Local management after neoadjuvant treatment for breast cancer

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Abstract: Neoadjuvant chemotherapy (NAC) was originally used in patients with locally advanced breast cancer. Then, it is used in operable breast cancer to downstage the primary breast cancer and axillary lymph nodes metastasis, result in improving the cosmetic outcome and decreasing surgical morbidity. However, it is sometimes difficult to assess the extent of residual disease after NAC, as the NAC reduces the lesion and obscure the original images both breast and axilla. Thus, detailed assessment of primary breast cancer and axillary lymph nodes metastasis are required from the time of before NAC until the time of surgery. These assessments include the accurate location, the extent of intraductal component around primary tumor and the axillary nodal status. Multimodality imaging with intervention for cytopathology can help to delineate the size and location of breast cancer and lymph node metastasis and predict the residual tumor burden in primary breast cancer and involved axillary nodes. In the future, with development of new targeted therapy, technologies in medical imaging diagnosis and ongoing trial data will provide further individualized treatment option for patients with breast cancer. This article reviews the current evidence and management recommendations for optimal surgical treatment in this setting.

Keywords: Neoadjuvant chemotherapy (NAC); local treatment; breast cancer; assessment of breast; assessment of axillary nodal status

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Introduction

Traditionally, neoadjuvant treatment, which most often applied as neoadjuvant chemotherapy (NAC) before surgery, was used in patients with locally advanced breast cancer to convert them to operable disease. But NAC for early breast cancer patients is now recognized as a useful clinical tool for some reasons, the potential for converting patients requiring mastectomy to candidate for breast-conserving surgery (BCS), the potential for converting patients requiring axillary dissection to candidates for sentinel lymph node biopsy alone. Furthermore, tumor response to neoadjuvant treatment is an important prognostic factor and surrogate marker for overall survival and useful for response-guided treatment strategy at least for some subtypes of breast cancer (1). According to two prospective trials, von Minckwitz et al. (2) and Masuda et al. (3) reported that the additional treatment can improve long-term outcomes for patients who have not achieved best response with NAC and targeted therapy, who are at high risk for recurrence. The information of tumor response will guide postoperative systemic therapy.

There has been great improvement in pathologic complete response (pCR) rates in the past decade, especially in human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer. In patients with hormone receptor-negative and HER2-positive, pCR were noted in 63% women who received both anti-HER2 therapy and chemotherapy (4). With improved mortality of breast cancer, the quality of life of breast cancer survivor has become more important and attention has been focused on less-invasive, patient-friendly local treatment. In the
future, novel targeted therapy and technology will lead to further individualization of local treatment for breast cancer, including the possibility of no surgery in cases with achieving a good response. This article reviews the current topics surrounding surgery of the breast and axilla in patients with breast cancer receiving neoadjuvant treatment.

**Breast surgery after NAC**

One of the purposes of NAC from a surgical viewpoint is improving the cosmetic quality of life following BCS by reducing the tumor size even if the patient is a candidate for conserving surgery at diagnosis. A meta-analysis of 10 randomized controlled trials of neoadjuvant versus adjuvant chemotherapy demonstrated that patients allocated NAC were more likely to have BCS (65% vs. 49%) (5). Although there is not significant difference in distant recurrence between NAC and adjuvant chemotherapy (15 year risk 38% for NAC vs. 38% for adjuvant chemotherapy; P=0.66), NAC was associated with more frequent local recurrence than was adjuvant chemotherapy (15 year risk 21% for NAC vs. 16% for adjuvant chemotherapy; P=0.0001) (5). When considering the cause of this local failure, it is probably due to the difficulty in assessing the extent of residual disease after NAC.

**Assessment of breast cancer during NAC**

It is crucial for appropriate BCS to assess accurately the location and extent of the primary breast cancer with or without NAC. It could be often difficult to accurately assess the extent of the lesion, as the NAC reduces the lesion and obscure the original images. Thus, assessment of primary breast cancer from the time of diagnosis until the time of surgery is most important for controlling local managements. Physical examination, mammography, ultrasonography, and magnetic resonance imaging (MRI) can help to delineate the size and configuration of the tumor. Mammography can delineate the extent of malignant calcifications indicating an extent of intraductal component around primary tumor (6). MRI can also help to assess the extent of breast cancer and their response to NAC. Several studies have demonstrated the accuracy of MRI compared with physical examination, mammography, and ultrasonography in determining the presence and extent of viable cancer within the breast after NAC (7,8). Nakamura classified the patterns of breast tumor growth and shrinkage into concentric or dendritic pattern and concentric pattern was good candidates for BCS after NAC (9).

**No surgery (active surveillance) after NAC**

With improvements in new targeted therapy and chemotherapy regimens, pCR rate after NAC has increased over the last decade, specifically in triple-negative and HER2 positive breast cancer. Up to 40% of patients with HER2 positive who had given dual anti-HER2 therapy (trastuzumab plus pertuzuma) with docetaxel achieved pCR (4). If pCR has achieved to a patient, theoretically she may not need surgery at all. According to Özkurt et al. (12), one of the largest retrospective cohort study in the U.S., demonstrated that achieving a complete response after NAC may have a favorable outcome on patients OS, even in patients not undergoing local therapy to the breast. Although in a meta-analysis in a previous era by Mauri et al. (13) demonstrated the patients who adopted radiotherapy without surgery had a significantly increased risk of loco-regional recurrences, high pCR rates in the modern era and advanced pCR prediction methods using breast imaging with biopsy might enable the strategy of “No surgery” after NAC. Inserting a radiopaque marker under mammography or ultrasonography is recommended for some patients who have a potential to achieve pCR (14). Several groups have begun accrual on the trials to investigate the possibility of no surgery after NAC (15-17). The study ongoing in MD Anderson Cancer Center is designed to evaluate whether patients with residual carcinoma can be accurately identified using image-guided intervention (17). Safe omission of surgery in patients after NAC is depend on the accurate assessment of breast and axillary tumor burden.

**Axillary management after NAC**

The criteria for clinically node-negative disease is defined as no regional node metastases (by imaging or clinical
examination) in AJCC Cancer Staging manual, eighth edition. In the setting of NAC, imaging diagnosis is recommended for evaluation of axillary lymph nodes before NAC as baseline (18). Several reports have demonstrated the high diagnostic sensitivity of axillary lymph node evaluation by means of ultrasonography (19), CT (20,21), MRI (22) or EDG-PET. Although the diagnostic sensitivity with these modalities is higher than palpation, axillary ultrasonography and ultrasonography guided FNA or CNB of abnormal lymph nodes is minimally invasive intervention that can assess axillary lymph node repeatedly and provide direct information of the chemosensitivity of axillary metastases to NAC (19,23).

In cN0 patients at baseline, SNB might be performed after NAC considering its accuracy with a low false negative rate (FNR) (24) and recommendations of updated guidelines by the National comprehensive cancer Network (NCCN) and Japanese Breast Cancer Society (25).

For patients with 1 or more cytology/histology-proven positive nodes at baseline, axillary dissection has been the standard treatment in these patients according to initial studies that yielded an FNR >10% (26,27). Three prospective trials (SN FNAC, Z1071, SENTINA) addressing the feasibility of SLN after NAC in patients with clinically node-positive disease have demonstrated the lower FNR <10% in selected patients (23,28,29) when more than 2 lymph nodes were removed, dual agent were used for SLN mapping and positive lymph nodes were marked with a US-visible marker before starting NAC. These results suggest SNB is accurate if three or more sentinel lymph nodes are evaluated, but long-term outcome date from patients treated with SNB alone in this setting is lacking. Patients in this setting should be discussed at a multidisciplinary meeting to evaluate if axillary dissection can be omitted or should be recommended.

For patients with a large axillary lymph node involvement before NAC or for those who have residual disease in the axilla after NAC, standard therapy of the axilla is axillary dissection. However, detailed assessment of axillary lymph nodes by imaging and cyto-pathological intervention will probably provide more tailored management of axilla. Some prospective trials opened to investigate the role of SLN and regional lymph nodes radiation in patients with cN1 after NAC (30).

**Conclusions**

The local management of early breast cancer patients after NAC will probably be required more individualized approach based on the preoperative treatment response. Multimodality imaging with intervention for cytopathology can help to delineate the size and location of breast cancer and lymph node metastasis and predict the residual tumor burden in primary breast cancer and involved axillary nodes. In the future, with development of new targeted therapy, technologies in medical imaging diagnosis and ongoing trial data will provide further individualized treatment option for patients with breast cancer.

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