due to the excessive resection of breast tissue, particularly when false

(a) (b)

Figure 1: Photograph (a) of MarginProbe device showing vacuum mechanism that ensures full contact of the 7 mm sensor with the margin surface. Schematic (b) showing 7 mm diameter sensor and radiofrequency field that penetrates margin surface to detect cancer-associated electromagnetic changes.

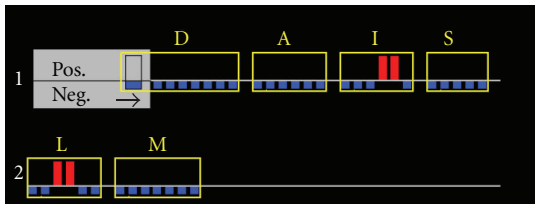

Figure 2: Visual binary signal display showing either positive (Pos.) or negative (Neg.) margin at multiple sites measured on each specimen margin surface [deep (D), anterior (A), inferior (I), superior (S), lateral (L), and medial (M)].

positive readings are encountered. However, comparison of the device and control arms in the Pivotal Trial showed minimal impact on breast cosmesis when analyzed by the volume of resected breast tissue. In fact, only 2.6% greater volume was resected in the device arm when normalized to breast size. This corresponded to 2 additional margin shavings per patient, which is less than the 4–6 margins that may be indiscriminately reexcised by some surgeons who routinely harvest margin shavings. Furthermore, among patients who ultimately required reexcision at a second operation, there was essentially no difference in the two study arms (−1.6% difference, normalized) in the total volume of resected breast tissue. Collectively, these findings resolved concerns that the use of the MarginProbe may adversely affect cosmesis.

5. Conclusion

The primary goal of breast conserving surgery is resection of breast malignancy with clear margins and acceptable cosmesis. While this goal is not always achievable at the initial operation, every reasonable effort should be made avoid multiple surgeries, undesirable cosmetic outcomes, increased treatment burden, and increased medical costs associated with these factors. The MarginProbe represents a practical advancement in the field of surgical specimen margin evaluation. When combined with the standard of care techniques, the MarginProbe may significantly lower the rates of reexcision for breast cancer patients, achieve comparable tissue volume removal at the first surgery, and reduce the amount of tissue removed among patient requiring a second operation. The end result is significant quality improvement in the management of conservatively treated breast cancer patients.

Table 1: Total tissue volume removed.

Average per patient	Control	Device	Difference
Initial surgery			
Main specimen	61.3 cc	59.7 cc	−1.6 cc
True positive shavings	2.7 cc	6.7 cc	4.0 cc
False positive shavings	7.7 cc	21.1 cc	13.4 cc
Total volume	71.9 cc	87.5 cc	15.6 cc
Reexcision surgeries			
Tissue volume	49.5 cc	28.4 cc	−21.1 cc
Normalized tissue volume (normalized to breast volume)	5.6%	4.0%	−1.6%
All surgeries			
Total tissue volume	84.8 cc	93.3 cc	8.5 cc
Normalized total tissue volume (normalized to breast volume)	12.5%	15.1%	2.6%

Conflict of Interests

Drs. D. R. Holmes and L. Tafra were funded researchers as a part of the Pivotal Trial, the multicenter, randomized

controlled trial evaluating the MarginProbe device. Neither has any ongoing financial interest in the MarginProbe device.

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Research Article

Assessing Breast Cancer Margins Ex Vivo Using Aqueous Quantum-Dot-Molecular Probes

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Positive margins have been a critical issue that hinders the success of breast- conserving surgery. The incidence of positive margins is estimated to range from 20% to as high as 60%. Currently, there is no effective intraoperative method for margin assessment. It would be desirable if there is a rapid and reliable breast cancer margin assessment tool in the operating room so that further surgery can be continued if necessary to reduce re-excision rate. In this study, we seek to develop a sensitive and specific molecular probe to help surgeons assess if the surgical margin is clean. The molecular probe consists of the unique aqueous quantum dots developed in our laboratory conjugated with antibodies specific to breast cancer markers such as Tn-antigen. Excised tumors from tumor-bearing nude mice were used to demonstrate the method. AQD-Tn mAb probe proved to be sensitive and specific to identify cancer area quantitatively without being affected by the heterogeneity of the tissue. The integrity of the surgical specimen was not affected by the AQD treatment. Furthermore, AQD-Tn mAb method could determine margin status within 30 minutes of tumor excision, indicating its potential as an accurate intraoperative margin assessment method.

1. Introduction

Breast cancer is one of the most common cancers among women in the United States and in Western countries. An estimated 226,870 cases of invasive breast cancer and 63,300 ductal carcinomas *in situ* (DCIS) will be diagnosed among women in the United States in 2012 [1]. Breast cancer is increasingly being diagnosed at an early stage [2] allowing treatment with breast conserving surgery (BCS), in which only the tumor and a small amount of surrounding normal tissue are removed. Multiple clinical trials have concluded that patients who undergo BCS with clean margin coupled with radiation have survival rates equivalent to those with mastectomy [3–6]. In addition, it was found that for every four local recurrences avoided in patients treated by BCS, one breast-cancer related death was averted [7]. Furthermore, morbidity and local recurrence rate are higher in patients with positive or close margin (16%) than those with negative margin (6%) [8, 9]. Positive and close margins usually refer to margins where cancer cells are present within 2 mm from the surface of the excised tissue. Consequently, it is best to have the tumor removed cleanly with negative margins on the first surgery [10].

Current BCS procedures rely on margin assessment in the pathology department to ensure completeness of tumor removal. It is only after the pathology report is completed that a final determination of surgical margin adequacy can be made. If the margin is found to be positive, reexcision is required, which often results in additional cost, let alone the additional pain to the patients. Currently, there is no real-time intraoperative method to rapidly and accurately assess the status of lumpectomy margins as a standard of care. Several techniques have been studied including gross examination, touch preparation cytology (TPC) [11, 12],

frozen section analysis (FSA) [13, 14], radio-frequency spectroscopy (RFS) [15], tomography (TM) [2], and Raman spectroscopy (RS) [16, 17], each of which have various limitations with false negative diagnoses in 20–50% of the patients or prolong surgical time [18]. Although RFS, TM, and RS are more sensitive than TPC, they are limited by their dependence on tissue homogeneity. As a result, they are not as sensitive in heterogeneous tissues such as breast. It would be desirable to have a method that is not affected by tissue heterogeneity.

On the other hand, molecular imaging has increasingly become more popular as a tool for fluorescence-guided surgery due to its sensitivity and specificity for cancer cells [19, 20]. Molecular imaging of cancer margin requires a biomarker that is specific to cancer but not the normal breast tissues. It also needs a fluorescent label that has little overlap with tissue autofluorescence. It is commonly accepted that there is no known unique biomarker for breast cancer due to the dynamic characteristics of the disease. However, for margin assessment purpose, the biomarker does not need to distinguish breast cancer from all other types of cancer but rather to distinguish cancer from the surrounding normal breast tissues. For this purpose, tumor-associated carbohydrate antigens (TACA) may be ideal as they are only associated with cancer but not the normal tissues. One of the most common TACAs is Tn antigen (GalNAc-*O*-Ser/Thr), a core glycan associated with mucins on the cancer cell surface of more than 90% of human epithelial carcinomas [21–24]. Tn antigen is formed due to the lack of activities of β1–3 D-galactosytransferase and α-2,6-sialyltransferase enzymes leading to incomplete elongation of O-glycan saccharide chains [25, 26]. It is a truncated form of a major type of glycosylation [27, 28]. Tn antigen is present in malignant breast lesions, invasive carcinomas[29, 30], and some types of benign lesions such as ducal hyperplasia or atypical lobular hyperplasia [30, 31]. Tn antigen has gained attention in antitumor vaccine applications as it is known to generate immune response in cancer patients. [32, 33]. From a study of Konska et al. [34], Tn antigen is expressed in 60%–80% of cancer cells in ductal carcinomas *in situ* (DCIS) and 20%–50% of cancer cells in lobular carcinoma *in situ*. In invasive ductal carcinoma (IDC), Tn is expressed in 70% of cancer cells of stage I cancer, 90%–100% of cancer cells in stage II cancer, and 40%–60% of cancer cells in stage III cancer. In addition, Tn is expressed in 20%–70% of cancer cells in invasive lobular carcinoma. The expression of Tn is uniform throughout the tumors [34].

The recent development of nanomaterials has provided considerable improvement in specificity and sensitivity for tumor imaging by using targeted contrasting agents [35, 36]. Quantum dots (QDs) are semiconductor nanoparticles that have unique photoluminescent capabilities. They exhibit a high fluorescence efficiency, are resistant to photobleaching [37], and comparable to green fluorescent protein (GFP) in size [38]. By changing particle's size, the emission spectra can be tunable which allows simultaneously imaging of different markers at the same pathological sites [39]. Bioimaging applications of QDs include cell labeling and tracking [40–42], cell proliferation [43], sentinel lymph node mapping [44], brain imaging [45], molecular beacons for DNA detection [46–48], and *in vivo* tumor detection [49, 50]. For specific target imaging, QDs can be coupled with antibody to detect biomarker on cell's surface. QDs can be used as labeling agents in immunofluroescence-based assay.

Recent studies have shown that quantum dots can be directly made in an aqueous environment at room temperature (AQDs) with their capping ligands directly in place [51, 52]. The advantages of such AQDs are that they are more stable and easier to conjugate for bio-imaging. A recent conjugation study of CdSe AQDs showed that CdSe AQDs were more than 20 times more efficient in protein conjugation than commercial QDs which were made in an organic solvent (OQDs) and required ligand and solvent exchanges. Furthermore, CdSe AQDs are very bright with a high quantum yield (79%). It also worked well with a 700 nm long-pass emission filter [51], therefore will have little if any interference from tissue autofluorescence [53]. These attributes make CdSe AQDs a good candidate as fluorescent tag of molecular probes.

The purpose of this study is to demonstrate the use of a molecular probe consisting of a monoclonal antibody of Tn antigen coupled with CdSe AQDs to image margin status of human cancers grown in nude mice. This approach is molecularly specific, rapid, and not affected by tissue heterogeneity, which sets it apart from all other technologies that are available or being developed.

2. Materials and Methods

2.1. Cell Line and Cell Culture. The HT29 human colon cancer cell line was obtained from the American Type Culture Collection as it is the best characterized Tn antigen expressing in solid tumor that is easily available and reproducible. The HT29 cell line is a colorectal adenocarnioma which secretes carcinoembryonic antigen (CEA), transforming growth factor beta binding protein and mucin with high level of Tn anigen. Under standard growth conditions, the cells form a multilayer of non-polarized cells that display an undifferentiated phenotype [54]. Therefore, the HT-29 cells are aggressive. They form solid tumor in a short amount of time (2-3 weeks) compared to other carcinomas cell lines. HT 29 cells were maintained in McCoy's 5A medium supplemented with 10% fetal bovine serum (Bioexpress, Kaysville, UT) and 1% penicillin and streptomycin (Mediatech Inc., Manassas, VA) and cultured at 37°C in a 5% CO_2 incubator.

2.2. AQDs Synthesis and Conjugation. CdSe AQDs were synthesized following the aqueous synthesis procedure developed by Li et al. [51, 55] with an optimal MPA : Cd : Se ratio = 4 : 3 : 1. The AQDs were conjugated to monoclonal Tn antigen antibody (mAb) (Tn218 IgM, Abcam, NJ) for direct tumor imaging. The details of the CdSe AQDs conjugation will be published in a separate publication.

2.3. Subcutaneous Mouse Xenograft. Human HT29 cancer cells were harvested by trypsinizing a confluent T-150 cell culture flask. Viability was verified to be greater than 95%

using trypan blue (Amresco, Solon, OH). The cells were resuspended at 10^6 cells per 10 μL of PBS, mixed 1 : 1 with Matrigel (BD Biosciences, San Jose, CA). The 10 μL of prepared mixtures were injected subcutaneously in eight-week-old female nude mice having an average weight of 20 g. The tumors were allowed to grow for three weeks to reach the suitable size for study.

2.4. Immunofluorescent Staining. To test the staining capability of the AQD-Tn mAb conjugate, HT29 cells were grown on cover glass overnight and then fixed with 4% paraformaldehyl for 15 minutes. Cells were washed with PBS three times. Cells were blocked with 10% normal goat serum for nonspecific binding for 1 hour at room temperature. Slides were then washed with 0.1% Tween/Tris buffer saline (TBS) for 3 times. AQD-Tn mAb complex was added and slides were incubated for 1 hour at room temperature. Slides were washed with TBS for 3 times and mounted with DAPI (Mounting medium with fluorescence, Vector Laboratories, CA, USA) for nucleus staining. Samples were stored in the dark at 4°C. A negative control was the sample without primary antibody. The slides were observed under an Olympus BX51 fluorescent microscope.

2.5. Tumor Resection and Imaging. A total of 12 nude mice were used in the experiments. One mouse was used as a negative control without any cancer cell injection. Three weeks after injections, the mice were euthanized. Sharp dissection was used to excise the tumors with a small amount of the surrounding muscles still attached to the tumors. The tumors were round and regular in shape with unifocal characteristics on macroscopic appearance. The fresh tumors were immediately processed ex vivo with the staining procedure as described below, imaged and analyzed with IVIS imaging system (Lumina XR, Caliper, CA). First, the entire tumor's surface was washed with TBS then emerged in 1% bovine serum albumin solution (BSA) for nonspecific blocking for 10 minutes. Next, the tumor was removed from BSA solution and washed with TBS to remove BSA residue. The tumor was then immersed in AQD-Tn mAb solution for Tn-antigen staining of cancer cells. Finally, the tumor was washed again with TBS. The tumor was placed inside of IVIS for acquiring images. Each image acquisition would take about 30 seconds to complete.

2.6. Optimal Blocking Time Evalutation. To find the optimal blocking time, fresh livers were washed with TBS for 2 min twice and then immersed in 1% bovine serum albumin (BSA) for various amounts of time. After washing in TBS three times, the livers were stained with AQD-Tn mAb complex for 1 hour at room temperature. The livers were suspended in 1% BSA solution by thin wire to maximize surface exposure. The blocking solution was stirred continuously to help the diffusion of BSA onto the tissue's surface. The livers were then washed again with TBS and imaged. After the optimal blocking time was identified, staining time was evaluated to develop the optimal margin assessing procedure for the whole tumor.

2.7. Whole Mouse Imaging. One tumor was left inside a mouse. The mouse was euthanized and the entire peritoneum was opened to expose the tumor and internal organs on the ventral side. On the dorsal side, the tumor was left underneath the skin. However, since the skin around the shoulder blade was removed and exposed abdomen, the AQD-Tn mAb probe could get to the tumor even if it was covered with skin. Although the cancer cells were injected subcutaneously on the back of the mouse, the tumor invaded through the ventral side. There was little to no muscle on the tumor's surface. The whole animal was immersed in blocking solution and then AQD-Tn mAb probe suspensions. All the internal organs (such as lung, liver, kidney, etc.) and the tumor were exposed to the probe. This experiment was done to demonstrate the specificity and sensitivity of the probe when the tumor was surrounded by many normal tissues. The total staining procedure was 25 minutes. The mouse was then washed with TBS and imaged with the IVIS system.

2.8. Interference on Microscopic Examination of the Operative Specimen. To examine the potential interference of the method with standard pathological procedures, we studied 10 tumor bearing nude mice. Each mouse had one control tumor and an average of two AQD-treated tumors. A total of 17 AQD-treated tumors and 10 control tumors were evaluated. The AQDs-treated tumors were stained with the AQDs-probe as described in Section 2.6. The control tumors were untreated by AQDs-probe. Both the AQDs-treated and the control tumors were submitted to the pathological department for the same regular pathological examination. Both the AQDs-treated tumors and the control tumors were fixed in 10% formaline for 12 hours and then embedded in paraffin. The blocks were cut into 5 μm sections at the surfaces of the specimens where the AQDs-treated tumors were stained by the AQDs-probe. Both sets of sections (control and treated) were stained with H&E and immunohistochemistry (IHC) stained for 8 different markers: Tn antigen, VEGF, MSH6, MLH1, PMS2, p27, p53, and ki67. Interpretation was performed using Aperio ScanScope XT IHC Image Analysis algorithms (FDA-cleared *in-vitro* Diagnostic) and light microscopy (Olympus BX50) in the carcinoma component.

3. Results

3.1. Tn Antigen Expression in HT29 Cells. Immuofluorescent staining was performed on the HT29 cell lines to validate the functionality of QD-mAb complex. The expression of Tn antigen was evident as can be seen from Figure 1(a). AQDs without antibody showed no binding to HT29-cells (Figure 1(b)). These results indicate that QD-mAb complexes selectively bind to the Tn antigen protein. Furthermore, AQD-Tn mAb complex was compared with Cy3-labeled Tn mAb. Both AQD-Tn mAb and Cy3-Tn mAb bound to the HT29 cell at similar pattern, indicating AQD-Tn mAb complexes were functional (data not shown).

3.2. Minimizing Background Signal. Autofluorescence has always been a challenge for fluorescent imaging especially

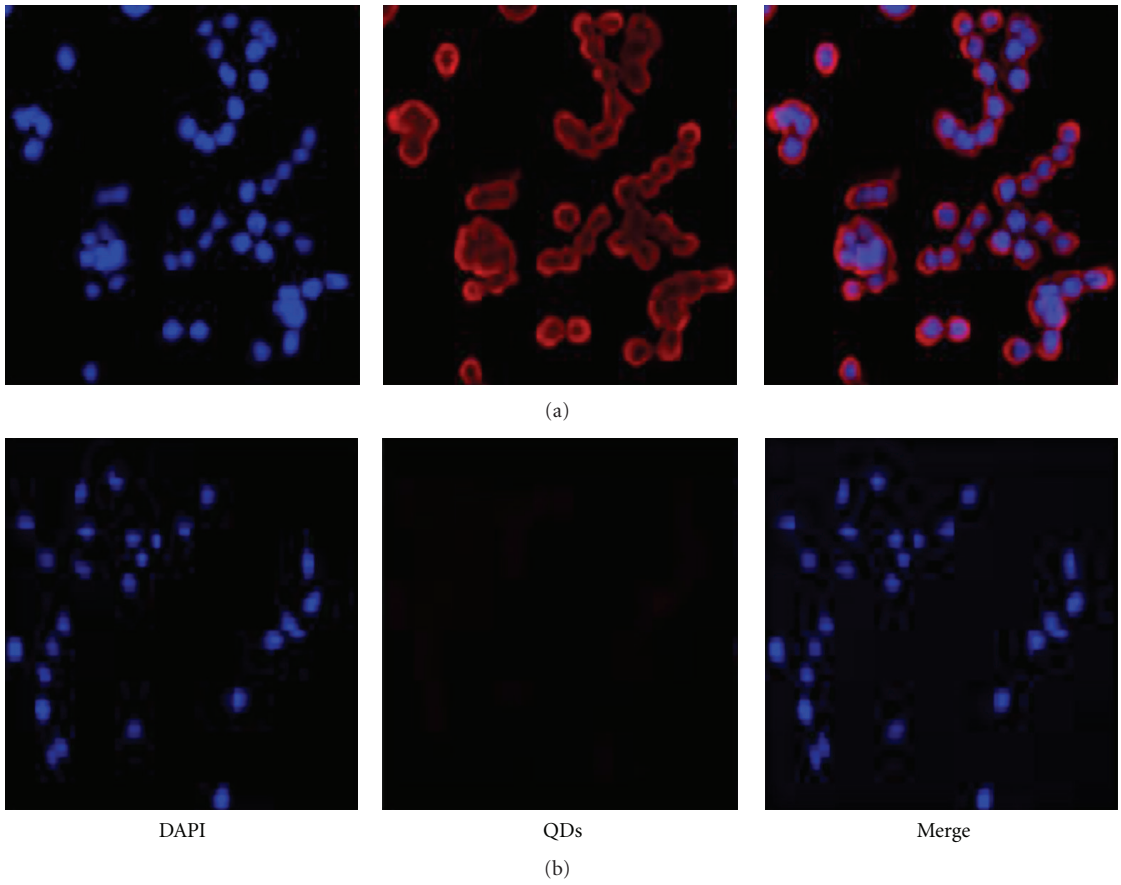


Figure 1: Immunofluroscent staining of HT29 cells for Tn antigen expression. (a) HT29 cells stained with AQD-Tn mAb complexes; (b) negative control, PEG activated AQD without antibody. Blue: nuclei, red: Tn antigen expression.

in tissue with high adipose content such as breast and liver. Normal tissues are known to emit autofluorescent signal that ranges from 380 nm to 550 nm under UV light excitation (350–400 nm) [16, 53]. Here, we tried to establish a clear cut-off threshold to separate the background autofluorescence signal and the positive signal. Livers, muscles, and kidneys were used as normal tissue (negative controls) to evaluate the background threshold (Figure 2). At emission wavelength 509 nm, autofluorescent signal could be observed in liver (Figure 2(b)). Although other tissues did not show positive signal in the images, there were still background signals when the analysis was performed. With the emission at 610 nm, the background signals were reduced in all of the tissues especially livers (30% reduction) compared to emission at 509 nm (Figure 2(d)). A fluorescent intensity threshold of 400×10^6 could be used as the cut-off to separate normal tissues since all the tissues autofluorescence background was below this level.

3.3. Protocol Development. The total staining process of AQD-Tn mAb probe to evaluating excised tumor margin is summarized in Figure 3. First, lumpectomy specimen is removed from patient and oriented with sutures. The tumor is washed with TBS and then blocked with 1% BSA solution. Next, the tumor is removed from BSA solution, washed with TBS and immersed in AQD-Tn mAb probe suspensions for staining. Finally, the tumor is washed again with TBS and imaged on each side with correct orientation. There are two major steps that affect the sensitivity and specificity of AQD-Tn mAb probe: blocking time and staining time. First, blocking time was investigated. Different time periods were examined and it was narrowed down to 15 minutes as the sufficient blocking time. Smaller time intervals were studied to further shorten the blocking time. As shown in Figure 4(a), no BSA blocking resulted in strong nonspecific binding of the QD-mAb probe on liver's surface both dorsal and ventral sides. As the blocking time increased, nonspecific binding decreased and reached the saturated point at 10 minutes. The integrated intensity was similar between 10 minute and 15 minute blocking (Figures 4(c) and 4(d)). This was also at the same level as a control liver without QD-Tn mAb probe exposure (data not shown). Therefore, 10 minutes blocking should be sufficient to prevent nonspecific binding

3.4. Simulation of Intraoperative Margin Assessment. As previously mentioned, although livers and kidneys showed no positive signal, they still had some background intensity around 400×10^6. Thus, this was the cut-off level to

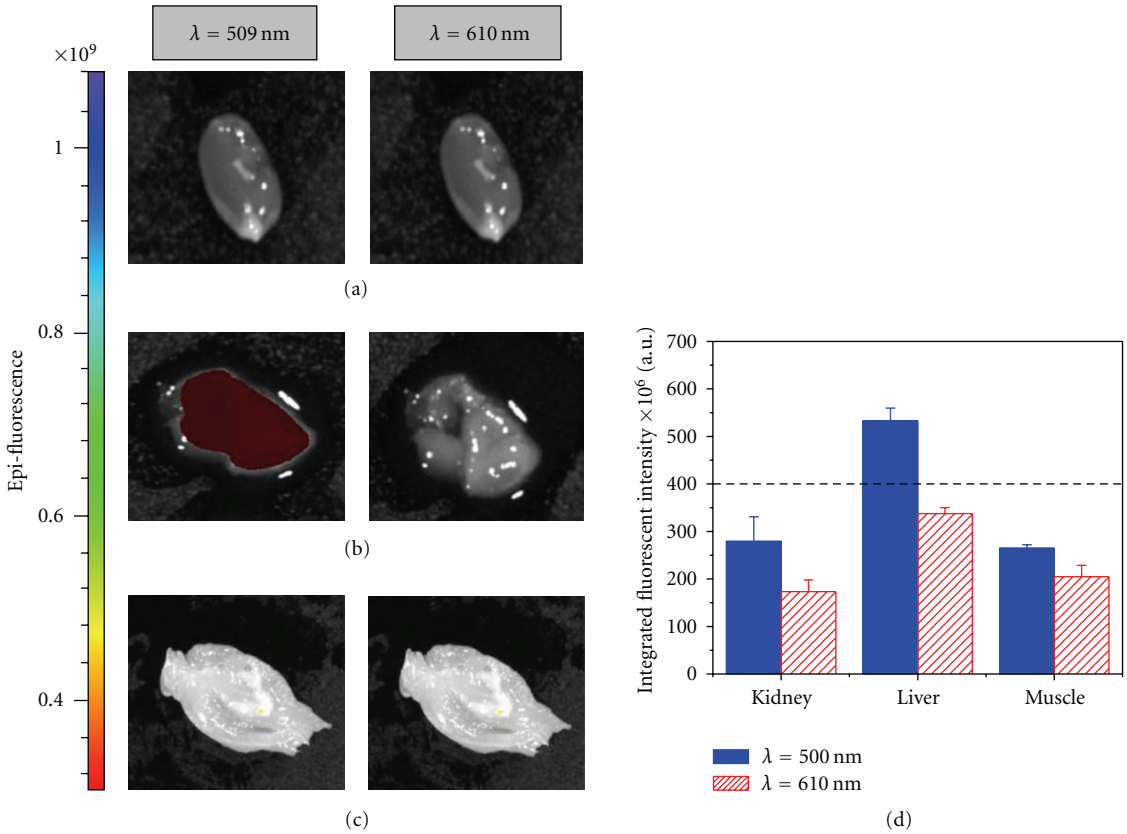


Figure 2: Background signal from normal tissues when excited at 460 nm. There were 2 emission cut-off wavelengths: 509 nm and 610 nm. (a) Kidney; (b) liver; (c) muscle; (d) integrated fluorescent intensity depended on the emission cut-off wavelength. Dash-line indicates background signal.

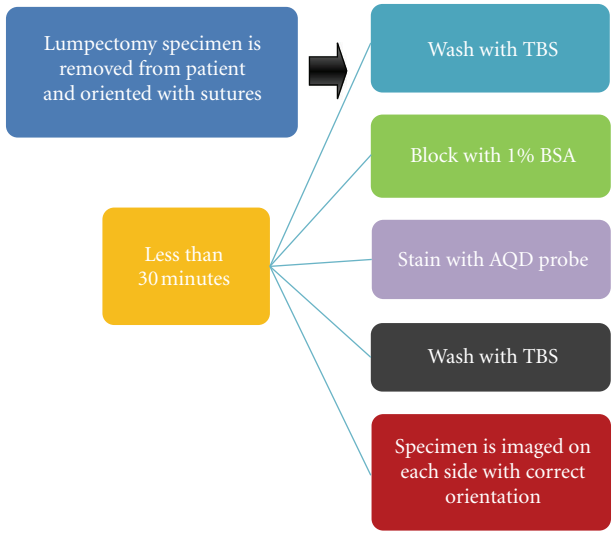


Figure 3: The proposed process of margin determination using AQD-Tn mAb probe.

differentiate between cancer and normal tissue. Optimal staining time was 15 minutes (data not shown). The excised tumors were divided into 3 different regions: a tumor region, a muscle region, and an overlap between tumor and muscle or margin region. Comparing the fluorescent image with the bright field image, we could see that bright dark to turquoise blue-region (region 1 in Figures 5(a) and 5(b)) correlated with the tumor and gray region correlated with the muscle (region 3). The tumors were clearly identified by the AQD-Tn mAb probe. AQD probe was also specific to the tumor and not the muscle as evidenced by the unstained muscle area. Region 2 was more ambiguous based on the image in Figures 5(a) and 5(b). In the dorsal view (Figure 5(a)), the color map showed that region 2 was red corresponding to integrated fluorescent intensity of less than 400×10^6 (Figure 5(c)). This indicated the region to be free of cancer cells. Meanwhile, the ventral bright field image looked like muscle area whereas the fluorescent image indicated the presence of cancer cells with quantitative fluorescent intensity value of 503×10^6, indicating the method was sensitive and specific to detect small non-palpable lesions. The red color in the images could be interpreted as negative region (integrated fluorescent intensity less than 400×10^6).

To further confirm the presence or absence of cancer cells in region 2 of both dorsal and ventral sides, the tumor was embedded in paraffin and examined using the H&E-stained sections of these regions. Figure 6 showed the areas in the square boxes of the tumor, with each region separated by the red line. For the dorsal side, the square box

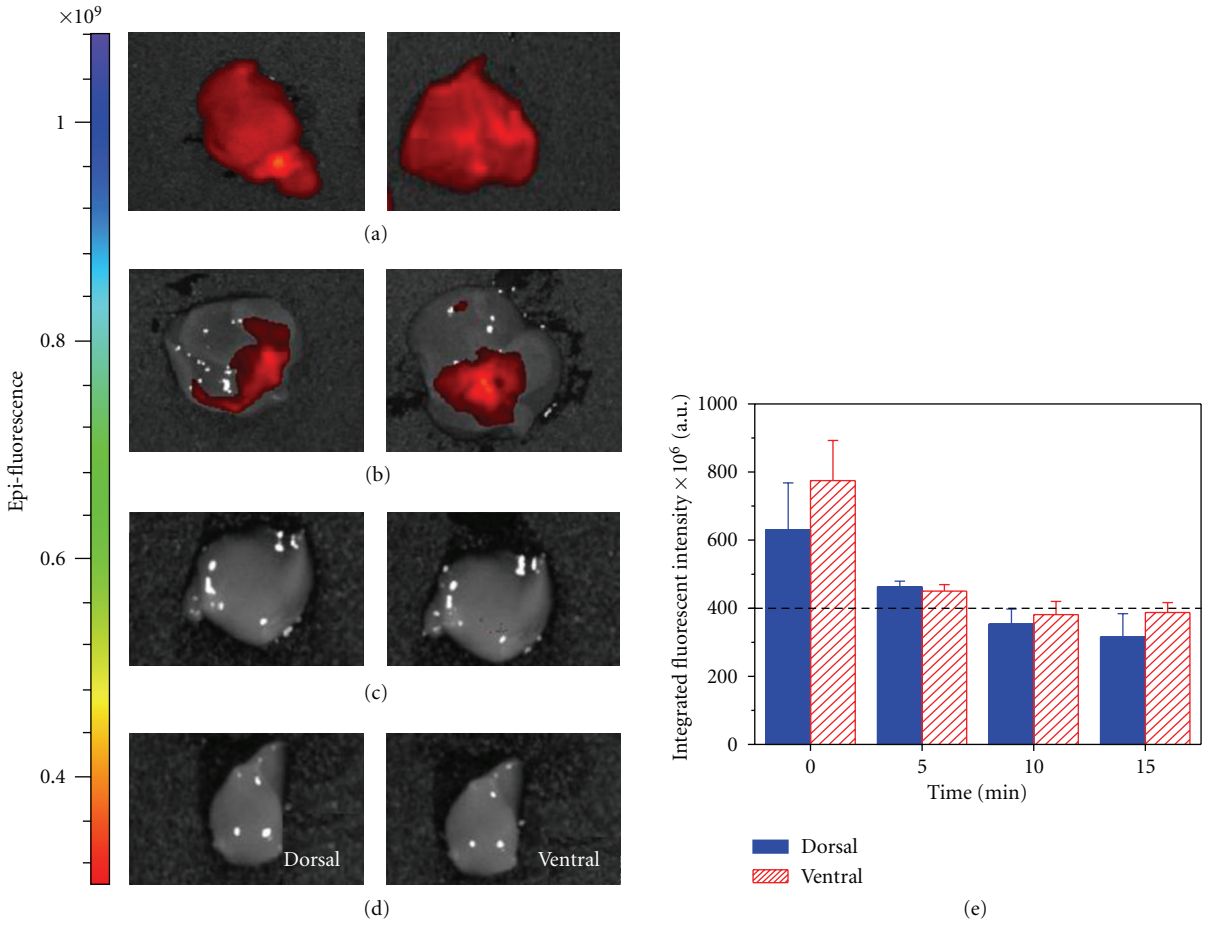


FIGURE 4: Blocking study for nonspecific staining using liver. (a) no blocking—0 min; (b) 5 min blocking; (c) 10 min blocking; (d) 15 min blocking; (e) quantification of the integrated fluorescent intensity versus time. Dash-line indicates acceptable background signal.

contained all three regions—tumor, interface, and muscle. Meanwhile, the square box in the ventral side consisted of only region 2 and region 3 due to larger area of region 2 to be included in the image. Clearly, dorsal region 2 (Figure 6(a)) contained only inflammatory and fibroblasts cells, which correlated to the red color in the whole tumor examination indicating negative signal. The presence of cancer cells were observed in H&E section of ventral region 2 (Figure 6(b)), which confirmed the above positive assessment. The results suggested that this method was sensitive and specific to identify cancer cells in areas that could have been missed by gross examination during tumor removal process. By applying the quantitative analysis of AQD-Tn mAb probe signal, normal, and cancer regions could be distinguished in real-time.

3.5. Whole Mouse Imaging. To further demonstrate the capability of the method, one tumor was left inside of the mouse body. Figure 7 shows the dorsal and ventral pictures of the mouse. The tumor was exposed at the ventral side and underneath the skin at the dorsal side. We found that AQD-Tn mAb probe resulted in the ability to visualize areas of tumors that were not apparent with white light because the appearance of the tumor was not easily distinguished from the other tissues with good fluorescence contrast, indicating highly specific tumor targeting of AQD-Tn mAb probe. The positive signal was strong enough to identify the outline of the tumor surface (fluorescence was much greater than 400×10^6). All the other organs showed no positive signal confirmed the specificity and sensitivity of the AQD-Tn mAb probe.

3.6. Interference on Microscopic Examination of the Operative Specimen. We examined the potential impact of AQD-Tn mAb probe on the microscopic examination of the operative specimen by submitting the treated tumors to pathology department for standard processing. Using multiple routine evaluated markers, we found that there was no difference between the H&E staining of an AQDs-stained tumor and that of a control tumor. There was also no difference between the IHC staining of the various markers: Tn antigen, VEGF, MSH6, MLH1, PMS2, p27, p53, and ki67 on an AQDs-treated tumor and that of the various markers on a control tumor. As examples, Figure 8 showed the H&E staining and IHC staining of ki67, p53, and Tn antigen of a control tumor (Figure 8(a)) and those of an AQD-treated

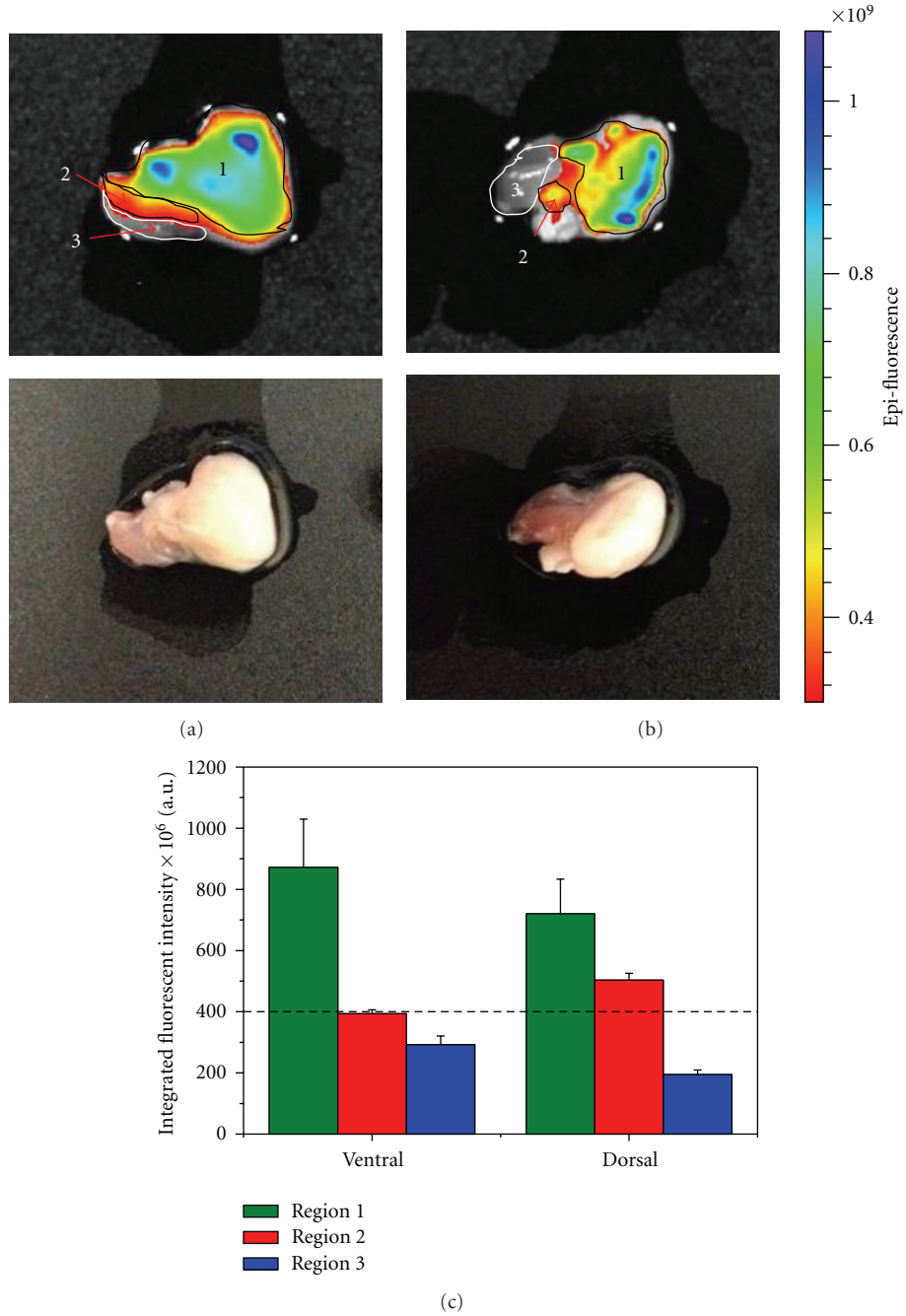
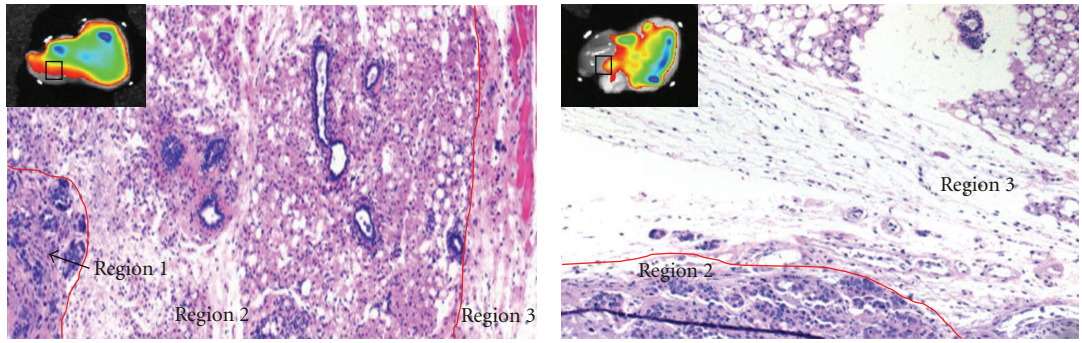


Figure 5: Animal tumor imaging. Top panel: fluorescent imaging using IVIS system. Bottom panel: bright field images of the same tumor. Two orientations of the tumor were imaged: (a) ventral side; (b) dorsal side. (c) The integrated fluorescent intensity was quantified using IVIS software for 3 regions of the tumor. Dash-line indicates the cut-off between normal and cancer areas.

tumor (Figure 8(b)). As can be seen, there was no difference between the H&E staining of the control tumor and that of an AQDs-treated tumor nor was there a difference between the IHC staining of ki67, p53, and Tn antigen of a control tumor and of an AQDs-strained tumor. Furthermore, quantitative grades of ki67 expression were 38.2 ± 5.2% in the control tumors and 31 ± 6.4% in AQD-treated tumors. For p53 expression, the quantitative grades were 38.6 ± 3% and 41.5 ± 3.7% in the control tumors and AQD-treated tumors respectively. This result clearly indicates that the AQDs-based assessment method would not interfere with the standard histological examinations of the surgical specimens.

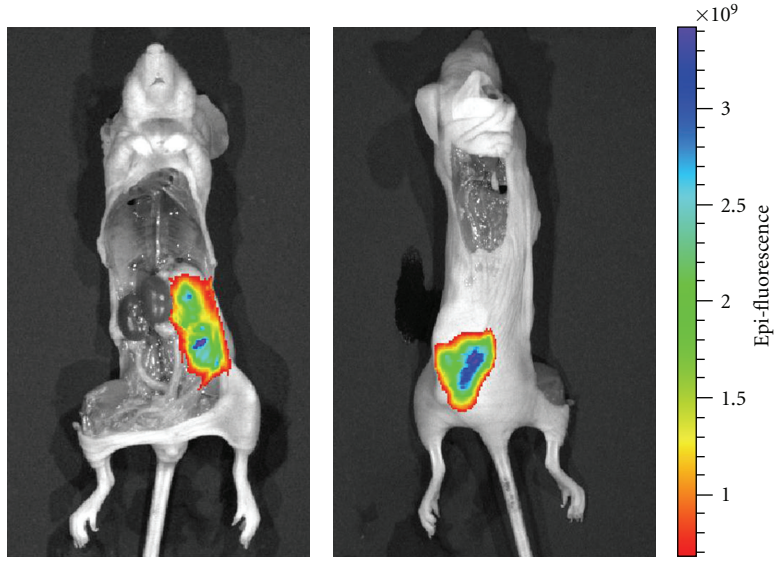
4. Discussion

It is well known that incomplete removal of a tumor is a major factor that compromises the long term survival rate of cancer patients. This study presents the first demonstration



(a) (b)

Figure 6: H&E stained sections correlated to the regions (square box) of the examined tumor. (a) Dorsal side; (b) Ventral side. Cancer cells were absent in region 2 of the dorsal side. Cancer cells were detected in region 2 of the ventral side by AQD-Tn mAb probe and confirmed by H&E stained section.



(a) (b)

Figure 7: Whole mouse tumor imaging. (a) Ventral site where the tumor was exposed. (b) Dorsal site, tumor was underneath the skin. Other organs had negative signal, indicating AQD-Tn mAb prove was specific and sensitive to the tumor.

of molecular imaging for intraoperative ex vivo tumor margin assessment. By providing a quantitative threshold level, AQD-Tn mAb probe provides surgeons the ability to evaluate margin status in real-time, potentially reducing the number of positive margins found postoperatively, and thus reducing the need for the second operation and risk of local recurrence. AQD-Tn mAb effectively identified cancer areas that could be missed by the current gross visual examination. Furthermore, AQD-Tn mAb bound specifically to the cancer cells and not adipocytes and stromal cells as verified by histopathology.

Tissue autofluorescence is a serious background noise issue in any fluorescent imaging and can lead to false positives. Many biomolecules exhibits endogenous fluorescence including amino acids, structural proteins, and lipids. Their emission maxima range between 280 nm to 550 nm [53]. For epithelial tissues such as breast, the concentration of endogenous fluorophores can be substantial between the surface epithelium and the underlying stroma to result in strong autofluorescence in adipose tissue and the stroma. In this study, the CdSe AQDs were imaged with a 610 nm emission filter due to the constraint of the imaging system. However, the CdSe AQDs probe can be viewed with a 700 nm long-pass emission filter, which will allow the signal of the AQDs further separated from tissue autofluorescence, with a higher signal to noise ratio and make the QD-Tn mAb probe even more sensitive and specific in the future. Meanwhile, unlike fluorophores, AQDs can undergo constant light exposure with minimal photobleach, which often leads to loss of signal. AQDs allow convenience in handling the probe without the need of a dark room.

Current technologies such as wire-guided localization (WGL) can perform intraoperative tumor localization with positive margin ranges from 23% to 46% [56, 57] and does

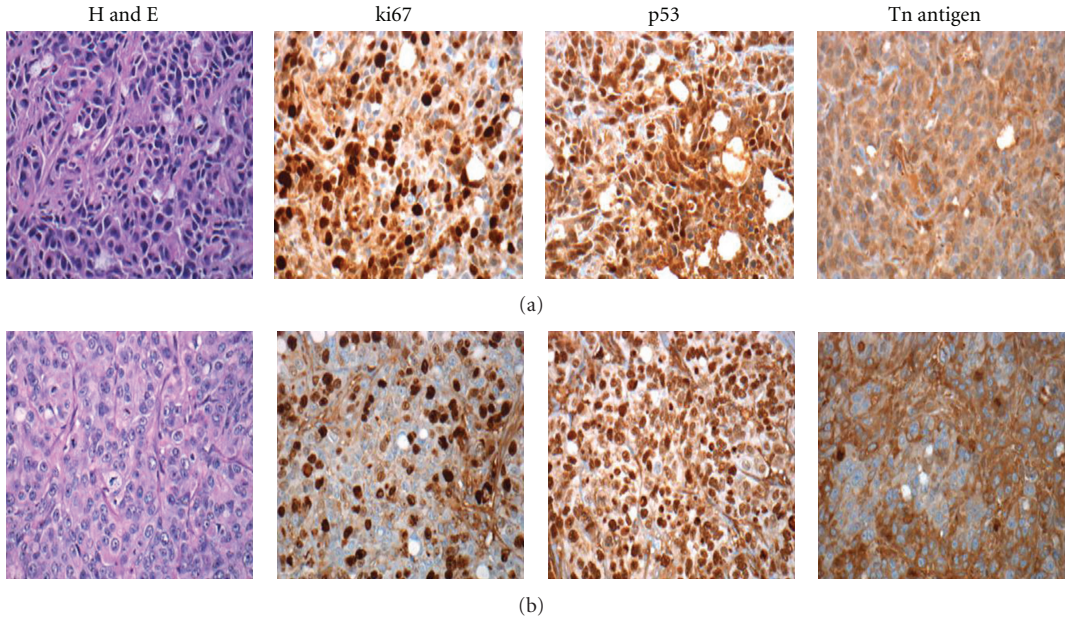


Figure 8: Interference examination of AQD-Tn mAb probe on standard pathological evaluations. (a) Control tumors; (b) AQD-treated tumors. Different markers were evaluated such as Tn antigen, p53, and ki67. No interference with the following pathological examination was found.

not provide a clear three-dimensional image of tumor edges [58]. Ultrasound guided resection is limited to ultrasound visible tumors while specimen radiography detects clips or calcifications in a tumor specimen, but both are limited in ability to establish clear margins reliably [59]. New developing optical-based imaging technologies appear to be applicable for intraoperative imaging due to their portable size and low cost. For example, the optical spectroscopy method developed by Wilke et al. transforms optical images into tissue composition maps with parameters of total hemoglobin concentration, β-carotene concentration, and scattering [60]. The MarginProbe method [15] is a near-field radio frequency (RF) spectroscopy device that detects differences between dielectric properties of malignant and normal breast tissue. These methods, however, depend on the intrinsic measurements, such as tissue scattering and autofluorescence of the tissues, leading to unacceptable false-negative rates due to the high heterogeneity of malignant and benign tissues [15, 17, 61]. The present AQD-Tn mAb probe does not depend on the physical-mechanical characteristic of the tissue but assessing the differences between normal and cancer at the molecular level. TACA Tn antigen has been reported to be expressed exclusively in cancer cells and not normal tissue. Using this molecular signature of cancer cells, tissue heterogeneity is not an issue as the results presented above clearly showed that the AQD-Tn mAb probe was capable of displaying very small spots consisting of 100 to 200 cancer cells. This is a key advantage compared to most of the current developing optical-based imaging technologies which rely on signal average over a large area and thus are unable to image cancer in a heterogeneous background.

Total margin evaluation time is one of the most critical requirements for intraoperative margin status determination. FSA has been reported to have good sensitivity and specificity to cancer cells but has difficulties in performing frozen sections on adipose tissue results in increasing surgery time and cost due to additional pathology evaluation [13]. The most significant disadvantage of FSA is the inability to evaluate the entire surface area with sampling rate of 10–15% surface area. Using antibody-antigen binding mechanism, the AQD-Tn mAb probe was able to stain and identify cancer areas quantitatively in less than 30 minutes to prevent the prolonged anesthesia period for patients. All sides of the tumor are evaluated which give the surgeon the exact location of cancer area. Furthermore, no additional intraoperative pathological evaluation is needed to decide whether an area contains cancer cells or not. Manipulations of the surgical specimen have no impact on the microscopic examination of the operative specimen as shown in the interference study is another advantage of this method. The specimen can undergo normal histologic examinations for further margin confirmation and other necessary markers evaluations.

In this study, we used HT29 colon cancer cell as our tumor model instead of a breast cancer cell line. HT29 cells expressed Tn antigen strongly without any need of transfection to express the protein, as verified by Western blot. Because this was a proof of concept study, we wanted to ensure that our tumors express the marker strongly so that we could control over the methodology development. Furthermore, we have showed that AQD-Tn mAb probe was capable of staining the whole tumor inside the mouse body locally once the tumor surface was exposed. Although there

was positive signal of tumor underneath the skin at the dorsal side, the skin was relatively thin (less than 1 mm). With the depth of 2 mm (consider negative margin), no signal would be observed due to the penetration depth of 610 nm wavelength. We will examine this aspect in our future studies. The tumor imaging inside the mouse further indicated that AQD-Tn mAb probe was very sensitive and specific to cancer cells only. This can potentially be developed as a tool to examine the cavity after tumor is removed for additional information about the margin.

5. Conclusion

In conclusion, we have demonstrated the use of a molecular probe AQD-Tn mAb to assess the surface of excised human cancers grown in nude mice. The AQD-Tn mAb molecular probe consisted of the antibody to target cancer-specific Tn-antigen on the cancer cell surface that is covalently linked to CdSe AQDs. The advantages of the CdSe AQDs as the fluorescent tag of a cancer molecular probe include brightness, without photo-bleaching, and can be accessible to 700 nm long-pass emission filter that minimizes background tissue autofluorescence. The results showed that the AQD-Tn mAb was effective to image tumor margin in less than 30 min. Tissue heterogeneity which was an issue for optical- and electrical-current-based imaging technologies did not have an effect in AQD-Tn mAb imaging due to its specific binding capability which allows a more precise margin assessment. The integrity of the surgical specimen was not affected by the AQD treatment and there was no difference in the quality and intensity of standard H&E as well as IHC stains. The AQD-Tn mAb molecular probe offers the potential to quantitatively and accurately assess margin during surgery to help reduce reexcision rate.

Acknowledgments

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Review Article

Optimizing Surgical Margins in Breast Conservation

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Adequate surgical margins in breast-conserving surgery for breast cancer have traditionally been viewed as a predictor of local recurrence rates. There is still no consensus on what constitutes an adequate surgical margin, however it is clear that there is a trade-off between widely clear margins and acceptable cosmesis. Preoperative approaches to plan extent of resection with appropriate margins (in the setting of surgery first as well as after neoadjuvant chemotherapy,) include mammography, US, and MRI. Improvements have been made in preoperative lesion localization strategies for surgery, as well as intraoperative specimen assessment, in order to ensure complete removal of imaging findings and facilitate margin clearance. Intraoperative strategies to accurately assess tumor and cavity margins include cavity shave techniques, as well as novel technologies for margin probes. Ablative techniques, including radiofrequency ablation as well as intraoperative radiation, may be used to extend tumor-free margins without resecting additional tissue. Oncoplastic techniques allow for wider resections while maintaining cosmesis and have acceptable local recurrence rates, however often involve surgery on the contralateral breast. As systemic therapy for breast cancer continues to improve, it is unclear what the importance of surgical margins on local control rates will be in the future.

1. Introduction

Breast-conservation therapy (BCT), including lumpectomy and sentinel lymph node biopsy followed by radiation therapy, is the treatment of choice for women with early stage breast cancer. Randomized trials have shown that overall survival of women undergoing BCT is equivalent to mastectomy [1, 2]. The goal of lumpectomy is to completely excise the tumor with negative margins while maintaining acceptable cosmesis. Rates of margin positivity at initial lumpectomy have been reported ranging from 15% to 47% [3–6]. Positive margins are usually addressed with surgical reexcision, since the risk of local recurrence associated with a positive margin is approximately 2 to 3 times that compared with a negative margin [7]. Reexcision can include reoperative lumpectomy or possibly mastectomy. This additional surgical reoperative procedure can result in increased psychological trauma to the patient, delay of adjuvant therapy, worsened cosmesis, and increased cost [7].

It is well accepted that complete removal of tumor is necessary, however, there is aconsiderable debate regarding what margin of normal tissue surrounding the tumor constitutes a negative margin. Definitions range from no ink on tumor surface (NSABP B-06) to 1 cm or more [8]. Blair et al. sent a survey to nearly 1000 breast cancer surgeons, and found that 15% defined a negative margin as no tumor on inked margin, 21% accepted a 1 mm margin, 50% accepted a 2 mm margin, 12% accepted a 5 mm margin, and 3% accepted a 1 cm margin [9]. A meta-analysis by Wang et al. found that wider margins minimize the risk of ipsilateral local recurrence, with lowest recurrence rates achieved with a negative margin larger than 10 mm rather than 2 mm. This finding was independent of whether or not the patient received radiation [10].

In another meta-analysis of 21 retrospective studies which included 14,571 patients, Houssami et al. demonstrated an odds ratio for local recurrence of 2.42 ($P < 0.001$) with positive margins. This meta-analysis did not identify

a statistically significant difference in local recurrence associated with margin widths of more than 1 mm, more than 2 mm, or more than 5 mm after adjustment for a radiation boost and endocrine therapy [11]. This suggests that a 2 or 5 mm margin is not necessarily better than a 1 mm margin.

When considering optimal margin width, it is useful to remember that a "negative" margin does not indicate the absence of residual unresected tumor in the breast [12]. It simply suggests that the residual tumor burden is probably low enough to be controlled with radiotherapy. Even the widest margins resulting from mastectomy do not eliminate risk of local recurrence. This indicates that residual disease burden is not totally eliminated by local surgery and that tumor biology, radiation therapy, and systemic therapy may play an important role in controlling local recurrence [13].

In further defining this idea of residual disease burden, Margenthaler et al. have proposed calculating a "margin index" as a predictive tool for residual disease after breast-conservation surgery [14]. This margin index is calculated by dividing the closest margin (in mm) by the tumor size (in mm) $\times$ 100. They found that with a margin index >5, the risk of residual disease was 3.2%. With a margin index of 20, no residual disease was found in the reexcision specimen.

The NSABP B-06 study showed that in 1851 patients who underwent breast conservation, the positive margin rate was 6.8% and the in-breast tumor recurrence rate was 14.2% over 20 years of followup [1]. Other randomized controlled trials described a range of local recurrences rates from 5.9% at 20 years to 19.7% at 13 years [22]. These randomized trials do not explicitly define margin width, which ranged from no ink on tumor to 1 cm gross margin. While the B-06 trial was conducted in the 1970s, several subsequent NSABP trials in the 1990s showed improvement in 10-year local recurrence rates ranging from 3.5% to 6.5% [23]. Although developments in breast imaging and pathological evaluation of lumpectomy specimens probably contributed to these improvements, significant strides were also made in systemic therapy during this time. This suggests that the likelihood of local recurrence is related to not only the surgical margin width as well, but also to the underlying tumor biology as well as the effectiveness of adjuvant therapy.

Multiple retrospective studies have attempted to define predictors of a positive margin at lumpectomy. These studies identified a number of independent predictors of local recurrence including age less than 40 years, microcalcifications on mammography, palpable tumors, large tumors, multicentricity, presence of DCIS or lobular histology, and lymphovascular invasion [24]. While these studies showed that 1-2 mm margins were associated with decreased local recurrence rates, it is unclear what the impact of improved systemic therapy and boost radiation therapy is on these results. Cabioglu retrospectively assessed patient and tumor characteristics as well as IBTR rates in two cohorts of patients (those treated from 1970 to 1993, and those treated from 1994 to 1996) [25]. Patients treated after 1994 were less likely to have positive or unknown margin status (2.9% compared to 24.1% before 1994,) and the 5-year IBTR rate was lower in patients treated after 1994 (1.3% compared to 5.7% in those treated before 1994). These investigators postulated that multidisciplinary management, including improvements in pathologic evaluation and systemic therapy, could be credited for the improvement in IBTR.

Further evidence supports the fact that systemic treatments not only reduce the risk of distant metastases but also reduce the risk of local recurrence. In the NSABP B-14 trial, women with node-negative, estrogen-receptor (ER)-positive tumors were randomly assigned to tamoxifen or placebo [26]. The 10-year rate of local recurrence after breast-conserving surgery was reduced from 14.7% in the placebo group to 4.3% in the tamoxifen group. Similarly, in the NSABP B-13 trial, women with node-negative, ER-negative tumors were randomly assigned to methotrexate and fluorouracil or to no treatment [27]. A reduction was noted in the 10-year local recurrence rate from 13.4% in the no-treatment group to 2.6% in the treatment group. In both studies, the NSABP definition of no ink on tumor was used to define a negative margin.

Studies examining the effect of adding trastuzumab to adjuvant chemotherapy in women with human epidermal growth factor receptor 2 (HER2)-overexpressing tumors have shown an additional 40% reduction in the risk of local recurrence over a median follow-up of 1.5 to 2.0 years [28]. Triple negative tumors have the highest risk of local recurrence after both breast-conserving therapy and mastectomy [29–31], and retrospective studies do not show an improvement in local control after mastectomy as compared with lumpectomy and radiation in this subgroup of patients with biologically aggressive tumors [32, 33].

The effect of tumor biology on local recurrence was clearly shown in a study examining the usefulness of the 21-gene recurrence score (Oncotype DX) in predicting local and regional recurrence [34]. The recurrence score was developed to predict the likelihood of distant metastases in patients with ER-positive, node-negative breast cancer who received tamoxifen [35]. Mamounas et al. found that without systemic therapy, 18.4% of patients with a high recurrence score ($\geq$31) had a recurrence of local or regional disease [34]. The addition of tamoxifen had a minimal effect on the rate of local and regional recurrence, with a decrease to 15.8%. In contrast, the combination of chemotherapy and tamoxifen was associated with a reduction in the local recurrence rate to 7.8%.

Interestingly, the majority of the studies describing local recurrence rates do not make the distinction between true local recurrences and new ipsilateral primary tumors. Yi et al. suggested that approximately 50% of IBTRs are actually new primary cancers as differentiated by histologic subtype and receptor status [36]. This would lead us to expect that the true local recurrence rate may be half of what is reported in the above studies, if in fact half of in-breast recurrences are new primaries. These new primary tumors therefore would not be expected to be affected by margin width.

2. Preoperative Imaging and Treatment Strategies

Thorough preoperative imaging is necessary to plan the extent of resection while minimizing positive margins.

Standard preoperative imaging includes mammography and ultrasound, and often MRI. Mammography can delineate tumor size and borders, as well as identify extent of microcalcifications, presence of multifocality, and multicentricity. Mammography is also important for assessment of the contralateral breast. Compared to mammography, ultrasonography can often give more accurate estimation of tumor size and borders, particularly in patients of young age with dense breasts.

MRI is a more sensitive test that can detect additional foci of disease not appreciated on mammogram and ultrasound. Houssami et al., in a metaanalysis of 19 studies, found that MRI detected additional disease in 16% and led to more extended surgery in 5.5% with a change from lumpectomy to mastectomy in 1.1% [37]. Crowe et al. demonstrated that MRI identified occult or separate tumors in 13% of patients [38]. MRI has a high false-positive rate, so it is clear that additional lesions identified on MRI must be biopsied to demonstrate malignancy prior to changes in surgical planning. Of note, the clinical consequence of detecting these additional lesions on MRI is unknown since no study has demonstrated that use of MRI translates into improved local recurrence rates or survival.

Another theoretical advantage of MRI is the potential to better define the extent of the index lesion in order to better plan surgical resection. However, Bleicher et al. in a retrospective review of 577 patients (130 of which had preoperative MRI) failed to demonstrate a difference in margin positivity or the need to convert from breast conservation to mastectomy in the group who had MRI [39]. At this time, preoperative MRI does not improve surgical planning and does not reduce the need for reexcision. Furthermore, Shin et al. in a retrospective analysis showed that breast MRI provided more accurate estimation of tumor size in comparison to ultrasound for both invasive and in situ breast cancer. However, no clear benefit in terms of lower reexcision rate, higher rate of success of breast conservation, or reduced rate of local recurrence emerged with routine use of breast MRI before BCT [40].

There is some suggestion that MRI may be better at assessing DCIS than conventional imaging. Kropcho et al. prospectively evaluated patients diagnosed with DCIS with and without MRI [41]. In this study, the correlation between MRI and tumor size was found to be significantly higher; however, no significant difference was found in between-group analysis of the incidence of margin involvement with MRI versus without MRI (30% versus 24.7%, $P = 0.414$, resp.).

Neoadjuvant chemotherapy can often shrink larger tumors to allow for breast conservation. Sweeting et al. demonstrated that over 6-year median followup in young women <age 45, locoregional recurrence rates were no different after breast conservation than mastectomy (13% versus 18%) in patients who underwent neoadjuvant chemotherapy [42]. Higher posttreatment, but not pretreatment, stage was associated with higher locoregional recurrence rates. Recently, Moon et al demonstrated that the accuracy of MRI after neoadjuvant chemotherapy is influenced by the molecular subtype of the tumor. MRI was most accurate in predicting residual tumor extent for triple-negative breast tumors, and least accurate in the Luminal A subtype (Pearson correlation coefficient of 0.754 and 0.531.)

Multivariate analysis suggested that ER status was an independent factor which influenced the accuracy of MRI. In HER2 amplified tumors, the use of HER2-targeted agents was associated with a less accurate MRI prediction of residual tumor extent.

Huang et al. proposed a prognostic index score for patients receiving neoadjuvant chemotherapy composed of four points: (1) clinical N2 to N3 disease, (2) lymphovascular invasion, (3) pathologic size >2 cm, and (4) multifocal residual disease [43]. Patients with an index of 0 or 1 had similar LRR rates between mastectomy and BCT. Patients with a score of 2 had a trend towards less LRR that was not significant (12% after mastectomy versus 28% after BCT), and patients with a score of 3 or 4 had a significant difference (19% after mastectomy versus 61% after BCT.) This index provides a framework in which to guide surgery selection after neoadjuvant chemotherapy, however, does not explicitly address the impact of margin status on LRR rates.

Other novel preoperative imaging strategies include optical spectroscopy and molecular vibrational imaging. Optical spectroscopy uses properties of tissue microstructure and biochemical composition to characterize tissue. It can differentiate normal from malignant tissue by distinguishing deoxy-hemoglobin, oxy-hemoglobin, water, and lipids, and thus is not limited by mammographic tissue density. This has also shown promise in assessing tumor response to neoadjuvant chemotherapy [44]. This technology is limited in distinguishing DCIS from normal tissue. Molecular vibrational imaging is another quantitative imaging technology that uses Coherent anti-Stokes Raman scattering (CARS) microscopy to visualize cellular and tissue features. This technology shows promise in differentiating invasive ductal from invasive lobular lesions, as well as DCIS from normal tissue.

3. Lesion Localization, Margin Assessment, and Intraoperative Techniques

Preoperative tumor localization for nonpalpable lesions was traditionally performed by the radiologist with either a mammographically or sonographically guided wire placement into the tumor. The limitation of this technique is that it identifies the lesion in one plane only, with limited ability to guide a three-dimensional resection of the lesion. Lesion bracketing with multiple guidewires as opposed to a single wire would theoretically improve margin clearance by facilitating complete resection of an imaging abnormality. However, Liberman et al. found that while bracketing a lesion (particularly if the lesion was a large area of calcifications) with multiple wires may help to ensure removal of the entire mammographic lesion, it still did not improve on rates of margin positivity [45].

Intraoperative specimen radiography using the Faxitron can be done immediately after specimen excision. The Faxitron allows the surgeon to visualize an eccentric location of a tumor or clip so that additional tissue can be removed.

Bathla et al. demonstrated a reexcision rate of 14.3% when 2-dimensional Faxitron was used to guide further tissue removal at the time of initial lumpectomy [46]. In this study, 95.8% of patients who would have required subsequent reexcision were spared further surgery since additional margins were taken at the time of lumpectomy based on Faxitron imaging findings.

Intraoperative ultrasonography allows for improved guidance on extent of resection. This technique is quite promising for lesions that can be visualized with ultrasound. This was demonstrated by Rahusen et al. in a randomized clinical study comparing ultrasound guided lumpectomy of nonpalpable breast cancer to wire-guided resection. Using ultrasound to localize the cancer improved rates of margin positivity from 45% with wire guided localization alone to 11% with intraoperative US localization [47]. However, many lesions are not visualized on ultrasound; in particular DCIS lesions which are diagnosed as calcifications on mammography often have no ultrasound correlate. For this reason, it is essential for the surgeon to document presence of the lesion on ultrasound preoperatively to ensure visualization.

For lesions not visible on ultrasound, a hydrogel based-breast biopsy clip can be placed at the time of biopsy. This clip is visible on ultrasound and enables the surgeon to use US guidance rather than preoperative wire localization for excision of sonographically occult lesions. However, this approach has limitations. Klein et al. reported that while the clip was very well visualized with intraoperative US, there was a high rate of clip migration either prior to the procedure (6.4%) or when the biopsy cavity was transected (45.2%) [48].

Another technique to enable use of intraoperative ultrasound for lesion excision involves cryoprobe assisted localization (CAL), in which an ultrasound-guided cryoprobe is placed into the tumor to freeze it. This enables the tumor to be easily palpable and visible on ultrasound. Tafra et al. demonstrated that although similar rates of margin positivity (28% with CAL compared to 31% with wire guided localization) and reexcision (19% and 21%) were noted, the cosmetic outcome was improved with CAL since less healthy surrounding tissue around the tumor was removed [49].

Another technique that is showing promise in improving margin clearance is radioguided occult lesion localization (ROLL). This involves placement of a small radioactive seed under imaging guidance. This seed can be detected with a hand-held gamma probe at the time of surgery. A recent metaanalysis of four randomized controlled trials including 449 patients comparing radioguided seed localization to wire guided localization showed improvement in margin status as well as reoperation rates with the ROLL technique [50]. However, when Krekel et al. compared wire guided localization, intraoperative US localization, and the ROLL technique, the rate of positive margins was the lowest in the intraoperative US group [51].

These studies suggest that the ability to visualize the lesion in multiple dimensions facilitates complete removal, however, rates of margin positivity may still be unchanged. Therefore, efforts have been focused on methods of evaluating the lumpectomy specimen intraoperatively to assess margin positivity. Traditional margin assessment intraoperatively consists of either frozen section histology or imprint cytology. Frozen section histology, while relatively accurate in reflecting margin status, is limited due to time, cost, and loss of tissue for permanent section evaluation. Furthermore this method is very labor intensive and can only examine a limited amount of tissue, with false negative rates reported in 19% of patients [52]. Imprint cytology or "touch prep" involves touching the lumpectomy margins to a glass slide, then fixing and staining them based on the principle that cancer cells will stick to the slide and fat cells will not. This method only assesses tumor cells at the lumpectomy surface and does not indicate when margins are close. The accuracy is extremely variable and experience dependant, with positive predictive values ranging from 21% to 73.6% [53, 54]. In addition, both of these pathologic techniques are limited in their ability to predict invasive lobular cancer as well as DCIS at the margins [52].

Besides pathologic techniques to assess margins, significant efforts have been directed towards intraoperative margin probes to assess the lumpectomy specimen margins at the time of surgery. The MarginProbe (TM, Dune Medical Devices) uses radiofrequency spectroscopy to assess margin status. Using this probe, Allweis et al. reported a decrease in reexcision rate from 12.7% to 5.6% [55]. High frequency ultrasound probes have also been developed for intraoperative margin assessment [56]. This technology may have the ability to differentiate carcinomas and precancerous lesions such as ADH from normal tissue. It can also differentiate invasive lobular cancer from normal tissue, which is a limitation of other techniques.

Dooley et al. described ductoscopy-assisted lumpectomy based on the "sick lobe" hypothesis, with the idea that the entire lobe of the breast containing disease should be evaluated and all affected areas should be removed in order to minimize local recurrence rates [57]. His nonrandomized series showed a lower rate of local failure in those patients who had ductoscopy assisted surgical excision. Furthermore, 42% of patients were noted to have extensive disease within the affected lobe.

Since a primary drawback of large excisions to achieve negative margins is due to removal of excess volume of tissue and resultant cosmetic deformity, several ablative methods have been investigated to provide a larger perimeter of margin clearance without resecting additional tissue. Manenti et al. demonstrated that cryoablation of unifocal small malignant tumors led to complete necrosis in 14 of 15 patients [58]. Laser ablation has been demonstrated to ablate mammographically detected breast cancer [59]. Klimberg et al. have demonstrated that radiofrequency ablation at the time of surgical excision (eRFA) creates a 5–10 mm zone of ablation around the resected tumor, without removing excess of volume of tissue to achieve the same result [60]. These technologies hold promise in achieving wider margins without compromising cosmesis.

Since most true in-breast recurrences occur at or near the initial lumpectomy cavity, partial breast intraoperative radiation has been investigated as an alternative to traditional external beam. The use of a single dose of intraoperative

radiation using a spherical applicator placed in the surgical cavity was compared to traditional external beam radiation in the TARGIT-A trial [61]. This trial showed that at 4 years of followup in selected patients, a single intraoperative radiation dose is an acceptable alternative to external beam radiotherapy.

4. Pathologic Assessment

There is no universally accepted pathology standard for assessing breast specimens, and translation of intraoperative findings to the pathology lab can be quite difficult. After a lumpectomy specimen is removed from the breast, there may be distortion of the margins due to compression of the specimen for radiographic lesion confirmation. The breast tissue is fatty, and often with compression of the tissue for specimen radiograph to confirm lesion excision, the specimen flattens out or "pancakes," resulting in distortion of the specimen and spurious positive margins [62]. Furthermore, even with minimal handling, the breast tissue is fatty and often slides off a tumor which remains firm.

Therefore, in addition to assessing the lumpectomy specimen margins, surgeons often submit additional tissue from the cavity margins once the primary specimen has been removed (cavity shave margins). Assessing the cavity margins rather than lumpectomy margins is likely a better indicator of presence of residual disease in the cavity since it avoids the issues of compression and specimen processing artifact. The technique involves resecting thin samples of tissue from all 6 margins (superior, inferior, medial, lateral, anterior, and posterior) for pathology evaluation. This technique can direct the surgeon to the exact location of a positive margin in the event that reexcision is necessary; however, the drawback is that it further increases resection volume [63]. Although the volume of tissue resected is increased, Rizzo et al. demonstrated a higher rate of pathologic margin negativity and therefore a lower rate of reoperation with this technique [64]. While there is a cost savings associated with fewer reoperations, there is additional time required by pathology to assess the extra tissue removed and may adversely impact cosmesis.

Another challenge as the lumpectomy specimen moves from the operating room to the pathology lab is specimen orientation. Marking sutures have traditionally been placed on 2 or more of the 6 surfaces of a lumpectomy specimen by the surgeon in the operating room, followed by inking of all 6 margins done by the pathologist in the lab. Molina et al. demonstrated that with 2 marking sutures placed by the surgeon, there was a 20% rate of discordance between surgeon and pathologist interpretation of the margins in specimens larger than 20 square cm [65]. In smaller specimens less than 20 square cm, the discordance was as high as 78%.

Particularly disturbing for the surgeon are cases where a positive margin is noted on pathology from the initial lumpectomy, and no further disease is evident on reexcision, since it is unclear whether the reexcision removed the correct area. Dooley and Parker demonstrated that when a single margin was close or positive, reexcision showed tumor in only 35% of cases [66]. When multiple margins were close or positive, reexcision showed tumor in 47% of cases.

Pathologic processing includes inking with close attention so that ink does not run into cut surfaces. Multiple samples are taken perpendicular to each inked surface, with additional samples taken based on gross appearance of the tissue [67]. In order to more accurately orient the specimen for the pathologist and to help guide reexcision, Singh et al. compared standard inking by the pathologist after lumpectomy versus intraoperative inking with surgeon input [68]. This study demonstrated a decrease in margin positivity rate from 46% to 23%, as well as a decrease in reexcision rates from 38% to 19% when the surgeon was responsible for inking the margin. Importantly, residual disease at the time of reexcision was noted to be 67% in the group inked by the surgeon (as opposed to 23% in the group inked by the pathologist). This simple technique of surgeon staining the lumpectomy specimen with 6 different ink colors at the time of lumpectomy can enable orientation to be maintained when evaluating the margins. Furthermore, directed reexcision also decreases the volume of tissue excised when compared to the whole cavity reexcision [69].

5. Oncoplastic Surgery to Achieve Wider Margins

Oncoplastic breast surgery combines the principles of cancer resection with plastic surgery to achieve wide tumor-free margins in such a manner as to maximize resection volume while optimizing cosmetic outcome. The two main techniques used involve volume displacement and volume replacement. Volume displacement techniques combine resection with a variety of different breast-reshaping and breast-reduction techniques and include radial ellipse segmentectomy and circumareolar approach. Lesions in the upper or central breast can be resected with the crescent mastopexy, batwing incision, donut mastopexy, and central quadrantectomy. Lesions of the lower breast can be resected with the triangle incision, inframammary incision, and reduction mastopexy [70].

These procedures can be done by the breast surgeon and/or plastic surgeon at the time of cancer resection. Of note, the three dimensional orientation of the tumor bed is frequently altered with these techniques so that identification of the initial resection cavity for postoperative radiation therapy is not possible. At the very least, placement of surgical clips after tumor resection and before oncoplastic reconstruction may be the most accurate method to localize the RT local boost field. Additionally, oncoplastic techniques commonly prevent a simple further excision in the event of positive margins, so that most patients with involved margins will need a mastectomy [71]. Oncoplastic procedures for cancer often result in the need for a contralateral symmetry procedure. The contralateral procedure can be done at the same time as the cancer resection, or at a later time.

Volume replacement techniques are performed less frequently, and involve autologous tissue flap placement when there is insufficient tissue for a satisfactory cosmetic result. These procedures can retain the volume and shape of the breast and avoid contralateral breast surgery. However, these

Table 1: Oncoplastic surgery and margin involvement, local recurrence rates, and survival rates.

Author	Year	Number of patients	Weight (g)/volume of specimen	Close/involved margins (reexcision/mastectomy)	Local recurrence rate	Survival rate	Median followup (months)
Clough et al. [15]	2003	101	222		9.4%	95.7%	44
Kaur et al. [16]	2005	30	200	16%			
Rietjens et al. [17]	2007	148	198	2.02%	3%	92.47%	74
Giacalone et al. [18]	2006	31	190	21%			
Meretoja et al. [19]	2010	90		12.2%	0%		26
Fitoussi et al. [20]	2010	540	187.7	18.9%	6.8%	92.6%	49
Chakravorty et al. [21]	2012	146	67 (11–1050)	2.7%	4.3%		28

techniques are more complex, require a donor site, and lead to increased recovery time following autologous tissue harvesting. Autologous flaps for volume replacement include transverse rectus abdominus (TRAM), adipofascial flap, a lateral thoracodorsal flap, a thoracoepigastric flap, an intercostal artery perforator (ICAP) flap, a thoracodorsal artery perforator (TDAP) flap, and a latissimus dorsi (LD) myocutaneous flap [72].

Oncoplastic breast conserving surgery (oBCS) has the potential to improve the aesthetic outcome of BCS as well as extending the role of BCS in situations previously considered unsuitable for conservation (large tumors relative to breast size, central and lower pole tumor location, or multifocality). While tumor size, or more precisely tumor-to-breast volume, is a key indication for oBCS, tumor location is an equally important consideration. However, the application of aesthetic techniques for therapeutic purposes must never compromise the main objective of breast cancer surgery: clear margins with good local disease control [72].

There is now agrowing evidence through prospective series that oncoplastic techniques offer patients a safe oncological outcome (Table 1). Clough et al. from Institute Curie published their first evaluation of 101 patients and concluded that oncoplastic techniques allow larger resections, however a recurrence rate of 9% was reported with median followup of 5 years [15]. Kaur et al. found that a larger volume excision is possible in a subset of patients treated by oncoplastic techniques however; this series reported a re-excision rate of 16% [16]. Giacalone et al. concluded in their study on 74 patients comparing oncoplastic surgery with quadrantectomy that oBCS extends the indications for breast conserving surgery [73]. Asgeirsson et al. from the European Institute of Oncology have reported long-term results with a 5-year local recurrence rate of 3% [74]. A recent Institute Curie review of 540 oncoplastic conservation procedures between 1986 and 2008 revealed a local recurrence rate of 6.8%: they also noted involved or close margins in 18.9% with 9.4% requiring further surgery as a mastectomy [20]. It is possible that oBCS using reduction mammoplasty techniques may be oncologically superior to sBCS by allowing larger excision volumes and wider margins without compromising cosmesis [18, 19, 21, 74, 75].

It appears that oncoplastic breast surgery extends the indications of breast conservation and allows for achievement of large resection volumes with good cosmesis. However, drawbacks include frequent necessity to operate on the contralateral healthy breast, increased cost, and increased possibility of complications delaying adjuvant therapy. While there has been some concern that oncoplastic surgery could confound subsequent mammographic imaging, Roberts et al. demonstrated that in patients who underwent reduction mammoplasty, no increase in subsequent imaging or diagnostic interventions was noted [76].

6. Looking Forward

Trends in breast cancer care continue to progress towards less invasive surgical treatment. Recent data from the ACOSOG Z11 trial suggests that axillary dissection may not be of benefit in node positive patients who receive maximal systemic therapy and radiation. As systemic therapy improves, and individualized and targeted approaches evolve, it is unclear what role surgery will play in achieving local control. Primary ablative therapies may make questions of margins obsolete, in that if a tumor is ablated and resolves on imaging, then surgical excision may not be necessary.

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Review Article

Atypical Ductal Hyperplasia at the Margin of Lumpectomy Performed for Early Stage Breast Cancer: Is there Enough Evidence to Formulate Guidelines?

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Background. Negative margins are associated with a reduced risk of ipsilateral breast tumor recurrence (IBTR) in women with early stage breast cancer treated with breast conserving surgery (BCS). Not infrequently, atypical ductal hyperplasia (ADH) is reported as involving the margin of a BCS specimen, and there is no consensus among surgeons or pathologists on how to approach this diagnosis resulting in varied reexcision practices among breast surgeons. The purpose of this paper is to establish a reasonable approach to guide the treatment of ADH involving the margin after BCS for early stage breast cancer. *Methods*. the published literature was reviewed using the PubMed site from the US National Library of Medicine. *Conclusions*. ADH at the margin of a BCS specimen performed for early stage breast cancer is a controversial pathological diagnosis subject to large interobserver variability. There is not enough data evaluating this diagnosis to change current practice patterns; however, it is reasonable to consider reexcision for ADH involving a surgical margin, especially if it coexists with low grade DCIS. Further studies with longer followup and closer attention to ADH at the margin are needed to formulate treatment guidelines.

1. Introduction

Breast conserving surgery (BCS) is a widely accepted treatment option for early-stage breast cancer based on several prospective, randomized trials that demonstrate equivalent survival after BCS compared to that after mastectomy [1–7]. The recent 20-year followup of the NSABP B-06 trial recognizes an increased risk of ipsilateral breast tumor recurrence (IBTR) after BCS; however, this risk is decreased with the addition of whole breast irradiation and obtaining negative margins [1]. While the validation of BCS requires that a negative margin be obtained, there is still no consensus definition of what constitutes an adequate negative margin width resulting in marked variation in BCS reexcision practices among surgeons [8–10]. While all agree it is not appropriate to have tumor cells involving the inked margin, there is no compelling or consistent evidence to indicate how widely free a margin should be [11–15]. Accordingly, margin width alone may not be sufficient to prove adequacy of excision and qualitative and quantitative pathologic characteristics of the cells within the margins may be important to consider [16]. One of those factors is proliferative lesions and in particular atypical ductal hyperplasia (ADH) at the margin of BCS specimens [17]. Interestingly, despite the high volume of studies investigating the question of adequate margin width, there is a paucity of studies that address the pathological characteristics of the cells within the margin. Not surprisingly, in the setting of no evidence-based guidelines, neither pathologists nor surgeons know what to do with the diagnosis of ADH involving a margin of a BCS specimen performed for early-stage breast cancer [18–20]. The purpose of this paper is to address

the significance of a diagnosis of ADH at the margin and evaluate if there is evidence to guide the surgical decision for reexcision.

2. Methods

We searched the PubMed database for studies evaluating atypical ductal hyperplasia published in English with no date range qualification. We searched Medical Subject Headings (MESH), titles, and abstracts for the terms atypical ductal hyperplasia (ADH), breast conserving therapy (BCS), ADH at margin, proliferative lesion of the breast, ipsilateral breast tumor recurrence (IBTR). All major studies evaluating margin status and IBTR after BCS were evaluated for purposeful attention to ADH at the margin.

3. Results

3.1. Atypical Ductal Hyperplasia: A Histopathologic Prospective. Atypical ductal hyperplasia (ADH) is an atypical proliferative lesion that falls in between the continuum from normal hyperplasia to low grade ductal carcinoma in situ (LG-DCIS). There is currently no general agreement on quantitative versus morphologic criteria to separate ADH from DCIS. However, some define ADH as the cells with morphologic characteristics of LG-DCIS (i.e., a cribiform or micropapillary proliferation of uniform cells with low-grade nuclei) with partial involvement of the terminal duct lobular unit (TDLU) or involvement in less than 2 separate duct spaces or less than 2 mm in aggregate diameter [17, 24–26]. This is a purely quantitative and not a biologic distinction [27, 28], and as such it can be a subjective diagnosis in practice. A recent review acknowledged differentiation between ADH and LG DCIS is one of the most challenging areas in diagnostic pathology [28]. Consequently, the diagnosis has proven vulnerable to a large interobserver variability even between highly trained breast pathologists in optimal conditions as demonstrated in multiple studies [18, 21–23]. Table 1 demonstrates the differing rates of agreement between pathologists observed in 3 well-known studies that investigated concordance rates among pathologists interpreting proliferative lesions. Rosai [21] and Jain et al. [23] found complete agreement amongst pathologists deciphering ADH from DCIS only 0% and 32% of the time, respectively. Schnitt et al. [22] found slightly improved agreement after diagnostic criteria for proliferative lesions was provided to the pathologists prior to slide interpretation, but still only found all pathologists agreed <60% of the time when diagnosing a lesion as DCIS versus ADH. A recent study by Ghofrani et al. [18] is consistent with this phenomenon. They sent a single diagram depicting a partially involved duct adjacent to unequivocal DCIS to 230 pathologists known for their expertise in breast pathology and asked them to interpret the diagrammatic representation. When looking at the exact same lesion, 56.5% of the pathologists considered it ADH and 43.5% interpreted it as DCIS.

3.2. Significance of ADH. It is well established in the literature and in practice that the diagnosis of ADH on core needle biopsy (CNB) necessitates a subsequent excisional biopsy [19]. This recommendation is based on the difficult pathologic distinction between ADH and LG DCIS especially in settings of small tissue samples, and also the fact that ADH on CNB is associated with a high degree of upstaging to in situ and invasive cancer on subsequent excisions at published rates varying between 24 and 45% [29]. Historically, ADH was considered only a risk factor of subsequent cancer conferring a 4-5x increased risk of invasive carcinoma in either breast [30]; however, recent studies have challenged this and provided some genetic and molecular evidence that ADH is a precursor to a low grade cancer [27, 31]. When ADH is diagnosed in the setting of a known DCIS or invasive, some pathologists report it as a distinct lesion from ADH diagnosed independent of a neoplastic lesion. In a study by Lennington et al. [32] that investigated patterns of DCIS, the authors found that ADH associated with DCIS located at the periphery of the lesion; thus, indicating that when ADH is at the margin of a BCS specimen, it likely represents the most peripheral extent of the neoplastic lesion. Goldstein agrees with this concept when he describes a foci of ADH identified near the margin of an excision specimen for DCIS or invasive carcinoma represents partial involvement of lobules by intraluminal neoplastic cells and is the farthest tentacular extension of low-grade intraductal carcinoma [17].

3.3. ADH at the Margin of a BCS Specimen for Early Stage Breast Cancer: Current Trends among Surgeons and Pathologists. Nizre et al. [19] conducted an important survey capturing the current management of breast borderline lesions. The survey was sent to members of the American Society of Breast Surgeons (ASBS).Responses from 477 surgeons were received and analyzed. Importantly, 337 of the respondents dedicated more than 50% of their practice to breast surgery and 50% were from academic, cancer center, or dedicated breast centers. When asked about how to manage a diagnosis of ADH within 1 mm of a BCS specimen, 61% favored no further surgery while 30% recommended selective reexcision. Interestingly, the amount of training affected response tendencies towards no further surgery. For example, among surgeons practicing at a cancer center, 80% would recommend no further surgery, 20% would recommend selective reexcision, and 0% recommended routine reexcision when ADH involved the margin. This is compared to private practice where 54% would recommend no further surgery, 40% would selectively reexcise, and 5% would routinely reexcise. This difference between groups was found to be statistically significant and the same significant trend favoring not to reexcise was seen amongst surgeons participating in weekly tumor boards and those trained in surgical oncology. Another questionnaire study involving 200 breast surgeons in the United Kingdom showed less variation in surgeon practices with 91% of respondents favoring no further surgery if there was ADH at the margin of excision, but both invasive and in situ disease were 10 mm clear of the margin [20].

Table 1: Interobserver variability among pathologists in cases of borderline ductal proliferative lesions.

Investigator	no. of pathologists/no. of slides reviewed	Concordance rates (%)
Rosai [21]	6/24	5/5 agreed 0% 4/5 agreed 20% 3/5 agreed 50%
Schnitt et al. [22]*	5/10	6/6 agreed 58% 5/6 agreed 71% 4/6 agreed 92%
Jain et al. [23]	9/81	9/9 agreed 32% 8/9 agreed 52% 7/9 agreed 63%

*Standardized criteria and formal education differentiating proliferative lesions provided to pathologist prior to reviewing slides.

Table 2: Atypical ductal hyperplasia (ADH) and ipsilateral breast tumor recurrence (IBTR).

Investigator	no. BCS specimens	no. lumpectomy + for ADH	IBTR ADH (+) no. (%)	IBTR in ADH (−) no. (%)	Median Followup (years)
Goldstein et al. [33]	94	54	**3/54 (5.6)**′	0/36 (0)′′	6.5
Fowble et al. [34]	460	99†	1/99 (1.0)	17/329 (5.2)	4.8
Greene et al. [35]	155*	87	0/87 (0%)**	1/68 (1.5)**	2.2

′ADH (+) at margin more recurrence than ADH (−) at margin $P < 0.01$.
′′Represents lesions negative for both ADH and COL.
†ADH involved somewhere in specimen, not specifically involving margin.
*Lumpectomy performed for ADH, no malignancy in original specimen.
**denotes malignancy development and not recurrence as initial lumpectomy was negative for malignancy.

There is a large practice variation amongst American pathologists as well as demonstrated in the study conducted by Ghofrani et al. [18], which was described earlier in our paper. In addition to classifying the proliferative lesion adjacent to DCIS as ADH or DCIS, the pathologists were also asked what to do with the lesion if it involved the margin of a BCS specimen. Regardless of whether the responders diagnosed the lesion as ADH or DCIS, the final impact on management was that 50.4% would recommend to reexcise based on the lesion being present at the margin while 47% would not reexcise. Of those that considered the lesion ADH, 37.7% recommended reexcision while only 28% of those who considered the lesion DCIS recommended to reexcise.

3.4. Studies Evaluating ADH at the Margin of BCS Specimens. There is a paucity of studies evaluating ADH at BCS margins. Only two studies were found in the literature that directly addressed the issue and they came to disagreeing conclusions. One study reported compelling evidence for reexcision if ADH involved the margin. It was a retrospective review at a single institution (Mt Sinai Medical Center, New York) that spanned 6 years (2000–2006) and sought to determine the rate of residual disease when reexcision was performed for ADH involving the margin of lumpectomies performed for ADH or early stage breast cancer [36]. They identified 44 lumpectomy specimens performed for ADH or early stage breast cancer where ADH involved the margin (at or within 1 mm). 27 of the 44 cases underwent reexcision and of the 27 that underwent reexcision and 26% had either DCIS or invasive disease. They included the diagnosis of the original lumpectomy to evaluate the rates of residual disease based on lumpectomy for ADH versus DCIS versus invasive disease. There were 7 lumpectomies for DCIS reexcised for ADH involving the margin and of those, 2 reexcision specimens had residual ADH (28.6%) and 4 had residual DCIS (57%). There were 2 lumpectomies for invasive disease reexcised for ADH involving the margin and both specimens had residual ADH, but no DCIS or invasive disease identified on reexcision specimens. Despite the small study sample, they concluded that ADH at the margin of a lumpectomy specimen is associated with a high rate of residual ADH or cancer, and they recommend reexcision in all patients with ADH involving the margin.

A different study by Goldstein et al. [33] investigated whether ADH involving the margin of a BCS specimen predicted IBTR. He retrospectively reviewed the slides of 94 patients treated with local excision followed by radiation with particular attention to the presence of ADH at the margins on the slides of final excision specimen. At a median followup of 78 months, true recurrence (defined as recurring in the same area as the original lumpectomy) developed in 6 patients. DCIS and ADH within .2 cm of the margin was associated with recurrence, but there was no association with recurrence when ADH appeared alone. Importantly, all 6 true recurrences occurred in cases where either ADH alone, DCIS + ADH, or DCIS + cancerization of the lobules (COL) was involving the margins of the initial specimen.

One limitation in this study is the short followup time which could be too short to detect recurrences in the specimens with only ADH at the margin as the interval to development of breast cancer in an ADH lesion is 8.2 years [31].

Greene et al. [35] performed an important study evaluating ADH at the margin of lumpectomies performed solely for ADH (none of lumpectomies evaluated were positive for malignancy). They identified 87 lumpectomies with margins positive for ADH. Of those with positive margins, none went on to develop a malignancy. A significant limitation of this study is a short followup of 26 months, and none of the lumpectomies with an initial diagnosis of malignancy were included in the study.

Some clinicians have used a study performed by Fowble et al. [34] to support no reexcision for ADH at the margin [20]. The Fowble study evaluated the influence of proliferative lesions in the background benign breast tissue of BCS specimens performed for stage I and II breast cancer. In their study, they retrospectively reviewed the pathology slides of 460 BCS specimens and found that 99 out of 460 specimens contained background atypical ductal hyperplasia. The authors did not demonstrate an increased risk of IBTR with median followup 5.6 years in the specimens with ADH compared to those specimens without ADH. Unfortunately, this study did not specify where the ADH was located in the specimen and did not identify which specimens had ADH involving the margin. Rather, they just confirmed the presence of ADH anywhere in the specimen, and thus, it is not possible to make assumptions about recurrence rates in those specimens where the ADH did involve the margin. Although the study did not find IBTR occurring at a significantly higher rate compared to the non-ADH population, there were 3 IBTR observed in the ADH population. It would be important to know if these specimens contained ADH at the margin compared to the cases where IBTR did not occur. Table 2 summarizes the findings from the aforementioned studies.

4. Conclusion

In conclusion, there is not enough evidence to direct reexcision when ADH is diagnosed at the margin of a BCS specimen for early stage breast cancer. The work of our paper did reveal that ADH at the margin of a BCS specimen is a controversial pathological diagnosis subject to large interobserver variability, and when this diagnosis is made in the setting of a known cancer, it may actually represent the peripheral extension of a neoplastic lesion. However, if ADH represents low grade DCIS, recent data supports that especially in ER positive tumors, when adjusting for hormonal and radiation adjuvant treatment, the significance associated with margin status and increased IBTR is less clinically likely. Further studies with longer followup and closer attention to ADH at the margin will be needed to answer this question directly. In the meantime, it is reasonable to consider reexcision of ADH at the surgical margin especially in the face of low grade DCIS, but further data is needed to provide more definitive recommendations.

Conflict of Interests

There are no conflicts of interest to disclose.

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Review Article

Evaluation of Resection Margins in Breast Conservation Therapy: The Pathology Perspective—Past, Present, and Future

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Tumor surgical resection margin status is important for any malignant lesion. When this occurs in conjunction with efforts to preserve or conserve the afflicted organ, these margins become extremely important. With the demonstration of no difference in overall survival between mastectomy versus lumpectomy and radiation for breast carcinoma, there is a definite trend toward smaller resections combined with radiation, constituting "breast-conserving therapy." Tumor-free margins are therefore key to the success of this treatment protocol. We discuss the various aspects of margin status in this setting, from a pathology perspective, incorporating the past and current practices with a brief glimpse of emerging future techniques.

1. Introduction

The B04 study of the National Surgical Adjuvant Bowel and Breast Project (NSABP) has continued to demonstrate no significant differences in long-term survival between patients undergoing mastectomy versus lumpectomy with radiation therapy [1, 2]. The following NSABP B06 trial, a randomized prospective analysis of 1851 women, showed in a 20-year follow up that there was a cumulative incidence of 39.2% for ipsilateral tumor recurrence with lumpectomy alone and 14.3% recurrence in patients who underwent lumpectomy followed by radiation ($P < 0.001$) [1]. However it did not demonstrate a significant difference in distant-disease-free survival between the patients in the two lumpectomy groups who had tumor-free margins. Subsequently, the 10 year results of the European Organization for Research and Treatment of Cancer (EORTC) 1080 and the EORTC boost trial showed a 15% cumulative risk of local recurrence with incomplete resection margins compared to only 8% cumulative risk with microscopically tumor-free resection margins [3, 4].

Although pathologic assessment of margins for tumor is standard practice in evaluation of lumpectomies and mastectomy specimens, the obstacles for obtaining consistently accurate results are the very nature of the tissue (adiposity), the extent of in situ component [5, 6], and the insidious manner of tumor infiltration and tumor multifocality. The evaluation of surgical resection margins in any cancer surgery is important, but it becomes particularly so when considering conservation of the afflicted organ. It is therefore important to have a clear understanding of what constitutes a positive margin, the impact of disease factors in margin assessment and the different methods used to assess margins.

In this review of margin assessment, we will describe the various methods and settings in which margin assessment is performed and the advantages and disadvantages of each. We will also discuss some of methodologies employed to better predict which patients have higher risk of residual disease and shortened disease-free intervals.

2. Definition of Positive and Negative Margins and Tumor Clearance

Classically, a margin was considered to be "positive" if invasive tumor had been cut across by the surgical blade, but margins in which tumor was close but not transected were considered "negative for tumor" (National Surgical Adjuvant

Breast and Bowel Project (NSABP) B-06 study. Currently a positive margin is generally interpreted to mean the presence of tumor, either invasive and/or ductal carcinoma in situ (DCIS), at the surgical resection line (Figure 1). However, lymphatic invasion at a margin is not considered a positive margin. Neither atypical ductal hyperplasia nor lobular carcinoma in situ at margin is considered a positive margin (Figure 2).

What constitutes adequate clearance of tumor at the surgical margin? (Figure 3). Measurements ranging from 1–3 mm have been described as "close". In the case of a pectoralis fascia margin, a single collagen strand separating tumor from margin is considered adequate clearance. Incised mammary tissue is considered differently. Oncoplastic surgery (combination of plastic surgery with breast-conserving treatment) defines a negative margin quantitatively as "no tumor cells within 1 cm of the cut edge of the specimen" [7] while the majority of the general literature appears to consider 2 mm as the cutoff point for a negative margin with anything less than that being considered a close margin [8].

Skripenova and Layfield found residual invasive carcinoma in greater than 25% of patients with margins less than 2 mm while only 16% had residual invasive carcinoma when the margin was greater than 2 mm [9]. The incidence of invasive residual disease is also impacted by the interval between primary and secondary excision. We found a 40% incidence of residual invasive carcinoma if the secondary excision was performed within 2 weeks of the primary but less than 25% of patients had residual invasive disease when the secondary excision was performed beyond four weeks whereas the incidence of residual DCIS is not so affected [10].

Understandably, size, location, grade, and cosmesis all factor into the surgeon's decision of what constitutes an adequate clearance in any given patient. A survey of radiation oncologists in the U.S. and Europe shows a significant variation in the definition of a negative margin with European radiation oncologists seeming to prefer a larger tumor-free margin (>5 mm) than their American counterparts [11]. Finally, the setting in which a patient's surgery is performed and how margins are procured impact the methods of margin assessment utilized.

3. Tumor Characteristics and Impact on Margin Clearance

The type of tumor transected or near the resection margin is significant in terms of residual disease (RD) found on reexcision [10]. Invasive carcinoma has a lower rate of RD than DCIS near a margin. We have previously shown that this may be a consequence of greater susceptibility of invasive carcinoma to host response to injury, due to its intrinsic lack of a well-developed vascular arcade and lack of protective basement membrane and stroma when compared to DCIS [6].

Studies have consistently shown that patients with extensive DCIS in the primary excision are at significantly higher risk for residual tumor than those without such extensive DCIS [5, 6, 12–14]. In a more recent analysis, Dzierzanowski et al, found that the presence of DCIS in the initial core biopsy correlated with the presence of extensive DCIS (eDCIS) in the resection specimen as compared to the cores with invasive carcinoma without DCIS in the core biopsy ($P < 0.0001$). They also found a higher incidence of positive margins on lumpectomy in patients with eDCIS (38%, $P = 0.05$) [15].

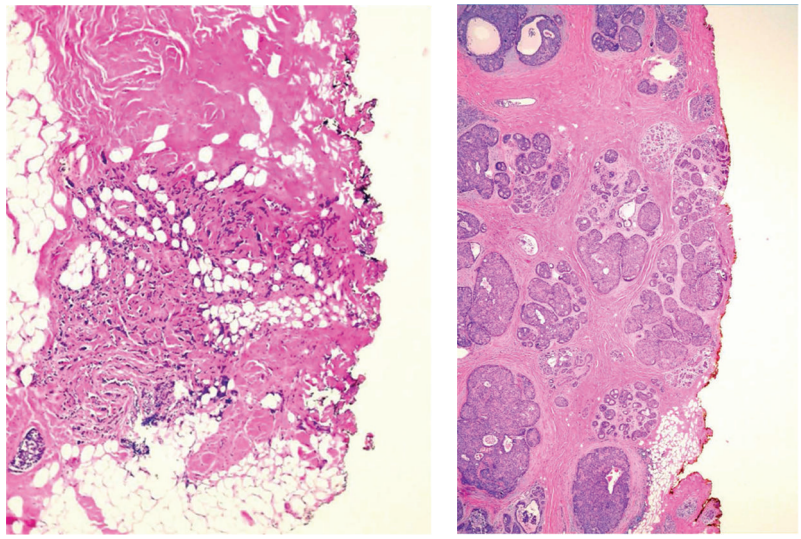
Rodriguez et al. defined extensive DCIS as DCIS having 1 or more dimensions measuring greater than 10 mm [6]. The presence of DCIS near a margin (less than 1 mm) carries a significant risk of residual disease (50%) [6]. Schnitt et al. [5] have further shown that the presence or absence of extensive DCIS in the primary excision was of greater value in predicting the nature and extent of residual disease in the reexcision than the presence of a positive margin in the primary excision. This, however, is not the case with classic lobular carcinoma in situ (LCIS) whose presence at or near the margin is not associated with an increase in local recurrence [16].

A few groups have also shown an association between high nuclear grade or histologic subtype of DCIS and the presence of residual disease [17–19]. Sahoo et al. showed that in addition to a positive margin status, a high nuclear grade was independently associated with local recurrence. In their analysis, young age at diagnosis was also an independent predictor of recurrence. Chagpar's group found positive tumor margins to correlate with larger tumor size and the lobular subtype of breast carcinoma. Schwartz's group found micropapillary to be associated with multicentricity (86%) and comedocarcinoma more likely to be associated with microinvasive DCIS (53%). Thus, for ductal carcinoma in situ, as much as one centimeter may be needed to adequately clear disease [20].

4. Effect of Different Methods of Margin Procurement

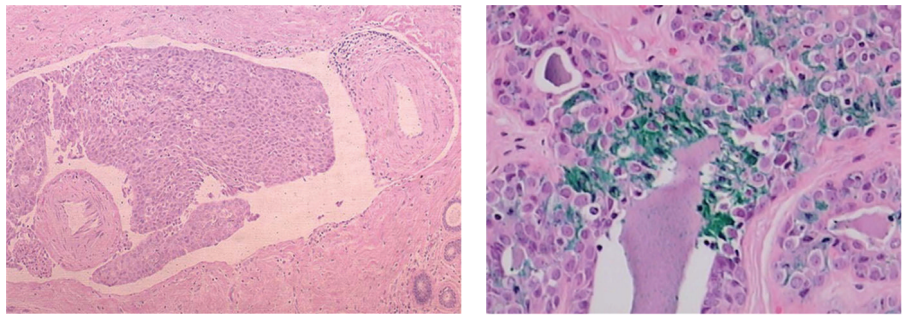
The effectiveness of pathologic margin assessment is impacted by utilization of imaging and other techniques in determining the extent of breast surgery. In the case of a palpable mass, one line of resection may be followed if done using palpation guidance and another if radiologic or ultrasound imaging is employed to assess the mass and surrounding tissue. Pre- or intraoperative detection of abnormal calcifications and tumor extension will alter the final excision margin to encompass more disease and reduce the risk of positive final margins and inadequate clearance of disease [21].

Once a lesion of interest is excised, intraoperative palpation assessment with additional tissue taken from suspicious areas of the wall of the resection cavity, either using palpation or ultrasound guidance, can yield additional disease. Guidroz reported that surgeon assessment of the lumpectomy cavity with selective excision of additional tissue resulted in decreased need for second surgery following primary lumpectomy [22]. Simply employing a systematic removal of six additional shave margins (covering the entire



(a) (b)

Figure 1: (a) Section of an invasive carcinoma that extends to and is transected in the surgical margin. (b) Section on extensive ductal carcinoma in situ focally transected in a surgical margin. (H and E).



(a) (b)

Figure 2: (a) Lymphatic invasion in a margin is not considered a "positive" margin. However, such disease present in a margin indicates the patient has high risk of both residual and systemic disease. (b) Image of lobular carcinoma in situ (LCIS) in an inked margin; however, the surgical margin is not defined as being positive for carcinoma.

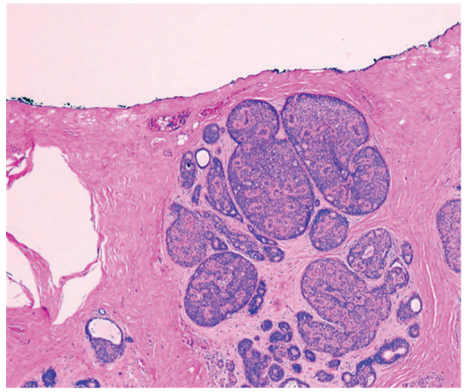


Figure 3: Section of ductal carcinoma in situ close to a margin but not surgically transected. There is some agreement that a clearance less than 2 mm is inadequate and places a patient at high risk for residual disease. (H and E).

cavity) from lumpectomy cavities halved the incidence of residual disease compared to patients who did not have the additional tissue submitted [23].

5. Methods of Pathologic Margin Assessment

5.1. Gross Examination. In theory, a mass is clearly identifiable and the distance to various resection margins measurable. In reality, often the mass is irregular with ill-defined tentacles cast out in different directions (Figure 4). An advantage of gross examination is that it is a rapid method of assessing margins and is useful in identifying grossly transected tumor and close invasive tumor. In the setting of intraoperative consultation, a grossly close or positive margin can be rapidly communicated to the operating room while additional margin assessments are completed. A grossly negative margin has little predictive value unless the margin clearance is several centimeters and the patient does not have extensive DCIS, multifocal disease or invasive lobular carcinoma.

5.2. Image or Faxitron Analysis. Many institutions confirm resection of lesions using specimen imaging. Conventionally this is a single dimension X-ray with compression of the excision specimen (Figure 5). A smaller set of institutions incorporate 2-dimensional digital specimen mammography (Faxitron) without specimen compression. This may be followed with a second specimen mammogram of the serially sectioned specimen (Figure 6). The Faxitron appears to be better than conventional radiography at delineating microcalcifications and parenchymal distortions near margins, thereby enabling pathologists to select tissue for microscopic assessment. In the setting of intraoperative consultation, immediate reexcisions can be performed resulting in tumor-free resection margins at the time of the primary surgery [24, 25]. The sensitivity of the Faxitron appears to range from 78.6–85.6% for magnification of 1.0–2.0 : 1.0, with a specificity of 100% [26]. However, if the Faxitron equipment and the ability to interpret the images is not housed within the pathology suite, there can be significant time delay with its use in intraoperative consultation.

5.3. Touch Imprints or Smears of Margins. An imprint (touch) or a scraping of the specimen surface, placed on glass slides and stained using either hematoxylin and eosin or diffquick, can be used to evaluate for tumor cells in a specimen margin (Figure 7). This method is employed only in the setting of intraoperative consultation. The advantage of this method lies in the fact that it does not alter the specimen, which can be later imaged, fixed, and/or sectioned. The disadvantages are many: the requirement for multiple imprints, the associated time consumption, the dependency on close visual inspection of the specimen, the ability to only detect transected disease, lower sensitivity, and the inability to measure the width of clearance. Klimberg et al. originally reported a sensitivity, and specificity of 100% for the use of touch preparation cytology in the evaluation of surgical margins in breast cancer [27]. The sensitivity and specificity of the method in reexcision margin assessment, however, is reportedly only 75% and 82.8%, respectively, producing a PPV of 21.4% and a NPV of 98.2% [28].

5.4. Intraoperative Frozen Section (FS). Mammary tissue is notoriously technically difficult to cryosection because of its adiposity. Freezing also introduces tissue artifact in the form of architectural distortion and resistance of adipose tissue to sectioning. In addition, if the tissue submitted for evaluation is more than one centimeter in largest dimension, there is the added risk of sampling error. This method therefore is not popular amongst most pathologists. Surgeons, however, like the method because it enables rapid microscopic examination of tissue during surgery and it can be used to determine the extent of surgery to be performed in a single operative setting. However, the use of frozen section for multiple margin assessment is time consumptive and adds significantly to operating time. In order to provide good turnaround for multiple margin assessments, a pathology frozen section suite would have to be equipped with multiple cryosectioning units and have reserves in both equipment and personnel so as not to impact other surgeries. More importantly frozen section alters the appearance of tumors, particularly ductal carcinoma in situ and infiltrating lobular carcinoma and benign lesions such as intraductal papillomas and sclerosing adenosis (Figure 8). The ability to read through the artifact and not call a benign lesion malignant or a malignant area benign is dependent on the skill and experience of both the pathologist and the entire frozen section staff.

Cendan and his group performed a retrospective analysis of FS margin accuracy compared to permanent sections and showed an 84% concordance per case, with 24% of the patients requiring immediate reexcision intraoperatively of the lesion and approximately 20% of patients needing second surgery due to false negative margins. Expectedly, invasive lobular carcinoma and DCIS cases had higher rates of false negative FS margins. In addition, 51.2% of all patients with positive margins had at least one false-negative margin on either the primary or secondary excision [26].

Osborn et al. compared the cost-effectiveness of routine FS analysis of breast margins against reoperation for positive margins assessed by routine examination of the resected specimen. Their experience has shown that the use of FS for margin assessment with the attendant increased operative time provide cost savings only when the reexcision rates are greater than 36% [29]. The use of intraoperative assessment of margins is driven in part by patient demographics. Institutions which have a large patient population that travels long distances for surgical treatment will spend more resources in attempting to achieve tumor-free margins at primary excision to avoid second surgeries than medical centers whose patients are local and who can readily return for a second procedure if needed. The expense and inconvenience of patients having to return from great distances is balanced against the greater expenditure of operating room time.

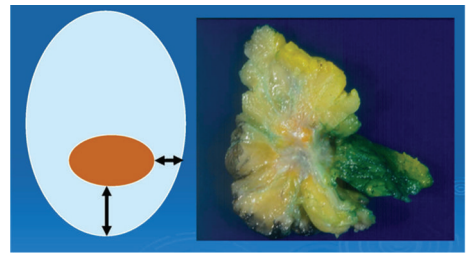


Figure 4: On left, gross inspection in theory: A clearly defined mass measurable from the margins. On right: Reality, an ill-defined mass with indistinct borders and irregular specimen edges.

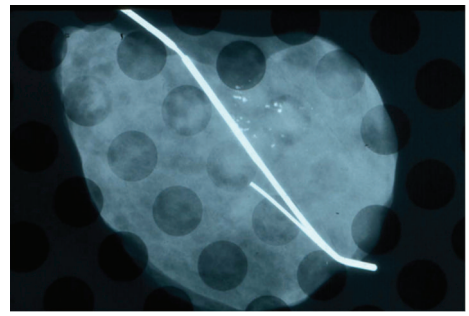


Figure 5: Specimen radiograph of a wire localization excission taken without compression. The cluster of abnormal calcifications is present but is not at the edge of the specimen. Often a second image is taken after rotating the specimen 90 degrees.

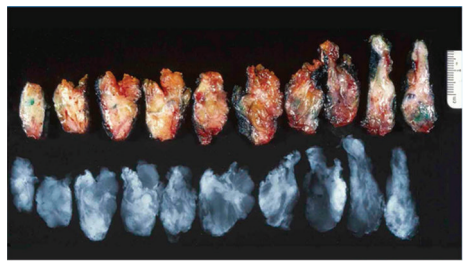


Figure 6: Serially sectioned excision specimen and its Faxitron X-ray. The X-ray image shows a stellate mass in the sixth section from the left with fingers extending very close to the surgical margins. (Image courtesy Dr. A. Sahin, MD Anderson Medical Center).

5.5. Shave Margins. Surgically, a shave margin is a thin piece of tissue obtained by shaving the surface of a lumpectomy cavity or other excision surface. This tissue will have two surfaces of interest: the original margin and the new margin surface. These two surfaces are differentially inked to maintain identification of the two margins. Most shave margins are large enough to require serial sectioning with submission of multiple tissue sections for microscopy to completely assess for presence or absence of disease. The pathologist can trace disease, if present, from the original margin to the new margin. Any disease present can be measured for distance from the "final" margin.

A shave margin taken by a pathologist is a very thin slice of tissue from a margin surface in question and is usually a size that can be frozen for microscopic intraoperative examination or placed directly in a tissue-processing cassette. Any tumor present in the section examined would indicate a positive margin (Figure 9). In the intraoperative setting, relatively larger surface areas can thus be examined compared to that of a perpendicular section through a margin, providing a yes or no answer. Disadvantages of a shave margin include difficulty in obtaining a shave of a soft surface and in maintaining tissue orientation. The nature of the section also precludes measurement of the clearance of a tumor from a margin. Pathologic shave margins for permanent section are most commonly used to assess margins that are distant from a tumor and are required for completeness of reporting margin status.

5.6. Perpendicular Margins. A perpendicular margin is a tissue section taken perpendicular to the margin surface. This type of margin section allows a pathologist to not only determine if a margin is positive or negative, but more importantly measure clearance of tumor from the margin. An excision specimen will be inked, either a single color or in multiple colors if the specimen is oriented and serially sectioned perpendicular to the longest axis of the tissue (Figure 10). This readily allows measurement of margin clearance both grossly and microscopically and relationship of the tumor to various margins (Figure 11). The drawback is that only a representational surface area can be examined from each section. Also, large, soft specimens are not as amenable to production of serial thin intact sections. This drawback can be mitigated by fixing a specimen utilizing special fixative with hardening agents, and/or chilling a specimen prior to sectioning. This methodology is preferred by pathologists because it allows assessment of clearance as

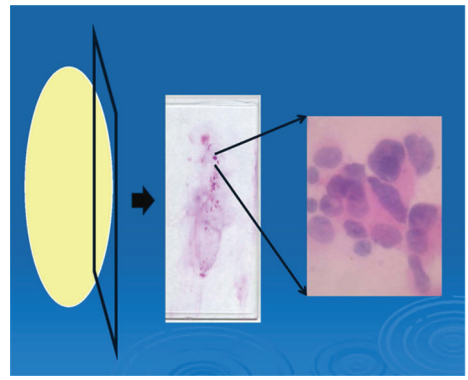


Figure 7: Method of obtaining touch imprints and/or smears. A slide is pressed against the surface of an excision specimen or the surface is scraped and smeared on a slide. The slide is then stained and examined for malignant cells. The microscopic image at the right shows enlarged irregular nuclei, consistent with carcinoma.

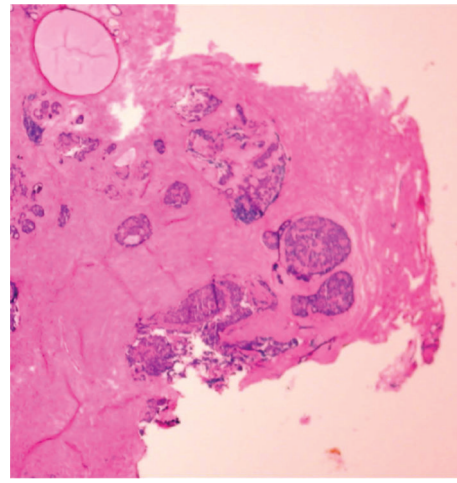


Figure 8: Frozen section slide showing thermal artifact, which obliterates microscopic details that a pathologist needs to diagnose carcinoma. The area bottom center on the edge of the tissue is ductal carcinoma in situ that has been transected in a margin.

well as tumor size, both very important factors in predicting residual disease and recurrence.

In the practice setting, pathologists will employ combinations of the above techniques to provide greater accuracy in determining margin status and the risk of residual disease being left in a patient. Good communication with the surgeon concerning how s/he is excising a lesion, whether there is additional tissue submitted separately for "margins" and the size and type of carcinoma are key. Meticulous gross examination and/or image assessment of the tissue will discover areas suspicious for tumor involvement. Such areas will be the focus of microscopic examination, both in the frozen section suite and at microscopic "sign out" of the specimen. The pathologist's goal in margin assessment is to provide an accurate assessment of margin status and accurate estimate of the risk of residual disease in each and every patient.

6. New Methods for Margin Assessment

Alternative methodologies for margin assessment have emerged recently.

Intraoperative Optical Coherence Tomography (OCT) is a high resolution imaging technique involving real-time exvivo microscopic images up to 2 mm beneath the tissue surface. In an initial analysis the method demonstrated a sensitivity of 100% and a specificity of 82% in evaluating disease at margins [28].

MarginProbe. Quantitative diffuse reflectance spectroscopy is used to non-destructively image entire lumpectomy margins. The multichannel probe has a sensing depth of 0.5–2.2 (45–600 nm) and demonstrates a sensitivity and specificity of 79.45% and 66.7%, respectively, in an initial study. Dune Medical Devices, Inc., the sponsor of the MarginProbe is seeking premarket approval from the FDA [30].

7. Margin Index

Margenthaler et al. retrospectively analyzed the margin status of 475 patients who underwent BCT and proposed a margin index as a more appropriate assessment of the optimum margin. The margin index was calculated using the formula: margin index = closest margin (mm)/tumor size (mm) $\times$ 100.

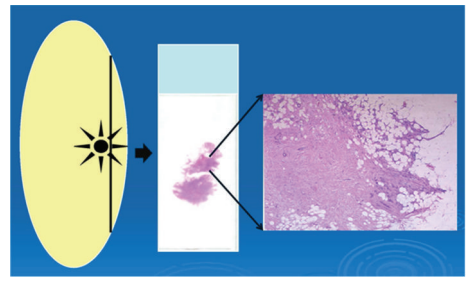
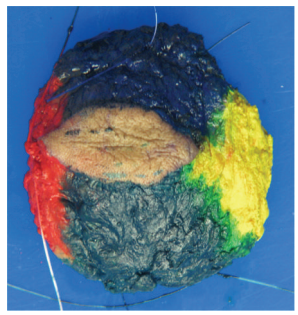
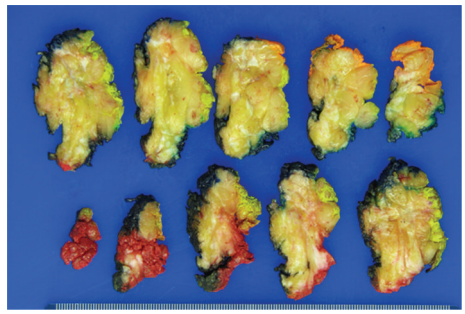


Figure 9: Method of obtaining a (pathologic) shave margin from a specimen. A thin piece is taken from the surface of a specimen and either frozen or processed for microscopy. The slide and microscopy show tumor present in the tissue. This would be considered a "positive" margin.



(a)



(b)

Figure 10: (a) Different colored inks placed on the surface of a specimen maintain the orientation during sectioning and processing. (b) Serial sectioning of inked specimen showing the different inks on the edges of the slices.

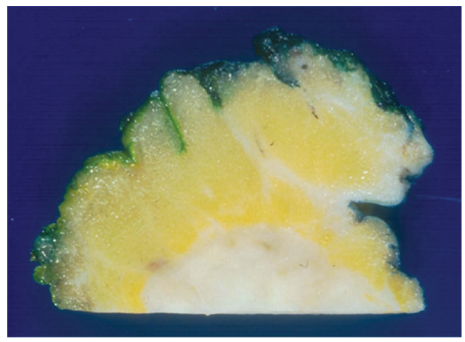


Figure 11: Close up of a perpendicular section of margins with tumor. The tumor is distant from the margin at the top of the image, but very close to a margin at the bottom right of the image.

A receiver operator curve (ROC) was created using the derived margin index and the presence or absence of residual disease in the reexcision specimen. A margin index >5, producing a sensitivity of 85% and specificity of 73%, was found to equate with a 3.2% risk of finding residual disease [31].

8. Recommendations

While there is consensus on what constitutes a positive margin, there is still no consensus on what constitutes an adequate clearance. As neither the NSABP-B04 nor B06 trials ever defined clearance or close margin, we recommend that objective data be incorporated in routine reporting. We utilize the format of "surgical resection margins are free of tumor/negative for carcinoma", and specifying the closest margin "with a clearance of "X" mm" in the main report. Documentation of margin clearance is also a component of the College of American Pathologists' (CAP) Breast Cancer Case Summary protocol.

We concur with Morrow et al. that systemic chemotherapy that reduces the risk of distant metastases also likely reduces the risk of local recurrence [32]. However, we believe that there may not be one standard for clearance as tumor biology probably dictates that determination. Ultimately, objective reporting formats may provide the correlative data needed to stratify clearance requirements based on grade, receptor status, and planned systemic chemotherapy.

We therefore recommend compliance with CAP Breast Cancer summary protocols and that all mammary tumor excisions (lumpectomy, mastectomy) routinely incorporate not only the margin status (positive/negative), but also document the width of clearance at the closest margins, particularly those less than 2 mm which have been shown to carry a >25% risk of residual disease.

9. Conclusion

Over the past fifty years, treatment of breast cancer has evolved from a single, radical procedure to techniques that limit the extent of surgery while improving disease free survival and overall survival of patients. With the introduction of limited surgical excision has come the need for accurate assessment of excision margins both intraoperatively and

postoperatively. We have defined what constitutes a positive and a negative margin and why tumor clearance rather than just a "negative" margin is important in eliminating residual disease. We have outlined the various methods of pathologic assessment of margins and the settings in which they are employed and two new techniques that have potential to provide assessment in real time.

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Review Article

Oncoplastic Breast Reduction: Maximizing Aesthetics and Surgical Margins

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Oncoplastic breast reduction combines oncologically sound concepts of cancer removal with aesthetically maximized approaches for breast reduction. Numerous incision patterns and types of pedicles can be used for purposes of oncoplastic reduction, each tailored for size and location of tumor. A team approach between reconstructive and breast surgeons produces positive long-term oncologic results as well as satisfactory cosmetic and functional outcomes, rendering oncoplastic breast reduction a favorable treatment option for certain patients with breast cancer.

1. Introduction

Surgeons who treat breast cancer strive to perform operations that are aesthetically pleasing without compromising oncologic outcome. Patients are more informed than ever and are encouraging their surgical teams to continue to evolve [1].

For treatment of their breast cancer, many women elect breast conservation therapy (BCT). BCT combines lumpectomy with postoperative radiation allowing a woman to preserve her breast. Factors leading to a greater use of BCT versus mastectomy include improved screening and earlier mammography which have resulted in an increased identification of small, early-stage breast cancers, an increased use of neoadjuvant chemotherapy which can shrink large tumors, and the patient's own preference to preserve her breast [2].

With breast preservation, cancer survival is affected by local control defined by appropriate clear margins. Despite a higher local recurrence rate, disease-free long-term survival is equivalent for patients undergoing total mastectomy and BCT. The premise of BCT involves both surgical excision and reconstruction, including an oncologically sound resection of the tumor, radiation of the resection bed, and preservation of the breast for enhanced aesthetic outcome [2].

To ensure clear margins of tumor resection in BCT, large volumes of breast tissue may need to be removed, leading to asymmetry, scarring, and deformity. Up to 30% of patients who have undergone BCT end up with a poor cosmetic outcome [3, 4]. Subsequent irradiation often then further compromises already suboptimal surgical results.

2. Oncoplastic Surgery

The initial reports of aesthetic techniques coupled with oncologic treatment were published in the 1990s [5]. The term "oncoplastic breast surgery" was coined in the mid-1990s [6]. Oncoplastic methods enable large tumor resections by marrying extirpative surgery with breast reduction surgery. Procedures are designed to anticipate and prevent unfavorable aesthetic outcomes, decreasing the rates to below 7% [7]. In addition, patients have the added benefit of a reduction mammaplasty, which may include a decrease in back, shoulder, and neck discomfort.

There are a number of oncologic advantages to oncoplastic breast reduction. A generous margin of tumor resection is feasible because a large volume of glandular tissue is removed [8, 9]. Furthermore, the resulting smaller breast size may improve the efficacy of radiation therapy. Lastly, reduction of the contralateral breast not only offers tissue sampling, but also theoretically reduces additional risk of breast cancer through removal of excess breast parenchyma [10]. The rate of occult breast cancers found in contralateral

symmetrizing reduction specimens in patients undergoing breast reconstruction ranges from 4.6 to 11% [11–14].

Cosmesis in BCT (standard lumpectomy alone) is affected by breast size, with both very small- and very large-breasted women faring worst. Macromastia has been estimated in up to 40% of women treated with BCT [15]. In patients with macromastia, aesthetic outcome with lumpectomy alone might not be ideal. BCT in a large-breasted woman may leave an empty sac and can result in a ptotic breast, which can lead to a heterogeneous dose distribution. This is due to repeated positioning over an extended course of treatment [16]. Oncoplastic breast reduction has been found to circumvent these complications, relieving symptoms related to larger breasts, as well as treating the cancer itself [17].

Breast volume is important when considering oncoplastic surgery. Cochrane et al. has shown that as much as 10% of glandular breast volume can be removed without notable cosmetic deformities. In addition, the larger the breast is, the more tolerant it is to resection [18]. Delay and Clough demonstrated that up to 20% of breast volume can be excised, requiring local parenchymal rearrangement or skin excision for satisfactory results [19].

Communication between the breast and reconstructive surgeon is crucial. Preoperatively, this team approach is critical in defining areas of excision and in designing reduction techniques. The breast surgeon needs to be cognizant of breast aesthetics, volume, and symmetry, keeping in mind that referral to a plastic surgeon may be helpful. In turn, the reconstructive surgeon should understand oncologic surgical principles when creating a sound operative plan.

3. Patient Evaluation and Counseling

Numerous factors are considered in patient selection. The most important selection criteria include (1) a patient's desire for smaller breasts and (2) the degree of the cancer surgeon's concern about aesthetic irregularities while resecting adequate specimen size. An ideal candidate requires a large-volume resection and has symptoms of macromastia (chronic headaches, back pain, neck pain, shoulder grooving, or intertriginous rashes). However, any patients with moderate-to-large sized breasts are still possible candidates for selection [10]. The oncoplastic procedure is applicable to either patients who have had no prior surgical intervention or those who have attempted breast conservation with positive margins.

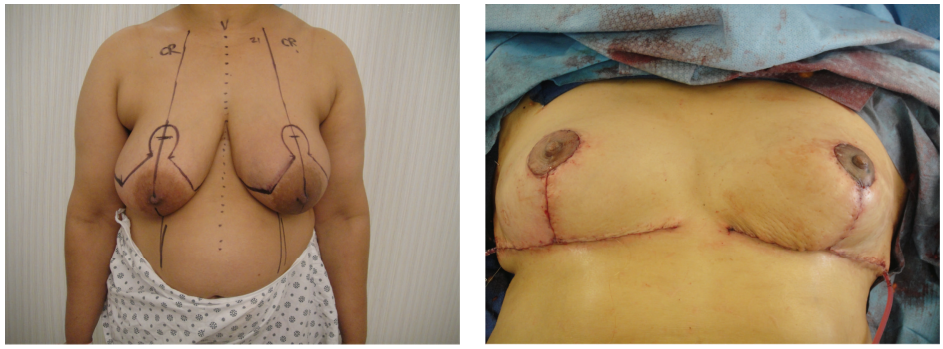
A detailed history is critical. Symptoms of macromastia should be documented as well as factors that can impact wound healing or breast tissue perfusion such as: steroid use, smoking, diabetes, prior breast surgery, connective tissue diseases, or irradiation to the thorax. The presence of any of these factors should prompt further counseling regarding increased risk of complications such as fat necrosis, nipple necrosis, or other wound healing complications. Also, because a history of smoking predisposes to increased nipple and flap necrosis, measures for smoking succession must be pursued if the patient is currently smoking. A focused physical exam is also important. Height, weight, and body mass index should be recorded. An emphasis on breast size, shape, prior scars, degree of ptosis, and position of lesion is important. In addition, measurements of breast width, sternal notch-to-nipple distance, nipple-to-inframammary-fold distance, and NAC width may be taken. Asymmetries should be documented and made evident to the patient. Photographs should be taken for the medical record.

Breast measurements are important as an indicator of breast size, ptosis, and volume. They help to point out preoperative asymmetries that may persist after surgery. There are no absolutes with breast measurements, but in general, patients with sternal notch-to-nipple (SN-N) distances of 35 or greater need to be counseled regarding the possibility of free nipple grafts. Greater SN-N distances risk poor perfusion to the nipple through the pedicle, leading to nipple/areola necrosis [20]. Patients for whom the SN-N distance will change by more than 10 cm are poorer candidates for vertical scar breast reductions because of the geometry of pedicle rotation within the skin reduction pattern.

After the decision for oncoplastic reduction has been made, the time course must then be considered. The immediate one-stage reconstruction approach is preferable, both for psychological and aesthetic reasons. Delayed reconstruction may be advisable for younger patients with extensive ductal carcinoma *in situ* (DCIS), as this group has a higher rate of positive margins. In such cases, preoperative counseling should be directed towards a two-stage procedure and reconstruction should be postponed until negative margins are confirmed [10].

Furthermore, both breasts should be integrated into the decision-making process and treatment plan. Immediate breast reconstruction on the contralateral breast is much more common, except in cases of patients with DCIS, as explained above. Symmetry is the most important factor for good cosmetic outcome. In order to spare additional surgery, surgeons will often reduce or symmetrize the contralateral breast in the first procedure. This, however, requires an educated approximation of the size and shape of the contralateral breast to the ipsilateral breast because it is impossible to know the final size of the ipsilateral breast following cancer ablation. Involution and edema of the breast following irradiation further exacerbates this situation. Following radiation, the treated breast will become firmer and often rise up on the chest wall. For this reason, some surgeons prefer to perform the contralateral symmetrizing reduction in a two-step delayed procedure. Fitoussi et al. showed a preferential shift from synchronous reconstruction to delayed contralateral symmetrizing reduction in 540 consecutive cases [21]. Despite these trends, studies show that immediate reconstruction is not only safe, but may also provide better aesthetic outcomes [22–24].

Patient counseling of possible complications, as well as the need for a total mastectomy (if margins are involved) is essential in the preoperative workup. After oncoplastic reduction, breast geometry is completely rearranged, potentially leaving margins unidentifiable. Patterns of recurrence can be significantly altered. Therefore, in our practice, if the margins are positive following this procedure, the necessary next step is usually a total mastectomy. In addition,



(a) (b)

Figure 1: (a) Preoperative markings before Wise pattern superomedial pedicle oncoplastic breast reduction. The patient's breast cancer is located in the inferolateral breast. (b) Immediate on-table result after oncoplastic breast reduction showing location of scars.

decreased sensation, partial or total thickness skin loss, asymmetries, and wound-healing issues of the nipple are also complications that may arise from ablation, reduction, and subsequent radiation.

4. Planning

The two main surgical decisions that must be chosen when planning a breast reduction are the choice of incision and the type of pedicle on which the nipple areolar complex will be transposed. This is influenced by numerous elements. While tumor location is the most important factor, other considerations include previous scars/needle biopsy sites and whether these need to be excised, as well as the need for access to the axilla. While not always applicable, excision of skin overlying the tumor and its extent can also be included. The surgeon's comfort and preference for reduction mammaplastic techniques is an important factor as well. Lastly, thought must be given to the effect of radiation and the potential to change the eventual size of the breast. Radiation can lead to chronic edema and involution or shrinkage of the remaining breast tissue resulting in a smaller, firmer breast, which rides higher up on the chest wall.

5. Margin Evaluation

The most important goal of the oncoplastic approach is to resect the cancer with histologically negative margins. Oncoplastic breast reductions enable wider margins than standard lumpectomy alone. In our practice, to optimize positive margins, we try to remove the skin over the tumor whenever possible as well as the breast tissue and muscle fascia posterior to the tumor. Positive margins are associated with a significantly higher incidence of local recurrence [25, 26]. Intraoperative assessments of margins are advised, utilizing both pathologic specimen examination and radiologic imaging. Microcalcifications can be assessed via specimen mammogram with two 90-degree images. Intraoperative ultrasound use has shown a decrease in reexcision rate, especially in the cases with solid masses [27, 28].

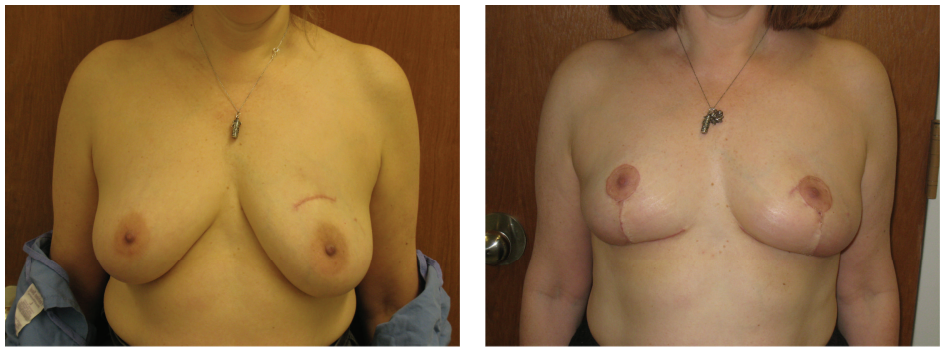
Histologic evaluation is also useful. Currently, frozen sections with touch preparation are one of the most accepted methods of intraoperative histologic assessment of margins. Other recently developed technologies, such as the Spectroscopy or MarginProbe (Dune Medical Devices, Caesarea, Israel), are now being evaluated for real-time intraoperative margin assessment [28].

In our practice, we often mark the margins of resection with hemoclips. The clips serve as a guide to radiation oncologists for radiation therapy, especially in the delivery of an appropriate boost dose.

6. Skin Incision Types

Following a preoperative evaluation and determination of timing, the next major decision to be made is the location and size of the incision. There are numerous incisions to choose from, each with their advantages and disadvantages. The Wise pattern (or inverted "T") is the most commonly used incision for oncoplastic breast reductions because it offers the most opportunities for breast reshaping. This incision travels along the inframammary fold (IMF) and traverses up to the nipple (Figures 1(a) and 1(b)). The Wise pattern offers the surgeon much flexibility, with wide access to the breast parenchyma for use for a tumor in any location. This procedure also allows skin excision in both vertical and horizontal dimension and can be used with any pedicle. For lymph node sampling or clearance, a separate small incision may be needed in the axilla, depending on the pedicle and desire to avoid wide undermining.

The vertical scar mammaplasty, first introduced by Lassus and modified by Lejour, is the second most commonly used incision for oncoplastic breast reduction [29, 30]. This incision is made around the nipple-areola complex (NAC) and extended down to the IMF. The vertical scar technique also allows good access to the breast parenchyma; breast skin reduction is accessible in the horizontal axis, and vertical size reduction is possible through cinching closure of the skin. One drawback of this technique is that the axilla is not easily reached. The classic Lejour breast reduction includes



(a) (b)

Figure 2: (a) Preoperative appearance of patient with left breast cancer. (b) Two-month postoperative appearance of patient after inferior pedicle Wise pattern breast reduction. Note incorporation of lumpectomy scar over superomedially located tumor into the incision for the areola.

a reduction in breast volume via liposuction. This step is not advisable in cancer operations because of the risk of seeding tumor cells.

The omegaplasty (or bat-wing incision) traverses above and alongside the nipple. While not cosmetically ideal, it does provide good access to superomedially located tumors [31]. Omegaplasty requires no undermining (which is better for radiation), but fails to decrease breast volume or address ptosis. This approach can also result in pseudoptosis if there is too much skin or parenchyma resected with an incision superior to the nipple.

The lateral mammaplasty incision runs from the nipple out laterally toward the anterior axillary line. It may also be extended superiorly to gain access to the axilla. Because most tumors are laterally located, this incision's lateral access makes it an important approach. One advantage of the lateral mammaplasty is the avoidance of thin, large surface area dermal flaps, creating thick flaps that are more tolerant to radiation. Medial mammaplasty incisions are the reverse of the lateral mammaplasty, traveling toward the sternum. This technique it the most useful for medially located tumors [32].

The periareolar approach is not as common because it does not permit a great deal of skin excision or volume reduction. The periareolar incision is solely around the nipple and does not extend out onto the breast. Still, this procedure has good access to the upper pole of the breast. Women with mild ptosis and for whom a mastopexy might be considered are good candidates for the periareolar technique.

7. Pedicle Options

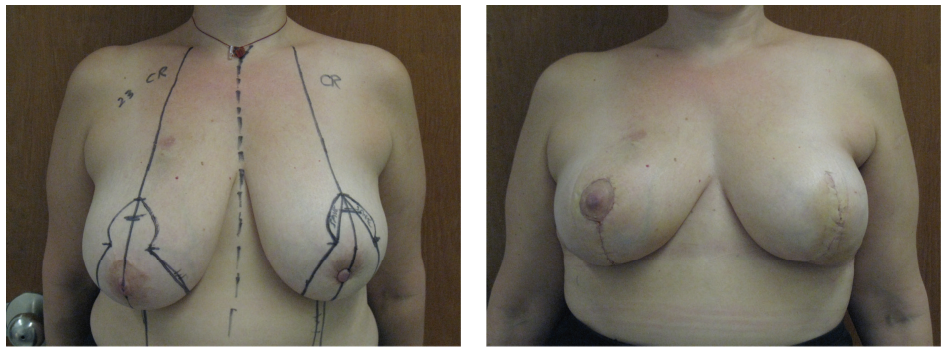
After the location and size of incision has been determined, and the extent of tumor resection has been defined, a decision must be made for the origin of the dermoglandular pedicle on which the vascular and nervous supply to the nipple will be carried. The pedicle is important not only to achieve a satisfactory aesthetic outcome, but also to preserve the blood and nerve supply to the NAC. There is a myriad of pedicles, all of which have their cosmetic and sensory advantages or disadvantages. In oncoplastic breast reduction surgery, the pedicle is chosen based on what remains after the ablation of the tumor. For example, a lower-pole tumor will require resection of glandular tissue in the lower half of the breast, leaving the reconstructive surgeon to choose between various superior pedicles. The pedicles most commonly used are superior, inferior, and medial.

The superior pedicle is preferred for being solid, reliable, and better able to preserve nipple sensation. Limitations of this pedicle arise from difficulty in moving the nipple long distances, especially in patients with significant hypertrophy of the breast. Use of this pedicle may be difficult with large reductions, where molding may result in only superior fullness. Superior pedicles are best for lower-quadrant tumors, particularly in moderate-sized breasts.

Inferior pedicles are reliable for tumors in any position. One caution to take is that it lacks parenchymal support and breasts may eventually sag or "bottom out," resulting in excess skin and tissue between the nipple and IMF. This technique is ideal for larger breasts with longer sternal notch-to-nipple distances as well as tumors located in the upper quadrants of the breast (Figures 2(a) and 2(b)).

The lateral pedicle is an option for medial tumors that extend into the upper or lower quadrants. This pedicle is not frequently used cosmetically because if the pedicle is too thick, the breast will be too full laterally. It is normally reserved for women with small-to-moderate-sized breasts and requires a mastopexy or a minor reduction.

Free-nipple grafting during reduction mammaplasty is most applicable for patients with gigantomastia. In such cases, preservation of blood supply and nerves to the nipple is limited by the length of the pedicle needed to carry the NAC into its new position and by the ability to reduce the breast with a large pedicle. The nipple-areola complex is removed as a skin graft, the breasts are reduced, and the NAC is then sutured in the appropriate position on the breasts. Nipple sensation is lost with this procedure, and hypopigmentation results, usually taking at least one year for pigmentation to return. In cases where oncologic margins require removal of the nipple-areola complex, it can be excised without negatively impacting breast shape, as long as adequate skin is



(a) (b)

Figure 3: (a) Preoperative markings for Wise pattern oncoplastic breast reduction with planned excision of the left nipple areola complex. (b) Two-week postoperative result showing bilateral oncoplastic breast reductions with excision of left nipple-areola complex. Patient will then have nipple-areola reconstruction after completion of radiation.

preserved (Figures 3(a) and 3(b)). The nipple and areola can then be reconstructed after completion of radiation, using any standard method.

8. Postoperative Radiation

Radiation therapy is the second phase of BCT, starting 3 to 6 weeks after the reduction procedure once the incisions have healed. Therapy includes whole-breast irradiation, as well as a boost to the tumor bed to kill any residual microscopic deposit of cells that surgery may have missed. Cosmetically, radiation also tends to diminish scarring on the breast [33]. During surgery, surgeons should be mindful of imminent radiation by avoiding extensive skin-gland dissection and avoiding excessively long parenchymal pedicles that may be compromised and predisposed to fat necrosis. Patients should be informed that radiation therapy can result in chronic edema of the irradiated breast, or contraction and scarring, such that initial postoperative symmetry can be permanently affected.

9. Complications

In the literature, the complication rate for oncoplastic bilateral breast reduction ranges between 17% and 24% [7, 10, 34]. Common complications include skin necrosis, infection, partial or complete nipple areolar complex necrosis, and suture-line dehiscence. Like reduction mammaplasty patients without cancer, obese patients and regular smokers suffer from higher complication rates postoperatively.

If adjuvant chemotherapy is planned, it may begin once healing of the incisions has occurred and can be followed by radiation therapy. Complications that interfere with wound healing may delay the onset of chemotherapy or radiation therapy.

10. Oncologic Results

Fitoussi conducted the largest study to date, following 540 patients who underwent oncoplastic breast surgery for cancer, with a median followup of 49 months. Close or positive margins occurred in 18.9%, with subsequent mastectomy being necessary in 9.4%. At five years, 90.3% reported a satisfactory aesthetic outcome. Five year overall and distant disease-free survival rates were 92.9% and 87.9% respectively, with local recurrence in 6.8% [21]. When compared to the standard BCT, comparable values have been found, demonstrating the equivalent oncologic safety between the two. Rietjens followed 148 women for a median 74 months to report a 3% rate of local recurrence [35]. Kayar recorded 116 patients over a period of 10 years, demonstrating overall survival rates at 100%, 89.1%, and 53.8% for stage I, stage II, and stage III, respectively [36].

Chakravorty et al. compared outcomes from 150 cases that had utilized the oncoplastic conservation techniques (77 of which were for oncoplastic reduction) with 440 cases, which used standard breast conserving surgery. At a 28-month followup and a subsequent projected 6-year local recurrence rate, oncoplastic breast conserving techniques were found to decrease reexcision rates, with oncological outcomes similar to that of standard breast conservation [37]. This finding of decreased reexcision rates is expected given the increased volume of tissue that can be removed with oncoplastic breast reduction and the need for mastectomy if there are positive margins.

11. Oncologic Surveillance

Less-experienced breast radiotherapists and radiologists may find the complex glandular reshaping from oncoplastic reduction techniques more challenging to examine on mammograms. Women with oncoplastic reductions are more likely to have a greater number of postoperative mammograms and ultrasounds as well as a greater rate of tissue sampling compared to women who have undergone partial breast reconstruction [38].

Oncoplastic breast reduction does not appear to affect cancer screening for recurrence. Although scar tissue, epidermal inclusion cysts, or fat necrosis may appear suspicious on physical exam, mammogram, ultrasound, or MRI, evaluation can be done with fine needle aspiration or core needle biopsy [39]. Typically, in postoperative healing, fat

necrosis will present early on and slowly resolve with time, with complete or incomplete resorption. Because of such situations, each follow-up visit should be with the same oncologic surgeon. Mammographic findings from a study by Mendelsohn et al. found scarring and fibrosis in 50% of patients, fluid accumulations in 40% of patients, and dystrophic calcifications in 10% of patients [39]. Even though cancer screening is not compromised, patients who undergo oncoplastic reduction require more postoperative tissue sampling than those who receive traditional BCT [10].

12. Oncoplastic Outcomes

Currently, a widely accepted objective study for investigating cosmetic outcomes is not available. The BREAST-Q is a validated data set tool that may bring more insight into this matter. Through pre- and postoperative questionnaires, the BREAST-Q quantifies patient satisfaction and health-related quality of life experience in a psychometrically sound and clinically meaningful manner [40]. Patients report significantly improved body image, functional quality of life, and cosmesis when treated with BCT versus radical mastectomy [41]. More specifically for oncoplastic surgery, available publications indicate an overall satisfaction in treated patients. Chang et al. collected surveys from 20 patients with 70% rating the cosmetic outcome as excellent and 100% reported a high degree of satisfaction with cosmetic and functional results [42]. Goffman et al. established a panel, which included a surgical oncologist, an oncology nurse, a radiation oncologist, and a patient to evaluate cosmetic and functional results. Out of 55 patients, 72% evaluations gave excellent and very good marks [43]. Lastly, in a study conducted by Losken et al. 95% of women reported satisfactory aesthetic results after a six month followup [10].

13. Authors' Experience and Technique

All patients who the breast surgeons feel will have a significant deformity following lumpectomy are referred to a plastic surgeon. Small-breasted women generally decide to undergo mastectomy and reconstruction. For women with moderate-to-large sized breasts, there is an extensive discussion regarding relative advantages and disadvantages to an oncoplastic breast reduction versus mastectomy and reconstruction (as detailed in the rest of this paper).

Once the decision is made for oncoplastic breast reduction, a combined operation is scheduled. If wire localization is required, two wires are generally used at each tumor site to precisely localize the cancer within the breast. If the patient has had a prior lumpectomy, all efforts are made to incorporate the lumpectomy scar within the skin incision. Skin markings are made to include prior scars and biopsy sites whenever possible (Figure 2). This can sometimes mean adjusting markings more superiorly, laterally, or medially. Patients are counseled that the new position of the nipple-areola complex can be affected by these adjustments away from their ideal position at the breast meridian, inframammary fold, or near the midhumeral line. The choice of Wise pattern or vertical skin markings is made based on breast size, degree of ptosis, location of tumor, location of prior scars, and sternal notch-to-nipple distance. The Wise pattern incorporates a larger skin excision area. It is therefore more useful for incorporation of prior scars or skin over the tumors and is used more often in oncoplastic breast reductions.

The plastic surgeon and breast surgeon perform the lumpectomy together in order to maximize margins and aesthetics. The plastic surgeon starts the operation, making the incisions and creating the pedicle, with the guidance of the oncologic surgeon. When possible, the skin over the tumor is included in the specimen. As the wires or lumpectomy cavity are approached, the breast surgeon takes over to excise around the tumor. Posteriorly, the breast tissue is removed deep to the tumor, including muscle fascia, in order to maximize the posterior margin. The corresponding author prefers to use a superomedial pedicle whenever tumor location permits (personal preference), although the operation is similar with any pedicle. The reduction proceeds in a standard fashion [44]. The entire breast reduction specimen is removed as a single specimen incorporating the lumpectomy specimen, in order to avoid cutting across a margin. Once the specimen is removed, the breast surgeon reevaluates the remaining breast and removes any additional margins deemed necessary. Breast closure then proceeds in a standard fashion, with rotation of the superomedial pedicle into the keyhole and closure of the lateral and medial pillars. This technique enables the removal of multiple lumpectomy specimens, even the ones in completely different areas of the breast, since a wide area of skin and breast is removed. The plastic surgeon does not hesitate to remove more tissue than required by a standard breast reduction, in order to provide the needed oncologic margins.

To make up for the changes in geometry, additional tissue rearrangement within the breast may be necessary to provide the best shape and symmetry. Consequently, we advise all patients that a mastectomy would be needed if the margins return positive. Theoretically, a reexcision can be attempted depending on the original location of the tumor in relation to the reduction, and the location of the positive margin. Alternatively, the patient and oncologist may decide to give a radiation boost to the involved breast. However, we generally do not advise patients that a reexcision is likely possible, and we prepare them for the possibility of mastectomy if the margins are involved.

Over the last 4 years, we have performed over 30 oncoplastic breast reductions. There has been one positive margin at a nipple and the patient ended up with a mastectomy on that side. No other patients were reported with involved or close margins. Although we have performed a relatively smaller number of oncoplastic breast reductions compared with mastectomy reconstructions, our rate of 3.33% positive margins compares favorably with published rates of positive margins (11-12%) after lumpectomy [45, 46]. As discussed preoperatively, the patient presenting with positive margins ended up with a mastectomy. In retrospect, if there was high suspicion for involvement of the nipple with cancer, she could have had a breast reduction with central breast removal and later nipple reconstruction, as the patient

in Figure 3 had. In an analysis of 540 cases, close or involved margins occurred in 18.9 percent, with mastectomy being necessary in 9.4 percent [17]. We postulate that our rate of positive and close margins is less than 18.9% because our techniques involve removing skin over the tumor site and/or fascia over the muscle, and we tend to use techniques that remove a large amount of surrounding tissue. Fittousi et al. described their experience with a variety of "aesthetic" and "combination" techniques for oncoplastic breast surgery, and it is not clear how many were specifically oncoplastic breast reductions [21]. The authors remark that one-half of the patients with involved margins were "satisfactorily managed oncologically with either repeated oncoplastic breast surgery or radiotherapy boost" [17]. The authors do not elaborate as to whether the patients who had repeat oncoplastic breast surgery initially had a reduction pattern surgery, or if they initially had a more limited tissue rearrangement that enabled repeat excision. In our practice, we counsel oncoplastic breast reduction patients that a mastectomy would likely be the next step if a margin is involved, but, of course, any case would be evaluated individually.

This issue of mastectomy if there is a positive margin would seem to argue against oncoplastic breast reductions, since patients usually have a chance at reexcision with lumpectomy alone. By agreeing to an oncoplastic breast reduction, they would seem to be agreeing to a single attempt at a lumpectomy only. However, for most patients in our practice choosing this procedure, the decision is not between a standard lumpectomy or oncoplastic breast reductions; it is a choice between oncoplastic breast reductions or mastectomy. Patients deemed candidates for oncoplastic breast reductions are those for whom standard lumpectomies would be too deforming (because of breast size, tumor size, multiple tumors, or tumor location) or those with symptomatic macromastia who desire breast reduction for the added symptom relief. Therefore, they are willing to try oncoplastic breast reductions as an alternative to mastectomy. Additionally, the rate of positive margins is much lower than that with standard lumpectomies, so it is rare that these patients do indeed go on to need a mastectomy.

14. Conclusions

In some parts of the United States, a potential lack of available reconstructive plastic surgeons limits combined treatment. Breast surgeons are then left with the choice of either referring their patients to larger centers or attempting to learn the reconstructive procedures themselves [47]. Despite these limitations, ideally, a combined approach with a breast surgeon and plastic surgeon provides the best results for the patient.

Management of patients with breast cancer is also changing. Surgeons are constantly looking for new, less invasive, and more cosmetically favorable techniques to help patients manage their disease and live with the results of their treatment.

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