



Extent of Margin Involvement, Lymphovascular Invasion, and Extensive Intraductal Component Predict for Residual Disease After Wide Local Excision for Breast Cancer

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Abstract

In the present study, we identified predictors of residual disease after an inadequate wide local excision. Residual tumor was more likely when tumor was present at the inked margin, when more than a single radial margin was affected, and in tumors associated with lymphovascular invasion and an extensive intraductal component.

Background: Positive margins after wide local excision (WLE) increase the probability of residual disease, and additional surgery is often recommended. However, residual tumor will be found in only two thirds of cases, suggesting that additional surgery can be avoided in many instances. In the present study, we sought to establish the frequency of residual tumor when the surgical margins are inadequate and to identify factors that predict for residual tumor. **Materials and Methods:** A retrospective review was performed of 720 consecutive patients who had undergone WLE for ductal carcinoma in situ and nonmetastatic breast cancer at a single unit from January 1, 2004 to December 31, 2010. **Results:** At least a single radial margin was affected (either involved or close, defined as tumor < 1 mm from the margin) in 244 patients who had undergone WLE, and either the anterior or posterior margin was affected in another 103 patients. Reoperation was performed in 215 patients with affected radial margins and 9 others with affected anterior or posterior margins. Residual disease was found in 98 of 224 patients (43.8%) and was more likely when tumor was present at the inked margin, when > 1 radial margin was affected, and when lymphovascular invasion (LVI) or an extensive intraductal component (EIC) was present. The association with tumor size was of borderline significance. No association was found with tumor histologic type or patient age. **Conclusion:** Additional evaluation is needed to determine whether additional surgery can be safely omitted in women with tumors without LVI or EIC when a single radial margin has been deemed to be close.

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Introduction

Breast-conserving therapy became the standard of care for early-stage breast cancers after large trials established that less extensive resection produced more acceptable postoperative cosmesis without

compromising long-term survival.^{1,2} Breast tissue remaining after wide local excision (WLE) of the primary tumor, which would have otherwise been removed with total mastectomy, is irradiated postoperatively. The completeness of surgical resection is one of the strongest predictors of local recurrence and neither escalated radiation doses nor systemic treatment can compensate for inadequate surgical margins.³⁻⁷ Consequently, women in whom the initial WLE has been deemed inadequate will be recommended for additional surgery because of the possibility of residual disease around the surgical cavity. Although tumor present at the inked margin indisputably increases the risk of local failure, the data have been inconsistent regarding whether wider margins confer additional benefit. This has led to many differences in practice, resulting in reoperation rates varying from 10% to 50%.⁸

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Residual Disease After Wide Local Excision

Reoperation will be unnecessary in $\leq 40\%$ of women, because no residual disease will be found at additional surgery.^{9,10} Repeat surgery stresses the healthcare system, adds to psychological anxiety, and confers no additional benefit when no residual disease is found. Furthermore, additional excision impairs the cosmetic outcome, and some women could even opt for mastectomy to avoid additional uncertainty. Several investigators have therefore sought to identify the predictors that will allow for a more selective approach to reoperation. Young age, multifocal disease, large tumor size, high tumor grade, and an extensive intraductal component (EIC) have been variously associated with an increased probability of residual disease.¹⁰⁻¹² However, to date, margin status has remained the single factor that determines the need for additional surgery.

At our institute, women with involved or close radial margins (in which tumor foci is found < 1 mm from the margin) are recommended additional surgery, either in the form of repeat excision of the affected margins or mastectomy. The primary objective of the present study was to evaluate the prevalence of residual disease found at additional surgery and to identify the clinicopathologic factors that would predict its presence. This could potentially enable us to identify a subgroup of women in whom the probability of residual disease would be so minimal such that additional surgery could be safely omitted. In addition, we also sought to determine whether residual disease, when completely excised at subsequent surgery, would correlate with disease recurrence and overall survival.

Materials and Methods

A retrospective analysis was performed of 720 consecutive patients who had undergone WLE at our breast unit at Tan Tock Seng Hospital, Singapore, from January 1, 2004 to December 31, 2010. The ethics committee approved the present study (DSRB/2010/00032). Patients diagnosed with invasive breast cancer or ductal carcinoma in situ (DCIS) who had undergone WLE for curative intent were included. Male patients, those who had received neoadjuvant chemotherapy or other preoperative treatments, and those who had presented with metastatic disease were excluded. Also excluded were those in whom a diagnosis of malignancy was made unexpectedly on histologic analysis after excision of a breast lump initially thought to be benign in nature and those in whom WLE followed an initial open excision biopsy.

The surgeons at our institute adopted a similar technique for WLE. Clinically nonpalpable tumors were localized by insertion of a hookwire by the radiologist under image guidance (ultrasound preferentially, except in cases in which the lesion was only visualized on the mammogram) before surgery. The technique of WLE involved excision of the tumor, together with a gross radial (superior, inferior, medial, and lateral) margin of ≥ 1 cm. Anteriorly, the resection extended to the subcutaneous layer just deep to the skin and, posteriorly, down to the pectoralis muscle. Thus, the anterior and posterior margins can be considered “nonbreast” margins. The adequacy of the resection was determined by gross palpation of the excised specimen. Additional excision was immediately performed if the surgeon deemed the tumor was too close to the edge of the specimen. For nonpalpable tumors, the excised specimen was sent for specimen radiography to ensure that the localized lesion had been adequately resected. No other forms of intraoperative assessment, such as frozen section analysis or imprint cytology, were used.

The specimen was oriented with 3 sutures on excision (1 marking the anterior/superficial surface, 1 marking the medial margin, and 1 marking the lateral margin) and then fixed in 10% neutral-buffered formalin before being dispatched to the Department of Pathology for additional histopathologic analysis. On receipt, the WLE specimen was oriented according to the orienting sutures, and the gross dimensions of the specimen were recorded. The 6 specimen margins (4 radial margins [superior, inferior, lateral, and medial], and 2 vertical [nonbreast] margins [anterior and posterior]) were then inked with different colors before specimen sectioning. The routine technique involved serial sectioning of the specimen in the medial-lateral direction to obtain consecutive 3-mm-thick slices. If the tumor was grossly identifiable, its characteristics, including the number of separate tumor foci, tumor size, and proximity to the gross margins, were recorded. When no obvious tumor could be identified grossly, the lesion features, such as hemorrhage or scar tissue, were documented. The entire WLE specimen was then submitted for microscopic examination. The tissue slices were placed in cassettes, fixed in formalin for at least another 6 hours, embedded in paraffin, and processed into hematoxylin and eosin–stained glass slides for microscopic examination. Standard pathologic parameters were reported in accordance with the latest cancer protocols from the College of American Pathologists. The distance from each of the 6 margins to the invasive and/or in situ carcinoma within the specimen was reported individually. The tumor distance from the superior, inferior, anterior, and posterior margins was assessed on each serial slice. Apart from the rare occasions in which the WLE specimen was large (> 6 cm in diameter), the shaved medial and lateral ends were sectioned further perpendicularly for a more accurate measurement of the tumor distance to the respective medial and lateral margins. An involved margin found on microscopy was defined as one in which the tumor was present on the inked margin. The distance of the tumor from the margin was reported in millimeters, and the margin was considered “close” if the tumor was < 1 mm away from the margin. In cases in which the shaved medial and lateral margins were submitted, an estimate of the tumor distance from the margin was obtained by counting the number of consecutive 3-mm slices between shaved margin and the tumor.

All cases were discussed at the weekly multidisciplinary breast tumor board meetings. Patients with involved and close radial margins were considered to have had inadequate surgical clearance and were recommended to undergo additional surgery, unless the surgeon deemed it unnecessary, such as in cases in which the margin of resection had already extended to the subcutaneous layer just deep to the skin. Additional excision of the anterior or posterior margins was not routinely recommended even if affected unless indicated otherwise by the surgeon. Whole breast irradiation, either 50 Gy in 25 fractions or 42.5 Gy in 16 fractions, would be recommended after adequate margins had been achieved. An additional boost to the tumor bed of 10 Gy was included for invasive carcinoma; this was increased to 16 Gy when the margins were inadequate and no additional surgery had been performed. The recommendations for systemic therapy were in accordance with the current National Comprehensive Cancer Network guidelines.

The presence of residual tumor, whether invasive carcinoma or DCIS, was correlated with the standard clinicopathologic

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