Review Article

The timing of breast and axillary surgery after neoadjuvant chemotherapy for breast cancer

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Abstract: Neoadjuvant chemotherapy (NAC) has traditionally been used in locally advanced and inflammatory breast cancer, allowing for a reduction in disease volume and therefore optimizing surgical resection of disease in the breast. NAC impacts both the tumor in the breast and the lymph nodes and may allow for the option of breast-conserving surgery and avoiding an axillary dissection. The aim of this review is to discuss the considerations and timing of surgical treatment of the breast and the axilla following NAC in patients with breast cancer.

Keywords: Breast cancer; neoadjuvant chemotherapy (NAC)

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Introduction

Neoadjuvant chemotherapy (NAC) has traditionally been the standard approach in patients with locally advanced and inflammatory breast cancer, allowing for a reduction in disease volume and therefore optimizing surgical resection of the disease in the breast. This has evolved to now also include NAC in patients with large operable cancers who desire breast conservation and patients with early stage breast cancer, especially HER-2 positive and triple negative tumors.

The optimal timing of systemic therapy in breast cancer has long been studied and debated. Several large randomized clinical trials have demonstrated no significant difference in disease-free and overall survival between patients receiving chemotherapy in the neoadjuvant and the adjuvant setting (1). The most striking advantage of NAC identified by these trials is an increase in the rate of breast conserving surgery (2-5). A number of additional benefits of NAC, leading to its increased use and acceptance, have also been demonstrated. These include the valuable prognostic information gained from the extent of pathologic response observed (6-8). Achievement of a pathological complete response (pCR) in the breast and lymph nodes after NAC has been shown to correlate with an improved outcome compared to those that do not achieve a complete response (2,7). Secondly, use of NAC has been shown to convert biopsy proven node-positive disease to pathologically node-negative disease at surgery with rates up to 70% (8-12). As a result, the extent of axillary surgery may be decreased in these patients, which ultimately reduces the potential morbidity related to surgery. For patients presenting with axillary disease, despite negative clinical and radiological examinations, NAC has been shown to treat this occult axillary disease and decrease the likelihood of node-positivity found at surgical resection (13,14). Furthermore, there has been increased realization that NAC is a valuable tool to assess tumor response *in vivo*, providing an opportunity to both evaluate the benefits of systemic treatments in a shorter time as well as obtain prognostic and predictive information that helps inform decisions about further adjuvant therapy. With the vast advances made

over the last two decades in breast cancer systemic therapy, the timing of drug development and approval has evolved from the metastatic setting to also include patients in the neoadjuvant setting with a study endpoint being disease eradication at surgery.

The aim of this review is to discuss the considerations and timing of surgical treatment of the breast and the axilla following NAC in patients with breast cancer.

Assessing response and surgical planning

Patients treated with NAC are monitored throughout their treatment with regular clinical examinations to assess tumor response and to ensure no disease progression is noted. There are no current guidelines for imaging recommendations, and practices may vary between institutions. The practice at our institution is to perform clinical examinations during treatment, which include an assessment of the breast as well as the axilla. Response may be demonstrated by a decrease in the size of the tumor by examination and a decrease or complete resolution of any palpable axillary disease. In the setting where there may be a concern about disease progression, mammography, breast ultrasound, or MRI during treatment can be used to assess for progression. Ultimately following completion of NAC, imaging to assess disease response and to guide surgical decision making is obtained. Axillary imaging is routinely performed at initial presentation; and in patients with node positive disease, axillary ultrasound is repeated after completion of NAC.

The evaluation of tumor response by imaging after NAC is challenging due to the variation in tumor response which may be observed as either a concentric or discontinuous (honeycomb) response. In addition, the use of chemotherapy may lead to treatment-enhanced lesions that may affect imaging interpretation. A study of 189 patients assessed with clinical examination, ultrasound and/or mammography ≤60 days before surgical resection showed that the size estimated by these imaging modalities only moderately correlated with residual pathologic disease (15). The correlation coefficients for these modalities were 0.42, 0.42, and 0.41, respectively, with an accuracy of ±1 cm in 66% of patients by physical examination, 75% by ultrasonography, and 70% by mammography. Keune *et al.* were able to demonstrate that ultrasound correctly predicted residual tumor size in 91.3% of patients compared with 51.9% when mammography was performed (P<0.001) (16). Ultrasound also was more accurate than mammography in estimating residual tumor size (59.6% *vs.* 31.7%, P<0.001). Combining mammography and ultrasound interpretation has been shown to demonstrate improved correlation with pCR and is more sensitive and specific than physical examination alone.

MRI is a valuable tool for assessing response to NAC and its use has increased in recent years. Studies to date have shown it to be superior with a higher accuracy than other imaging modalities (17-22). Yuan *et al.* published a meta-analysis in 2010 to determine the ability of MRI to predict pathologic complete remission in patients with breast cancer after NAC (23). This study, which included results from 25 studies, showed a pooled sensitivity and specificity of 63% and 91% respectively. A subsequent meta-analysis by Marinovich *et al.* showed that the capability of MRI in differentiating the presence of residual malignancy from pCR had an overall area under the curve (AUC) of 0.88 and that the overall accuracy differed according to the definition of pCR (17).

Other promising imaging tools for the assessment of response to NAC include molecular breast imaging (MBI), although the data is currently limited to smaller studies. MBI can be used when MRI is contraindicated. Mitchell *et al.* were able to demonstrate an area under the receiver operator characteristic curve for determining the presence or absence of residual disease of 0.88 (24). Using a threshold of 50% reduction in tumor to background ratio at 3 to 5 weeks, MBI predicted presence of residual disease at surgery with a diagnostic accuracy of 89.5%, sensitivity of 92.3%, and specificity of 83.3%.

Several factors have been shown to limit imaging accuracy. In the study by Peintinger *et al.* multivariate analysis showed that pathologic residual tumor size was underestimated for lobular carcinoma and overestimated for poorly differentiated tumors (25). However, the addition and use of MRI has been shown to be more accurate than other imaging modalities for defining the extent of disease in lobular carcinoma (26-28). The detection of response in triple negative and HER-2 positive tumors is also improved using MRI, while its use in hormone receptor positive, low grade tumors, and those with diffuse non-mass like enhancements is more limited (29).

Axillary ultrasound (AUS) with percutaneous biopsy of morphologically abnormal lymph nodes is indicated at time of initial diagnosis and enhances the clinical staging and allows identification of node positive disease. In patients with biopsy proven node-positive disease at presentation, axillary ultrasound can be performed after

NAC to evaluate the change in morphology of the axillary lymph nodes after chemotherapy and prior to surgery, and provide an assessment of whether the axillary nodes are now normalized or whether morphological abnormalities persist. AUS findings after chemotherapy have been shown to correlate with pathological findings at surgery. In the ACOSOG Z1071 trial, a secondary endpoint was to evaluate the role of AUS after NAC in women who presented with node-positive breast cancer (30). The study showed that the finding of abnormal nodes on axillary ultrasound after NAC was associated with an increased likelihood of finding residual positive nodes, in addition to increased axillary node burden. The study found that 71.8% of patients with an abnormal post-treatment AUS had residual nodal disease (30). These results are supported by a prior study from Mayo Clinic which evaluated the role of imaging of the axilla following NAC and delineated imaging findings of treatment response and correlated imaging response with surgical pathology. The sensitivity, specificity, negative predictive value, and positive predictive value of post NAC AUS was 69.8%, 58.1%, 56.8%, and 71.0% respectively (31).

Despite the limitations, imaging remains valuable to aid in assessing the response to chemotherapy and guide surgical options. Therefore, routine imaging is essential at the time of diagnosis and following the completion of NAC. Caution must be taken, however, when interpreting these results as imaging findings have limited accuracy and may under or overestimate response.

Considerations for surgery and timing of surgery after chemotherapy

Treatment decisions for patients treated with NAC are based both on the extent of the disease found at diagnosis as well as extent of residual disease after chemotherapy. As such, careful and accurate imaging is essential to identify the extent of both breast and axillary disease before and after treatment. By appreciating the patient history, examination and expectations prior to treatment, the surgeon will be able to use the documented response findings post treatment to plan surgical intervention and discuss options with their patient. It is routine practice to investigate all suspicious abnormalities noted within the ipsilateral or contralateral breast prior to initiation of chemotherapy (32). In addition, a radiopaque clip is routinely placed within all the abnormalities at the time of biopsy to mark the area for possible localization at time of post-chemotherapy surgical excision as well as to guide pathological assessment of the tumor bed, especially if a pCR is achieved. Recently, with the increased use of sentinel lymph node (SLN) surgery following NAC for patients with biopsy proven node-positive disease, methods have been suggested to decrease the SLN false negative rate, such as the use of a radiopaque clip within the positive node at the time of lymph node biopsy (33,34).

Breast conserving surgery versus mastectomy

Large clinical trials have reported that patients treated with NAC had higher rates of breast conservation compared with patients treated with adjuvant chemotherapy (2-5). In the NSABP-B18 study, 1,523 women with palpable, biopsy-proven breast cancer were randomized to receive four cycles of preoperative or postoperative doxorubicin and cyclophosphamide (2-4). Surgical intervention included lumpectomy and axillary lymph node dissection (with postoperative radiation) or a modified radical mastectomy. The 16-year results of the trial showed no statistical difference in overall survival, disease-free survival or relapse-free interval between the adjuvant chemotherapy and NAC groups (HR =0.99, P=0.90; HR =0.93, P=0.27; and HR =0.98, P=0.78 respectively) (4). There was a trend in favor of NAC chemotherapy for improved overall survival and disease-free survival in women younger than 50 years old. In relation to the type of operation performed, the frequency of lumpectomy was greater in the group treated with NAC (60% *vs.* 67%, P=0.002). In women with tumors ≥5.1 cm, there was an increase in the lumpectomy rate by 175%. In the European Organization of Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group 10902, 698 patients with T1c–T4b, N0–1, M0 tumors were enrolled and randomized to receive four cycles of fluorouracil, epirubicin and cyclophosphamide administered pre-operatively versus the same regimen administered postoperatively (5). At a median follow-up of 56 months, there was no significant difference in terms of overall survival, progression-free survival and time to locoregional recurrence (HR 1.16, P=0.38; HR 1.15, P=0.27; HR 1.13, P=0.61 respectively). Investigators were required to report the type of breast surgery indicated at the time of diagnosis. In the NAC group, 23% of patients were downstaged and underwent breast-conserving surgery and not the planned mastectomy.

Results from NAC trials have shown a non-significant increase in the local recurrence rate in patients treated with NAC. The NSABP B18 updated results showed no

significant difference in the rates of treatment failure at any specific site. The trial showed a trend toward having higher rates of ipsilateral breast tumor recurrence with NAC (13% *vs.* 10%, P=0.21). The NSABP B27 trial was designed to determine whether adding docetaxel (T) to preoperative doxorubicin and cyclophosphamide (AC) would increase survival in patients with operable breast cancer. Patients were randomized to receive four cycles of AC followed by surgery (group 1), to receive AC followed by T and then surgery (group 2) or to receive AC followed by surgery and then T (group 3). There was no statistically significant difference between the three groups for overall survival, disease-free survival or recurrence-free survival (7,35). More recently, meta-analyses of randomized trials of NAC have demonstrated a small and statistically significant increase in the risk of locoregional recurrence (1,36). A meta-analyses by Mauri *et al.* reported a relative risk of local recurrence of 1.22 (95% CI, 1.04–2.10) (1). In the Cochrane review by van der Hage *et al.* preoperative chemotherapy was shown to increase breast conservation rates at the associated cost of increased locoregional recurrence rates (36). The rate of locoregional recurrence was not increased as long as surgery remained part of the treatment after achieving complete tumor regression (HR 1.12; 95% CI, 0.92–1.37; P=0.25).

There have been no randomized studies that have compared breast-conserving surgery to mastectomy in patients who received NAC and radiation. A single institution study from MD Anderson Cancer Center reported on variables that correlated with ipsilateral breast tumor recurrence and locoregional recurrence in 340 patients treated with NAC followed by breast-conserving surgery and radiation therapy. The study found that clinical N2 or N3 disease, pathological residual tumor larger than 2 cm, a multifocal pattern of residual disease and lymphovascular invasion in the specimen correlated positively with recurrence (37). A model was subsequently constructed to predict locoregional recurrence based on a prognostic index on a scale of 0 to 4; an index score of 0 or 1 had a low risk of LRR of only 7%, a score of 2 predicting intermediate risk of LRR of 28% and a high score of 3 to 4 indicating a risk of 61% (38). A subsequent study compared the rates of LRR using the prognostic index for patients treated with mastectomy or breast conservation (39). In the 815 patients assigned the index score from 0 to 4, the 10-year LRR rates were low and similar for patients with a low score or 0 or 1. For patients with a score of 2, LRR was lower in those treated with mastectomy compared with breast conservation (12% *vs.* 28%, P=0.28). In patients with a score of 3 or 4 the LRR was significantly lower for patients treated with mastectomy (19% *vs.* 61%, P=0.009). Similarly, a more recent study by the same group evaluated the prognostic index in an independent cohort of 551 patients (40). The 5-year LRR free survival was similar between patients undergoing mastectomy or BCT when the score was 0, 1 or 2. When the score was 3 or 4, the 5-year survival was significantly lower for patients treated with BCT compared with mastectomy (31% *vs.* 7%, P=0.007). Together, these results support breast conserving surgery after NAC for appropriately selected patients.

Timing of breast surgery

The recommended time interval between completion of NAC and breast surgery has not been clearly defined. Large randomized clinical trials and reports from single institution studies evaluating the role of NAC in breast cancer did not address the relationship between interval from treatment to surgery and patient outcome. The practice to date has been based on results extrapolated from limited data in the adjuvant setting.

Two recently published studies evaluated timing of therapy, one looking at time to surgery after initial diagnosis and the other at time to initiation of adjuvant chemotherapy in patients with breast cancer. In the study by Bleicher *et al.* two independent population-based studies were conducted using the Surveillance, Epidemiology and End Results (SEER) Medicare-linked database and the National Cancer Database (NCDB) (41). The study showed that a longer delay from diagnosis to surgery is associated with lower overall and disease-specific survival. Chavez-MacGregor *et al.*, studied data from the California Cancer Registry and included 24,843 patients with stage I to III breast cancer and showed that there was no significant difference in patient outcomes provided that chemotherapy was started within 90 days of surgery, however adverse outcomes were associated with delaying the initiation of adjuvant chemotherapy 91 days or longer (42). This negative impact was greatest in patients with triple negative breast cancer, compared with hormone receptor positive and HER-2 positive patients. These data suggest that timeliness of treatment (both initiation of surgery and systemic therapy) impacts patient outcome. As such, we may be able to extrapolate that long delays to surgery in patients treated with NAC may affect patient outcome especially in those patients with high-risk tumor biology and those who do not achieve a pCR.

A recently published study by Sanford *et al.* was the first to evaluate the relationship between the time interval from completion of NAC to surgery and survival outcomes (43). This study from MD Anderson Cancer Center hypothesized that the time interval from completing NAC to surgery would not impact survival as the majority of the overall survival benefit from treatment is attributed to the systemic treatment of micrometastatic disease; and therefore, time to initiation of NAC would be the key time to impact survival rather than the timing between treatment modalities once therapy has been initiated. The study was a retrospective review of 1,101 patients diagnosed with stage I to III breast cancer. The study excluded patients who received NAC at an outside institution, those whose time interval from NAC to surgery was unknown and those with a time to surgery of more than 24 weeks. Time between NAC and surgery was categorized as <4 weeks (30.4% of patients), 4–6 weeks (47.6%), or >6 weeks (22%). The 5-year overall survival estimate was 79%, 87% and 81% respectively (P=0.03). There was no difference between the three groups in terms of locoregional recurrence-free survival or recurrence-free survival. The study addressed the timing of surgery in HER-2 positive and triple negative tumors and found that compared with 4–6 weeks, those that underwent surgery at ≤4 or >6 weeks had worse overall survival but this was not reflected in recurrence free survival or locoregional recurrence-free survival. Of note, the patients in these two cohorts was relatively small (n=275 and n=188 respectively). In addition, survival was not seen to be affected by achievement of a pCR. In multivariable analysis, patients who had surgery at 8–24 weeks had a worse overall survival but no difference in recurrence-free survival or locoregional recurrence-free survival. It is crucial to note that patients in the study were treated from 1995 through 2007 and as such would not be representative of a contemporary cohort treated today. In addition, causes of treatment delays were not assessed in the study.

Several considerations are to be kept in mind when deciding the timing to surgery including patient preference, chemotherapy regimen and dose given, the timing of the last dose of chemotherapy and complications noted during treatment with NAC. Complications during chemotherapy treatment are the key drivers to increased interval from treatment to surgery, and such complications may include sepsis, infections, requirement for transfusion or poor performance on treatment. With the goal of overcoming the neutropenic window, patients could generally be scheduled for surgery after a three-week interval in the absence of complications. In addition, accepted practice would include increased caution in patients receiving dose dense therapies as well as those with a suggestion of poor marrow reserve. A longer interval time is practiced to allow for recovery after treatment. The potential increased risk of surgical complications is an additional concern regarding the timing of surgery after NAC. However, studies to date have not demonstrated an increased morbidity in patients receiving NAC (44-47).

NAC regimens may include treatment with HER-2 targeted therapies, such as trastuzumab (Herceptin), which involves treatment extending to the adjuvant setting. Frequent cardiac monitoring is routine and continues at three-monthly intervals while on treatment and then six-monthly for at least two years following completion of Herceptin therapy. There is no evidence that Herceptin should be held during the peri-operative period, unless the patient develops a decline in the left ventricle ejection fraction (LVEF) of 16 or more percentage points from baseline or 10–15 percentage points from baseline to below the lower limit of normal. In this setting, Herceptin is withheld for four weeks and the LVEF is reassessed.

Data regarding treatment with newer and trial agents are limited. However, clinicians would practice caution and might prefer a slightly longer interval, especially in patients receiving anti-angiogenesis agents.

Timing of nodal staging

Historically, a complete axillary lymph node dissection was standard of care for axillary nodal staging. Level I and II (± III) dissection was accepted to provide local control and staging information at the expense of risk of significant morbidity from lymphedema and reduced shoulder mobility. SLN surgery subsequently emerged as a safe, accurate and minimally invasive alternative to axillary lymph node dissection in clinically node-negative breast cancer patients (48-50). Sentinel lymph node biopsy, in addition, is associated with a low false negative rate and a lower morbidity rate compared with axillary lymph node dissection.

It is accepted that axillary lymph node status remains an important prognostic marker for breast cancer patients impacting both local and systemic treatment decisions after NAC. The management of the axilla in patients treated with NAC has continued to evolve. Traditionally, axillary management was determined by nodal staging at presentation through both clinical and imaging assessment

and surgical staging of the axilla with SLN surgery. At that time, there was limited information available on the feasibility and accuracy of SLN biopsy following NAC.

Clinically node negative

The role of SLN surgery after NAC in patients with clinically node-negative disease has been questioned and addressed in the literature by several single institution studies, multicenter studies and several meta-analyses.

Several early small single institution studies reported low SLN identification rates, ranging between 70–100%, and high false negative rates, ranging between 0–39% (51-59). The NSABP-B27 multicenter trial sought to determine whether adding docetaxel to neoadjuvant doxorubicin/cyclophosphamide chemotherapy would improve disease-free and overall survival in patients with operable breast cancer (4). A subsequent analysis was performed to evaluate the role of SLN biopsy after NAC in 428 of the patients enrolled in NSABP B27 (60). The success rate for the identification and removal of a sentinel node was 84.8%. The success of the procedure was increased with the use of radioisotope (87.6–88.9%) compared with cases where lymphazurin alone was used (78.1%, P=0.03). The false negative rate reported in the study was 10.7%. There was no significant difference in the false negative rate according to age, clinical tumor size, clinical nodal status at presentation, method of lymphatic mapping and breast tumor location. The false negative rate observed in this study was comparable to other multicenter trials where SLN surgery was performed prior to NAC (false negative rates reported between 7–13%).

The Ganglion Sentinelle et Chimiotherapie Neoadjuvante (GANEA) study was a large French prospective multicenter study addressing the same question in 195 patients (61). The SLN identification rate was 90% and the false negative rate was 11.5%. The study found that patients with clinically node-negative disease prior to NAC had better SLN identification rates compared to clinically node-positive patients (94.6% *vs.* 81.5%, P=0.008). The false negative rate did not correlate with clinical node status at presentation (9.4% *vs.* 15%, P=0.66).

A more recent large single institution study from MD Anderson Cancer Center compared outcomes in clinically node-negative patients undergoing SLN after NAC versus patients undergoing surgery first (14). SLN identification rates were 97.4% in the patients treated with NAC and 98.7% in the surgery first group (P=0.017). The false negative rate was similar between the groups (5.9% *vs.* 4.1%, P=0.39). The study showed that the overall rate of axillary lymph node dissection (ALND) was similar between the two groups (27.1% *vs.* 28.9%, P=0.38), however this rate was lower in patients treated with NAC when the results were analyzed by presenting T stage. On assessment of survival, adjusting for clinical stage, there was no difference in the locoregional recurrences, disease-free or overall survival between the two groups.

Kelly *et al.* performed a systematic review and meta-analysis of 24 studies, including 1,799 patients, and reported overall SLN identification rate of 89.6% and SLN false-negative rate as 8.4% (62).

In summary, these data all suggest that SLN surgery after NAC, at time of definitive breast surgery, is a reliable procedure for axillary staging of patients treated with NAC to identify patients with residual nodal disease. Therefore, for patients with clinically node-negative disease at presentation one may proceed with SLN assessment prior to or following treatment. SLN surgery after NAC allows both the axillary staging and breast tumor resection to be performed at one operation and decreases the rate of positive lymph nodes found at surgery, lowers the axillary node burden and decreases the likelihood for ALND (13,14,63). Most importantly, it allows assessment of response to chemotherapy which is important to assess outcome.

Clinically node positive

Several prospective trials have been conducted to evaluate the false negative rate of SLN after NAC in patients presenting with node-positive breast cancer, including the ACOSOG Z1071, SENTINA and FN SNAC trials.

The ACOSOG Z1071 trial enrolled 756 women with clinical stage T0–T4, N1–N0, M0 breast cancer (64). Of 649 eligible patients, a SLN could not be identified in 46 patients (7.1%) giving an identification rate of 92.9%. The false negative rate of SLN surgery in patients with 2 or more SLNs resected was 12.6%. The false negative rate was significantly lower when a dual-agent mapping technique (10.8%) versus a single-agent mapping (20.3%, P=0.05) technique was used. In addition, the false negative rate was even lower when 3 or more SLNs are evaluated.

The SENTINA trial was a four-arm, prospective multicenter cohort study designed to evaluate the timing of SLN surgery in patients undergoing NAC (65). This included a group of patients with clinically node-positive

disease who converted to node-negative disease after treatment and underwent SLN surgery and ALND. The SLN identification rate in this group (arm C) was 80.1%. The false negative rate in this group was 14.2% (24.3% when one node was removed and 9.6% for those who had two or more SLNs removed). As in Z1071, dual mapping reduced the false negative rate (8.6%).

A Canadian trial (SN FNAC study) included 153 patients with biopsy proven node-positive breast cancer that underwent both SLN surgery and axillary lymph node dissection after NAC (66). SLN metastases of any size (including isolated tumor cells) were considered positive. The SLN identification rate in the study was 87.6% and the false negative rate was 8.4%. Similar to ACOSOG Z1071 and SENTINA, removal of only one SLN was associated with a higher false negative rate (18.2%) compared with a lower false negative rate (4.9%) when two or more SLNs are removed. Additionally, the dual tracer technique with radioisotope and blue dye was advocated as it was also associated with a lower false negative rate (5.2%).

Together the results from these trials show that SLN surgery after NAC with removal of at least two SLNs is reasonable for axillary staging of residual disease post chemotherapy and can be performed at the time of definitive resection of the breast tumor.

Most recently, analysis of a subset of patients who had a clip placed in the lymph node at the time of initial biopsy and confirmation of metastatic disease in the ACOSOG Z1071 trial was reported. The purpose of the study was to evaluate the clip location at surgery (in the SLN or ALND). The false negative rate of SLN surgery was 6.8% in the 107 cases where the clipped node was identified within the SLN specimen compared to 19.0% in the 34 cases where the clipped node was in the ALND specimen and not in one of the SLNs (33). In cases without a clip placed and in those where the clipped node location was not confirmed at surgery the false negative rate was 13.4% and 14.3%, respectively.

Caudle *et al.* reported a prospective trial determining the feasibility of image-guided localization and resection of lymph nodes containing known metastases (34). The study enrolled 12 patients with node-positive disease at diagnosis, 10 of whom were treated with NAC. A clip was placed in the lymph node targeted for biopsy. After treatment, two patients underwent wire localization and 10 patients underwent localization using I-125 radioactive seed placement. Image-guided localization and selective surgery was successful in all patients. From the overall group, and in those undergoing SLN surgery, seed placement did not interfere with lymphoscintigraphy and the clip-containing node was the SLN in 80% of the patients. In those that were treated with NAC and underwent an axillary dissection, 44% had residual nodal disease which was identified in all patients within the clipped node. This study did not assess the associated false negative rate of targeted axillary dissection, but was able to demonstrate that clipped nodes may be safely identified and removed at the time of surgery.

Advantages of SLN surgery before or after NAC

SLN surgery prior to NAC has the advantage of providing accurate pathological staging of the axilla at presentation and avoiding the historical uncertainty associated with the false negative rates of SLN surgery after NAC. Proponents of SLN surgery after NAC recognize the benefits of proceeding with one surgery for both the breast and the axilla, the prognostic information gained from SLN assessment after treatment, the reduced risk of having positive lymph nodes in addition to a lower axillary lymph node burden and reduction in the chances of proceeding to ALND.

Future directions

Two current trials are addressing the axillary management in node-positive patients treated with NAC. Patients who are found to be SLN positive may be enrolled in the Alliance 11202 trial which randomizes patients with T1–2, N1, M0 breast cancer to a completion ALND followed by breast/chest wall and nodal radiation (without radiation to the dissected axilla) versus no further axillary surgery and breast/chest wall and nodal radiation. Patients who are found to be SLN negative, on the other hand, may be enrolled in the NSABP B-51/RTOG 1304 (NRG 9353) which is evaluating the role of radiation in patients with documented positive nodes (T1–3, N1, M0 breast cancer) who convert to pathologically node-negative disease after NAC. In addition to the type of definitive surgery, patients are stratified according to hormone receptor and HER-2 status and whether a pCR was achieved. Patients are then randomized to no regional nodal radiation (breast radiation is given if the patient proceeds with breast conserving surgery, but no chest wall radiation is given to patients proceeding with mastectomy) versus regional nodal radiation (breast radiation is given if patients proceed

with breast conserving surgery or chest wall radiation in mastectomy patients). The results of these are forthcoming and will provide us with additional information about the management of patients with node-positive disease who are treated with NAC.

Conclusions

NAC has evolved to become an important treatment option for patients with breast cancer and impacts surgical decision making. NAC increases breast conservation rates with an associated low risk of local recurrence. In addition, NAC has been shown to convert clinically node-positive patients to pathologically node-negative status, treat occult axillary disease in clinically node-negative patients, and decrease the likelihood of node-positive status at surgery. SLN surgery has been shown to be accurate and acceptable in patients with node-negative disease and feasible in patients with node-positive disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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