Perspective

Locoregional recurrence after neoadjuvant chemotherapy

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Neoadjuvant chemotherapy (NAC) is a widely accepted treatment for operable early breast cancer. The advantages of NAC included the evaluation of the *in vivo* chemosensitivity of tumors in individual patients, minimisation of micrometastases, and surgical downstaging of tumors. National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted two trials of NAC, namely NSABP B-18 (1) and NSABP B-27 (2). NSABP B-18 demonstrated that no statistically significant overall differences in survival or disease-free survival between the two treatment groups, NAC and postoperative adjuvant therapy. In both studies, patients who achieved a pCR continue to have significantly superior disease-free survival and overall survival outcomes compared with patients who did not (3).

There has been limited information on rates and predictors of locoregional recurrence (LRR) for patients who receive NAC. Mauri *et al*. (4) previously performed a meta-analysis of clinical trials comparing patients who received NAC with those who received postoperative chemotherapy, and concluded that NAC, compared with adjuvant therapy, was associated with a statistically significant increased risk of LRR when radiotherapy without surgery was adopted, while NAC was apparently equivalent to adjuvant therapy in terms of survival and overall disease progression. The inaccuracy of a predictor of LRR has given obscurity for the indication of sentinel node biopsy or postoperative irradiation. Mamounas and colleagues (5) recently published, in Journal of Clinical Oncology, an information on predictors of LRR for patients with primary operable breast cancer who receive NAC in combined analysis of NSABP B-18 and NSABP B-27 trials. Mamounas *et al*. revealed that age, clinical nodal status before NAC, and pathologic nodal status/breast tumor response after NAC can be used to predict risk for LRR and to optimize the use of adjuvant radiotherapy in patients treated with NAC. The nomogram presented by Mamounas *et al*. is also useful to predict high risk of LRR in patients treated with lumpectomy or mastectomy. The high risk patients of LRR might need adjuvant therapy or frequent postoperative surveillance including ultrasonography. Although the indication of external radiotherapy (XRT) in patients with breast cancer is increasingly controversial, their data could be a useful tool for predicting risk of LRR and for decisions about the optimal use of XRT in patients treated with NAC and breast surgery.

Numerous consensus reports recommend that postmastectomy XRT in addition to systemic therapy is indicated in high-risk patients with 4+ positive nodes, but remains controversial in patients with 1-3 positive nodes. The risk of LRR was considerable (>10%) for most subsets of patients with 1-3 positive nodes, while the risk of LRR is increased with an increasing number of residual positive nodes. The indication for XRT seems therefore to be beneficial in patients with not only 4+ positive nodes but also 1-3 positive nodes.

Sentinel node biopsy provides a minimally invasive approach to detecting lymph node metastasis. However, the significance of sentinel node biopsy after NAC remains to be controversial (6). Mamounas *et al*. indicated that the clinical nodal status before NAC was an independent predictors of LRR in patients treated with breast surgery. There is still limited information on the feasibility and accuracy of sentinel node biopsy after NAC because chemotherapy may lead to fibrosis in the regional lymph nodes, resulting in the increase of false-negative sentinel

nodes. Therefore the status of the sentinel node after NAC cannot be used as a reliable indicator of the presence or absence of residual disease. Although a meta-analysis of the published data suggested that sentinel node biopsy is an accurate staging investigation of the axilla after NAC (7), those studies were performed in patients who had clinically negative lymph node status and excluded patients with suspected or proven axillary metastases prior to NAC. Sentinel node navigation surgery might be inadequate for patients with breast tumor presumed to be clinical node-positive before NAC.

The data from NSABP B-18 and NSABP B-27 provided the opportunity to examine the rates and patterns of LRR in patients treated with NAC and to identify independent predictors of LRR, because the sample derived from the two trials of NAC contained the large size of prospectively collected cohort of patients for whom information on rates and patterns of LRR is available. In both studies of NSABP B-18 and NSABP B-27, mastectomy patients were not permitted to receive chest wall or regional nodal breast XRT, and lumpectomy patients were required to receive breast XRT but were not permitted to receive additional regional nodal XRT. Moreover, both two trials were conducted before the era of trastuzumab treatments and adjuvant radiotherapy. To that extent, the two trials introduced few selection bias of a patient's status, and provided a large cohort of patients for whom the natural history of LRR can be assessed without the confounding effects of nonuniform post-mastectomy radiation. In contrast, this study lacked the information on estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) status, but may apply it to postoperative supporting radiologic adaptive determination. The information on the effect of hormone receptor status, HER2 status, and the therapeutic effect of adding trastuzumab to chemotherapy in patients with HER2-positive disease might be additional factors that will have to be incorporated in future analysis. Recently, cancer stem cells have been demonstrated to be resistant to chemotherapy and responsible for tumor recurrence (8,9). The high risk of LRR will probably be predicted more accurately by adding biomarker such as cancer stem cells marker (10) into the nomogram.

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