The Challenge of Individualizing Loco-Regional Treatments for Patients with Localized Breast Cancer

Le défi des traitements locorégionaux individualisés pour les patientes présentant un cancer du sein localisé

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It has traditionally been thought that disease burden is the primary determinant of local control after breast cancer surgery. The selection criteria for breast-conserving therapy (BCT) are related to the extent of disease in the breast as measured by margin status, multicentricity, and extent of calcifications as well as the ability to safely deliver radiotherapy. Biologic factors, such as tumor histology, grade, estrogen receptor (ER), progesterone receptor (PR), and HER2 status, are not considered as selection factors when deciding between BCT and mastectomy. The recognition that breast cancer is actually a group of genetically distinct diseases with differing prognosis has dramatically changed the approach to systemic therapy, with ER, PR, and HER2 status the primary determinants of treatment regardless of disease burden (i.e., node positive versus node negative). While this paradigm shift is well accepted, less attention has been paid to the impact of molecular subtype on local therapy outcomes.
Molecular Subtype and Presenting Features of Cancer

In a retrospective study of 6,072 patients undergoing surgery at Memorial Sloan-Kettering Cancer Center during the era when ER, PR, and HER2 were routinely obtained, significant variation in presenting tumor features was observed on the basis of these markers. As expected, patients with ER positive cancers were older and significantly less likely to have grade III tumors. Patients whose cancers overexpressed HER2 were significantly more likely to have multifocal or multicentric cancers \((p < 0.001)\) and cancers with an extensive intraductal component \((p < 0.0001)\). In multivariate analysis, after adjustment for age, tumor size, and grade, ER negative, HER2 positive cancers were 1.6 time \((95\% \text{ confidence interval } [CI], 1.2-2.1; p < 0.0001)\) more likely than ER/PR positive, HER2 negative cancers to be multifocal or multicentric. The presence and extent of nodal involvement also vary with subtype. In spite of their poor prognosis, ER, PR, and HER2 negative (“triple negative”) cancers were less likely than ER positive, HER2 negative cancers to have nodal involvement after adjusting for age, grade, and size \((\text{odds ratio } [OR], 0.6; 95\% \text{ CI}, 0.5-1.7; p < 0.0001)\). In contrast, HER2 positive, ER negative cancers were significantly more likely to have involvement of 4 or more nodes \((OR, 1.8; 95\% \text{ CI}, 1.3-2.4; p < 0.0001)\) [1]. Others have also reported a lower incidence of nodal involvement in triple negative cancers [2, 3].

Impact of Molecular Subtype on Local Therapy Outcomes

It is already clear that intrinsic tumor biology and the availability of targeted therapy have a major impact upon the outcomes of local therapy. Single-institution studies [4] demonstrated that patients with estrogen receptor positive, HER2 negative cancers have lower rates of local recurrence (LR) after BCT than do patients with ER negative, PR negative, and HER2 negative cancers. In a meta-analysis of 7,174 patients undergoing BCT, the relative risk of LR was 0.49 for non-triple-negative cancers compared with triple-negative cancers \((95\% \text{ CI}, 0.33-0.73; p = 0.0005)\) [5].

This increased rate of LR in triple-negative cancers is not improved with the use of more extensive surgery. In a study of 535 patients with triple-negative cancers, Pilewskie et al. [6] found no significant difference in LR with the use of margins greater than 2 mm \((n = 464)\) versus margins \(\leq 2\) mm \((n = 71)\) after adjusting for systemic therapy use \((5.1\% \text{ versus } 7.3\%; p = 0.08)\). This finding is confirmed
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by 3 retrospective studies that show no difference in rates of LR among T1 and T2, N0 patients, with triple-negative cancer undergoing BCT or mastectomy without radiation therapy (RT) [7].

A metaanalysis examining LR after mastectomy by subtype in 5,418 patients demonstrated a decreased risk of LR after mastectomy in non-triple-negative versus triple-negative cancers (relative risk [RR], 0.66; 95% CI, 0.53-0.83; p = 0.0003) [5]. Thus, unlike the situation with disease burden, where heavier disease burden is an indication for more extensive surgery (mastectomy rather than BCT), more extensive surgery does not overcome bad biology.

It is, however, increasingly apparent that effective targeted therapy improves local therapy outcomes, as illustrated in patients with HER2 overexpressing cancers. In studies antedating the use of adjuvant trastuzumab, patients with HER2 overexpressing cancers had rates of LR similar to those seen in triple-negative cancers [4]. The use of adjuvant trastuzumab reduces LR by approximately 40% compared with chemotherapy alone in randomized trials [8]. In studies at Memorial Sloan-Kettering Cancer Center, adjuvant trastuzumab reduced the 3-year rate of LR after BCT from 7% to 1% (p = 0.01) [9], and also decreased the rate of LR after mastectomy (1.5% versus 6.6%; p = 0.04). These findings, while helping to more accurately define the risk of LR in an individual, do not help to select one treatment over another. Efforts to identify genetic signatures that signal patients at higher risk of LR after BCT than after mastectomy have been unsuccessful to date; however, evidence is emerging that within molecular subtypes, genetic profiling may identify groups at higher and lower risk of LR, potentially allowing tailoring of local therapy. Mamounas et al. [10] showed that in node-negative breast cancer patients receiving tamoxifen and chemotherapy, patients with a low 21-gene recurrence score (Oncotype DX™) had a 10-year risk of LR of 1.6% compared with a risk of 7.8% in patients with a high score (p = 0.028). The same pattern was seen in node-positive patients, where those with a low recurrence score had a 10-year LR of 3.3% versus 12.3% in those with a high score (p < 0.001 in multivariate analysis) [11]. This finding was observed after both mastectomy and BCT, and in patients with 1-3 involved nodes as well as those with 4 or more involved nodes. These findings, if confirmed, suggest that postmastectomy irradiation (PMRT) could be avoided in patients with 1-3 involved nodes and low 21-gene recurrence scores, and even in patients with involvement of 4 or more nodes and low scores, a group for whom PMRT has long been standard.
Implications for Axillary Management

The beneficial effect of systemic therapy on local control in the breast raises the possibility that the extent of axillary surgery, with its associated morbidity, could be reduced in patients receiving systemic therapy. This was the question addressed in the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial. In this study, women with clinical T1 and T2, clinically node-negative cancers undergoing BCT with whole breast RT who were found to have metastases in fewer than 3 sentinel nodes were randomized to completion axillary lymph node dissection or no further axillary surgery. After a median follow-up of 6.3 years, no difference in total locoregional recurrence rate, disease-free survival, or overall survival was seen between groups [12]. These results are potentially practice changing, but concerns have been expressed that they do not apply to the entire spectrum of women undergoing BCT because the population of women entered into ACOSOG Z0011 was a particularly low-risk subgroup. In particular, there are concerns that younger women and women with ER negative cancers were underrepresented in the trial, and that these women might be more likely to have a heavy axillary tumor burden.

In August 2010, the Breast Service at Memorial Sloan-Kettering Cancer Center adopted as standard clinical practice the elimination of axillary dissection for women with fewer than 3 involved sentinel lymph nodes who otherwise met ACOSOG Z0011 eligibility criteria. Patients had to be clinically node negative on physical examination, but were not screened with axillary imaging. The Memorial Sloan-Kettering Cancer Center nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy was not used to estimate the likelihood of residual node disease. Axillary dissection was performed for metastases in 3 or more sentinel nodes, gross extracapsular extension or matted nodal disease, or if the patient required conversion to mastectomy. Between August 2010 and November 2012, 287 consecutive, unselected patients meeting eligibility criteria were treated: 215 with macrometastases and 72 with micrometastases detected by hematoxylin and eosin staining. Of these, 242 (84%) did not require axillary dissection [13]. Dissection was indicated in 29 of 45 patients for 3 or more nodal metastases, and for matted nodes or extracapsular extension in the remainder. A comparison of patients requiring axillary dissection and those who did not, demonstrated no difference in median age (60 versus 58 years, p = 0.35), hormone receptor
status (13% ER negative versus 10%), or histologic grade between the groups. Pathologic tumor size was a median of 0.6 cm larger in the axillary dissection group (p < 0.001). Although the median follow-up of 13 months is too short to draw any conclusions about the rate of regional control, there have been no nodal recurrences in either group. One patient in the sentinel node biopsy-only group has had an in-breast recurrence, and 3 patients in the axillary dissection group have developed distant metastases. A comparison of the patients avoiding axillary dissection in this consecutive, unselected series to those randomized in ACOSOG Z0011 [12] demonstrates that the median ages are similar (58 versus 55 years), tumor sizes did not differ, and the proportion of ER positive cases was actually higher in our series (91% versus 83%). Twenty-seven percent of patients in the axillary dissection arm of ACOSOG Z0011 had additional nodal metastases, while the Memorial Sloan-Kettering Cancer Center nomogram [14] predicted additional metastases in 34% of patients having sentinel node biopsy-only in our study. In contrast, 70% of patients undergoing axillary dissection in our study had additional nodal disease, indicating that the selection criteria used for axillary dissection (3 or more positive sentinel nodes, matted nodes, gross extracapsular extension) reliably identified a group at high risk of residual nodal disease. Our findings suggest that the patients entered into ACOSOG Z0011 are more representative of the general population of clinically node-negative women undergoing BCT than was initially thought, and that the morbidity of axillary dissection can be avoided in the majority of clinically node-negative patients undergoing BCT. Although further follow-up is needed, this approach illustrates the principle that as the effectiveness of other therapies increases, the extent of surgery may be decreased and excellent local control is still maintained.

These results also illustrate the ability to change standard surgical paradigms based on the use of the multimodal therapy. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B04 trial, in the simple mastectomy alone arm, where no systemic therapy or RT was used, the ratio of nodal disease left behind to axillary first failure was 2.2 to 1 [15]. In ACOSOG Z0011, this increased to 30 to 1 in the setting of virtually all patients receiving systemic therapy and whole breast RT [12]. This opens the door to the possibility that less surgery in the breast – for example, removal of only the gross tumor – without obsessive concern for margins, could result in high rates of local control in selected subgroups. Yet, at the same time that recognition of the impact of other therapies on local outcomes has allowed us to decrease surgery in the axilla, improvements in imaging may
be contributing to more extensive surgeries in the breast. Magnetic resonance imaging (MRI) detects cancer not identifiable by other means in approximately 16% of patients [16]. In a metaanalysis examining the impact of preoperative MRI on type of surgery, after adjusting for age, use of MRI increased the odds of mastectomy 3-fold, without reducing rates of re-excision for positive margins [17]. As molecular imaging continues to improve, it is very likely that an increasing number of patients will have disease too extensive for BCT – at least according the standards developed in the 1980s, and which continue to be used today. In the short term, the real challenge for local therapy is to re-define our concept of what extent of surgical reduction of tumor burden is needed to provide high levels of local control, recognizing that this is likely to differ among, and even within, molecular tumor subtypes. Looking ahead, the one thing that is clear is that the “one size fits all” approach to local therapy that has served us well for the past 30 years is not the path to future success.

Références