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Mini Review

Innovations in Reduction of Positive Margins during Breast Conserving Surgery

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Abstract

Assessment of margins during Breast Conserving Surgery (BCS) remains imperfect despite advancement in surgical, pathologic, and imaging technique. Reoperation after BCS is recommended when tumor is present at the margin, which has significant negative implications for the patients. This article aims to review current strategies for minimizing the rate of positive margin.

Keywords: Breast cancer; Breast conserving surgery; Lumpectomy; Margins

Introduction

Breast Conserving Surgery (BCS) which includes lumpectomy with radiation has demonstrated equivalent outcomes to mastectomy in patients with localized breast cancer. Surveillance, Epidemiology, and End Results (SEERs) database estimates 252,710 new breast cancer cases in the US in 2017, and approximately two-thirds of operable breast cancer cases are suitable for BCS. Recent studies indicated improved overall survival in patients undergoing BCS with whole breast radiation compared with patient undergoing mastectomy [1,2]. In order for BCS to be successful, negative margins should be obtained because patients with positive margins have higher rates of recurrence [3]. Despite advancement in surgical, pathologic and imaging techniques, the ability to achieve negative margins for BCS remains imperfect. The rate of second operation performed in the US to achieve negative margins vary widely in the literature, but are reported to range from 21 to 50% [4]. Society for surgical oncology and the American Society for radiation oncology released a consensus guideline on adequate margins for BCS with whole-breast irradiation in February 2014. This guideline endorsed "no ink on tumor" as the standard for a negative margin which decreased the rate of reoperation [5]. Re-excision has multiple negative morbidities including delay in initiation of adjuvant therapy, negative psychological impact to the patient, increased postoperative infection rate, poor cosmesis, and increased cost [6,7]. It is evident that further advancement in surgical, pathologic and imaging technique is necessary to improve breast conserving surgery to decrease or avoid second surgery to achieve negative margin.

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Current Options for Reducing Positive Margin Rate

There have been few methods to date to assess resection margins intraoperatively. These methods include frozen section, MarginProbe, spectroscopy, Near-Infrared (NIR) imaging, and MRI. Surgical technique such as full-cavity shaving has also been utilized. None of these methods are routinely used as standard methods as these procedures are time consuming, imperfect, expensive, require specialized training, and/or are experimental.

Frozen Section

The frozen section technique was developed at the Mayo Clinic more than 100 years ago. In this technique, tissue sections are cut from fresh tissue blocks by using open-air freezing platform called microtomes. The stage is rapidly cooled and chills the tissue. Tissue is then cut using microtome blade to sections approximately of 8 to 10 µm. The frozen section tissue is immersed in a toluidine blue stain for a few seconds then rinsed with clean water. The stained tissue is rolled onto a glass slide and covered with cover slip [8]. This technique is still used for intraoperative margin assessment for many oncologic surgeries. However, it is infrequently used for assessing lumpectomy margins. The Mayo clinic reported their positive margin rate of 3.6% compared to 13.2% nationally using the National Surgical Quality Improvement Program (NSQUIP) database. National Surgical Quality Improvement Program (NSQUIP) database is a validated outcomes-based database designed to assist participating hospitals develop quality initiatives and improve the quality of surgical care. Since 2012, the NSQIP database has collected detailed information on return to the operating room within 30 days of a procedure. Significant low-rate of positive margins was attributed to the use of frozen section analysis intraoperatively [9]. However, this technique is time consuming and labor intensive leading to prolonged operative time. Frozen section of lumpectomy specimen may be unreliable when performed by inexperienced pathologist. In most institutions, this method is not practical for routine use due to significant institutional resources required.

MarginProbe

The MarginProbe system is an intra-operative devise for identifying positive margin at margins of excised lumpectomy specimens. This system uses near-field radiofrequency spectroscopy signal to differentiate between dielectric properties of malignant and normal breast tissue for intraoperative assessment to guide re-excision of positive margins [10]. A recently published study using MarginProbe reported reduction of re-excision rates by more than 50% [11]. The drawback of this devise is that this devise adds an additional cost to the procedure. Further the device was designed with emphasis on sensitivity to increase detection of all positive margins, which reduced specificity and increased false-positive results. Excision of additional non-malignant tissue may lead to poor cosmetic outcome.

Full Lumpectomy Cavity Shavings

Some studies have demonstrated 48% reduction in re-excision rates when additional shaved margin is routinely removed from all six sides of the lumpectomy cavity [12,13]. However, there has been conflicting result reported in the current literature. A study from Massachusetts General Hospital showed no difference in re-excision rates in patients undergoing BCS alone or BCS with full-cavity shavings [14]. Due to conflicting result and concern for additional non-malignant tissues removed causing poor cosmesis, full-cavity shaving techniques has not been routinely used by many breast surgeons.

Spectroscopy

Intraoperative assessment of margins using spectroscopy is under development. Optical fiber probe-based diffuse reflectance spectroscopy and Intrinsic Fluorescence Spectroscopy (IFS) are being considered as tools for the intraoperative imaging of malignancy. DRS and IFS depend on the inherent optical properties of tissue for imaging without the use of exogenous contrast agents. The combination of DRS and IFS provides information regarding metabolic, biochemical and morphology of the tissue which is then translated into disease diagnosis. One of the drawbacks of this technique is that the tissue penetration is relatively shallow at ≤ 1mm. The benefit of this kind of imaging is that spectroscopic imaging can examine the entire margin of the excised tissue which reduces the sampling limitations which can be seen in frozen section pathologic examination. Few studies have demonstrated real-time assessment of surgical margins, however, these devises still remain an experimental technique [15,16].

Optical Imaging

Optical imaging has been gaining attention in the image-guided surgery coupled with near-infrared fluorophores. However, inevitable limitations have been identified with this method as these agents can only penetrate up to 1cm depth [17]. Another pitfall of this method includes photo bleaching limiting the number of images which can be obtained and the need for fluorescent camera system for detection, which requires operating room lights to be turned off. The requirements of turning off operating room lights during surgery is not practical and is a major limitation.

MRI

MRI guided breast conserving surgery has been evaluated where patients received 3D MRI under general anesthesia followed by standard breast conserving surgery with sentinel lymph node biopsy. If residual disease was seen following intraoperative MRI imaging, additional margins were excised [18]. Although the study concluded MRI guided BCS is feasible in the 8 patients enrolled in the study, obtaining MRI before and after surgery while the patient is under general anesthesia may not be practical. This process will result in prolonged operating time, longer anesthesia time, and additional equipment cost. Handful of institutions has the capability of intraoperative MRI, however, this technology is mostly used for neurosurgery to improve the extent of resection of brain tumor while avoiding neurological deficits.

Discussion

The rate of re-operation is reported to be ranging from 21 to 50%, which is not insignificant. Re-excision has multiple negative implications including delay in initiation of adjuvant therapy, negative psychological impact to the patient, increased postoperative infection rate, poor cosmesis, and increased cost. None of the modalities mentioned in this article are the current standard for evaluating the margin status intraoperatively. It is clear that there is an unmet need for a reliable and practical technology to localize the tumor and assess the excision margins intraoperatively. Although imaging modalities, such as MRI, mammography, and ultrasound have been of immense advantage in tumor detection, the need for accurate intraoperative imaging with the ability to function with standard operating room lights and to detect cancer based upon molecular features of the tumor would be ideal for successful cancer surgery. Even though the success of BCT depends on obtaining negative margins, intraoperative assessment of surgical margin has been inadequately addressed to date.

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