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Progress in the surgical management of breast cancer: Present and future

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ABSTRACT

Recognition of differing risks of locoregional recurrence (LRR) in breast cancer patients based on estrogen receptor, progesterone receptor, and HER2 status, coupled with a reduction in LRR in patients receiving adjuvant systemic therapy, offers the opportunity to tailor surgical treatment and reduce the morbidity of therapy. New guidelines for margins in breast-conserving therapy of tumor not touching ink and avoidance of axillary dissection in sentinel node positive patients undergoing breast-conserving therapy are examples of this approach which have entered practice. Increased use of neoadjuvant therapy offers the opportunity to identify which patients are responsive to chemotherapy prior to surgery, potentially allowing further tailoring of treatment, and ongoing clinical trials will address the question of the extent of axillary surgery and radiotherapy after neoadjuvant therapy in patients with and without pathologic complete response.

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Introduction

Traditionally, local control has been equated with disease burden, and the role of surgery has been to remove all carcinoma evident on clinical examination or breast imaging. With the availability of advanced imaging techniques, such as magnetic resonance imaging (MRI) of the breast, with the capability of detecting microscopic amounts of breast cancer previously only evident on pathologic examination, this focus on eradicating subclinical disease has led to an increased mastectomy rate in women who would traditionally be considered candidates for breast-conserving therapy (BCT) [1], without evidence of an improvement in patient outcomes [2]. The common use of re-excision in patients with margins-free of tumor [3] or large quadrantectomy-type resections in the belief that the removal of greater amounts of normal breast tissue decreases local recurrence is another example of surgery to minimize subclinical disease burden.

There is now a large body of evidence indicating that local control is a function not only of disease burden, but of tumor biology and the availability of effective systemic therapy. Primary tumor features, such as lymphovascular invasion and the presence of an extensive intraductal component, which are associated with local recurrence, vary with estrogen receptor (ER), progesterone receptor (PR), and HER2 status [4], as do rates of local recurrence after both BCT and mastectomy [5]. Effective systemic therapy significantly decreases the rate of locoregional recurrence. In the Early Breast Cancer Trialists' Collaborative Overview, 5 years of tamoxifen compared to placebo reduced locoregional recurrence with a relative risk (RR) of 0.47 [6], and aromatase inhibitors or extended duration endocrine therapy result in further reductions in local recurrence [7]. Similar results are seen with chemotherapy with an RR of 0.63 for women less than 50 years of age compared to no chemotherapy [6], while in HER2 overexpressing patients, the use of trastuzumab has also been demonstrated to significantly reduce locoregional recurrence [8]. The net impact of the increased use of systemic therapy in early-stage breast cancer and improvements in this therapy is well illustrated in a study of 86,598 patients participating in Phase III trials of chemotherapy and endocrine therapy between 1990 and 2011 [9]. During this time, locoregional recurrence as a proportion of first recurrence decreased from 30% to 15% of all treatment failures independent of patient age, type of

Abbreviations: BCT, breast-conserving therapy; ER, estrogen receptor; PR, progesterone receptor; RR, relative risk; RT, radiotherapy; ALND, axillary dissection; ACOSOG, American College of Surgeons Oncology Group; SSO, Society of Surgical Oncology; ASTRO, American Society for Radiation Oncology; ASCO, American Society for Clinical Oncology; ASBrS, American Society of Breast Surgeons; OS, overall survival; DFS, disease-free survival; NSABP, National Surgical Adjuvant Breast and Bowel Project.

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surgery (BCT or mastectomy), or use of radiotherapy (RT). The recognition that local control is dependent upon biology and the use of effective systemic therapy offers the opportunity to decrease the extent of surgery and to reduce the burden of treatment in some patients. Changes in practice reflecting this understanding have already occurred and include new guidelines on margin width in BCT and alternatives to axillary dissection (ALND) for patients with sentinel lymph node metastases.

Decreasing the burden of surgery

Alternatives to axillary dissection

The American College of Surgeons Oncology Group (ACOSOG) Z0011 study was a landmark trial which demonstrated that ALND was not necessary for clinically node-negative women undergoing BCT who had metastases in 1–2 sentinel nodes [10]. This trial was met with great skepticism when initially published. Concerns included the generalization of the results since participants were thought to be a selected, highly favorable subset of patients undergoing BCT, and the use of radiation to the axilla in patients randomized to sentinel node biopsy alone. Additional data are now available to address these concerns. At Memorial Sloan Kettering Cancer Center, consecutive, unselected patients meeting ACOSOG Z0011 eligibility criteria were managed with sentinel node biopsy alone, with ALND reserved for those with metastases to 3 or more sentinel nodes or matted axillary nodes. In the initial 287 patients, ALND was avoided in 84% [11], and age, ER, PR, and HER2 status were not predictive of the need for ALND. Expansion of this cohort to over 550 patients confirms the low rate of ALND (Morrow M unpublished data), and no isolated axillary recurrences have been observed to date. Others have confirmed that the majority of patients with “high risk” features, such as young age, triple-negative, or HER2 overexpressing cancer meeting ACOSOG Z0011 eligibility criteria do not require ALND due to a heavy axillary nodal disease burden [12].

A retrospective review of the radiation fields used in approximately 30% of the participants in ACOSOG Z0011 found that 81% of patients received tangent-only RT, and that there was no difference in the use of nodal RT, high tangents, standard tangents, or the omission of RT between treatment arms. Although these findings suggest a lack of consensus in the radiation oncology community regarding what constitutes a “standard tangent field”, they do not support the theory that the low rates of nodal failure seen in ACOSOG ZO11 were due to the selective use of more extensive radiation fields in the sentinel node-only arm of the trial.

The AMAROS [13] and OTOSAR trials [14] examined the use of axillary RT as an alternative to ALND and observed no differences in survival or axillary recurrence rates between treatments, and the AMAROS study [13] reported a lower rate of lymphedema in the axillary RT group. These studies raise the possibility that ALND could be avoided in patients undergoing mastectomy if the need for postmastectomy RT was clear based on the finding of metastases in 1 or 2 sentinel nodes, but do not answer the question of whether or not RT is necessary in all patients undergoing sentinel node biopsy alone as in the ACOSOG ZO11 trial.

In aggregate, these 3 trials indicate that in the majority of clinically node-negative women with 1 or 2 positive sentinel nodes, the residual axillary nodal disease burden is limited and is controlled with systemic therapy, or systemic therapy and RT, minimizing surgical morbidity. The effectiveness of an approach to the axilla which relies on chemotherapy to eradicate axillary disease is further supported by the ACOSOG Z1071 trial [15] and the SENTINA trial [16], which reported nodal pathologic complete response rates of 41%–52% after neoadjuvant chemotherapy in patients with nodal metastases at presentation.

Reducing unnecessary re-excision

The fact that microscopic disease in the axilla is controlled with systemic therapy and less-than-full-dose (ACOSOG Z0011) to full-dose RT (AMAROS, OTOSAR), coupled with the decrease in rates of locoregional recurrence discussed previously, prompted the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) to develop a multidisciplinary consensus on the optimal negative margin width in BCT. The consensus was based on a metaanalysis which included 28,162 patients in 33 studies examining the relationship between margin width and local control [17], and other relevant published literature. The panelists concluded that evidence that margins more widely clear than no ink on tumor reduces local recurrence was lacking, and that the routine use of re-excision to obtain larger margins was not warranted [18]. This conclusion was felt to apply to young patients, those with infiltrating lobular carcinoma, cancers with an extensive intraductal component, and triple-negative cancers. The consensus does not suggest that re-excision for patients with characteristics suggestive of a heavy residual burden of tumor is inappropriate even if margins are negative; however, it does indicate that the routine use of re-excision to obtain some arbitrary clear margin width is not supported by data for any patient subset with invasive carcinoma. It is important to note that the consensus statement does not apply to patients with pure ductal carcinoma in situ, those treated with neoadjuvant therapy, and patients not receiving whole breast irradiation who were not included in the evidence base. The consensus statement was endorsed by the SSO, ASTRO, the American Society for Clinical Oncology (ASCO), and the American Society of Breast Surgeons (ASBrS). A metaanalysis of the impact of margin width on local recurrence in ductal carcinoma in situ treated with and without RT is underway in preparation for a similar consensus conference in November 2015 devoted to ductal carcinoma in situ.

Conflicting studies in radiation oncology

While all of the studies discussed above aim to decrease the intensity of surgical therapy, 2 large studies suggest that all node-positive patients undergoing BCT benefit from node field RT after ALND. The MA20 trial [19] and the EORTC 22922-10925 [20] study examined patient populations which appear to be similar to those in ACOSOG Z0011 and AMAROS; the majority had T1 and T2 tumors and metastases to 1–3 sentinel nodes. The EORTC study also included node-negative patients with medial tumors who made up 44% of the study population. At 5 years, the 1832-patient MA20 study observed a 5.4% improvement in disease-free survival (DFS) with RT ($P = 0.002$) and a 1.6% ($p = 0.07$) improvement in overall survival (OS). In the 4004 person EORTC study, reported at 10 years, RT improved DFS by 3% ($p = 0.04$) and OS by 1.6% ($p = .06$). Any late toxicity in this study was increased from 21.8% to 25.5% ($p = 0.006$) with RT. In spite of the lack of a significant OS benefit and relatively modest improvements in DFS, these studies have been interpreted as indicating that all node-positive women should receive RT. Based on everything we have learned about breast cancer in recent years, it seems unlikely that the benefit of RT is uniform or clinically significant, across all subsets. A major challenge for the future of local therapy will be to determine which node-positive patients can be treated with the minimalist approach shown to be effective in ACOSOG Z0011, and which require more extensive therapy such as ALND and nodal RT.

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