Short communication

How much can improved molecular and pathologic discriminants change local therapy?

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When considering the role of improved pathological or molecular markers in local therapy, their potential impact on both treatment selection and its outcome must be taken into account. At present, the selection of mastectomy or breast conserving surgery (BCT), consisting of lumpectomy and whole breast irradiation, for an individual patient is determined by the extent of disease within the breast and ability to tolerate radiotherapy [1]. In the absence of medical contraindications, patient preference is the final determinant of treatment choice.

How accurately the extent of disease is assessed with currently available tools can be evaluated by examining mastectomy rates in patients who are initially selected for BCT and the use of re-excision to obtain negative margins in patients undergoing BCT. The available data indicate that disease too extensive to allow BCT is reliably identified with clinical evaluation, diagnostic mammography and ultrasonography. Morrow and coworkers reported that only 2.9% of 263 patients selected for BCT between 1989 and 1993 required conversion to mastectomy [2]. In a population-based study conducted in 800 patients from the Los Angeles and Detroit Surveillance, Epidemiology and End Results Registry (SEER) treated between June 2005 and May 2006, 12% of patients were converted from BCT to mastectomy [3]. However, in 8% this conversion took place after a single lumpectomy attempt, suggesting that re-excision would have allowed successful BCT in some of these cases. In contrast to the low rate of conversion from BCT to mastectomy, re-excision to obtain negative margins is a common surgical procedure. In the population-based study 22% of patients required re-excision [3], and in some studies the rate of re-excision approaches 50% [4]. These findings suggest that a more precise definition of microscopic extent of disease with molecular tools would facilitate surgical excision. Although this idea is attractive, it is associated with major pitfalls, illustrated by experience with magnetic resonance imaging (MRI) of the breast.

MRI is well documented to be a more sensitive method for detecting cancer than mammography or ultrasound. A meta-analysis of 19 studies involving 2,763 breast cancer patients revealed that MRI detected additional disease in 16% (range 6% to 34%) that led to more extensive surgical therapy [5]. It has been assumed that these larger surgical procedures were beneficial to the patient, but more recent studies have cast doubt upon this assumption. Bleicher and coworkers studied 290 patients with and without MRI and found no significant difference in conversion from BCT to mastectomy or in the likelihood of obtaining negative margins with a single surgical excision [6]. In that study, as well as in a study from the Mayo Clinic [7], the detection of additional foci of cancer was found to increase the mastectomy rate significantly. The MRI findings of additional disease are consistent with observations from pathological studies that employed serial subgross sections to examine the distribution of clinically localized cancers within the breast and found evidence of multifocality in as many as 63% of cases [8]. However, extensive clinical experience has shown that these foci are controlled with radiotherapy, and their incidence significantly exceeds local recurrence rates in modern studies of BCT [9]. Although it is clear that the clinical importance of microscopic multifocal disease is related to its volume, the threshold volume that influences clinical outcome is unknown. The indiscriminate application of molecular tools to detect this disease runs the risk of unnecessarily increasing the mastectomy rate without improving patient outcomes, as illustrated by the MRI experience.

An important contribution of molecular and pathological tools to selection of local therapy would be to identify tumour phenotypes with a high risk of local recurrence after BCT,

BCT = breast conserving surgery; ER = oestrogen receptor; HER = human epidermal growth factor receptor; MRI = magnetic resonance imaging; PR = progesterone receptor.

which would be best treated with initial mastectomy, or a group at such low risk for local recurrence that radiotherapy was not indicated. At present, the outcome of local therapy appears to depend upon interactions between tumour biology, disease burden and the therapy received. These are clearly not independent variables, but the relative contribution of each to outcome is poorly defined, making evaluation of molecular predictors difficult. In a study conducted to examine prediction of local recurrence with gene expression profiling, Nuyten and colleagues [10] evaluated 10-year local control rates as predicted by high and low scores on the wound response profile, 70-gene profile, and the hypoxia signature. Only the wound response profile was a significant predictor of outcome (95% local recurrence free for low score versus 71% for high score), and this was significant in a multivariate analysis that adjusted for age, tumour size and use of a boost dose of radiation. However, adjustments were not made for margin status and the use of systemic therapy, which are two of the most important clinical determinants of local control.

In another study, Mamounas and coworkers [11] used the 21-gene recurrence score (Oncotype Dx™, Genomic Healthcare, Inc., Redwood City, CA, USA) to examine local control in patients receiving no systemic therapy, tamoxifen alone, or tamoxifen plus chemotherapy. For each group, rates of local recurrence were significantly higher for patients with high risk scores than for those with low risk scores. The risk for local recurrence was 18.4% in patients with high risk scores receiving placebo, as compared with 7.8% in those with high risk scores receiving chemotherapy and tamoxifen. A high risk score indicates a high risk for systemic relapse and need for adjuvant therapy. This study appears to provide reassurance that a parallel benefit in reducing the risk for local recurrence is seen, but that the recurrence score does not identify a group with a risk for recurrence sufficiently high to warrant mastectomy.

Nguyen and coworkers [12] used oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER)-2 as surrogates for breast cancer subtypes to examine the 5-year risk for local recurrence after treatment with BCT. Local recurrence rates were 0.8% in those with ER-positive and/or PR-positive, *HER-2*-negative tumours (luminal A); 1.5% for ER-positive and/or PR-positive, *HER-2*-positive patients (luminal B); 8.4% for hormone receptor negative, *HER-2*-positive patients treated without trastuzumab; and 7.1% for ER-negative, PR-negative and *HER-2* negative (basal) patients. This study indicates that patients with hormone receptor positive tumours treated with appropriate endocrine therapy have extremely low rates of local recurrence. It is likely that similar results will be seen for *HER-2*-positive patients treated with adjuvant trastuzumab, because the randomized trials of adjuvant trastuzumab revealed an approximately 50% reduction in locoregional recurrence with trastuzumab treatment compared with treatment with chemotherapy alone [13]. In addition, a similar study examining locoregional recurrence after mastectomy with and without radiotherapy by tumour subtype in patients treated in the Danish Breast Cancer Group trials found that the lowest rates of local recurrence were seen in the ER-positive and/or PR-positive group who received radiotherapy, regardless of *HER-2* status [14]. The risk for chest wall recurrence with radiotherapy was higher in the *HER-2* group (without trastuzumab) and in the triple negative group, which is the same finding as seen in patients treated with BCT [12], and indicates that although these markers may be prognostic they are not predictive of benefit from a particular type of local therapy.

In summary, to date, pathological or molecular markers that identify a subgroup of patients who are at sufficiently high risk for local recurrence after BCT to justify mastectomy have not been identified. The availability of targeted systemic therapy has a major impact on risk for local recurrence, and differences in local recurrence rates on the basis of ER, PR and *HER-2* are present in patients treated with both mastectomy and BCT. The available information on molecular phenotypes and risk for local recurrence may be used to refine estimates of the benefit of treatment in controversial areas, such as the use of postmastectomy radiotherapy in patients with one to three involved nodes, the use of a boost dose of radiotherapy in postmenopausal women, or in assessing the adequacy of surgical resection.

Competing interests

The author declares that they have no competing interests.

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