3

Surgical Intervention Following Neoadjuvant Chemotherapy in Breast Cancer

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1. Introduction

The concept of pre-operative, or neoadjuvant, chemotherapy for breast cancer initially arose to deal with patients that were deemed non-operable at the time of diagnosis.[1] These were patients with locally advanced disease (usually Stage III) or those with inflammatory breast cancer. As experience in this population grew, it became obvious that many patients who were unresectable at the time of diagnosis were down-staged by chemotherapy. Not only did this improve survival by up to 25%, but it also made many tumors amenable to surgical intervention, usually with a mastectomy.[2, 3]

The first large prospective randomized trial to determine the usefulness of preoperative chemotherapy in women with operable tumors was the NSABP B-18 study that began in 1988. In this study, 1523 women with palpable, biopsy proven breast cancer were randomized to 4 cycles of preoperative or postoperative AC (doxyrubicin 60 mg/m^2 and cyclophosimide 600mg/m^2). [4] The surgical intervention was either a lumpectomy with axillary lymph node dissection or a modified radical mastectomy. The patients who had breast conservation underwent post-operative radiation treatment. The primary endpoints of this trial were overall survival (OS), disease free survival (DFS), and relapse free interval (RFI). The 16 year results of this study were published in 2008.[5] There was no statistically significant difference in OS (P=.90), DFS (P=.27) or RFI (P=.78) between the pre and postoperative chemotherapy groups. The B-18 trial did show a statistically significant improvement in the breast conservation rate following preoperative chemotherapy. That is, lumpectomy was more common in patients receiving preoperative chemotherapy (67% *vs* 60%, P=0.002).

The B-18 trial was followed in 1995 by the NSABP B-27 study. This study evaluated the addition of T (docetaxel 100mg/m^2) to the neoadjuvant regimen. Women were randomized to 1) 4 cycles of preoperative AC followed by surgery 2) 4 cycles of preoperative AC followed by 4 cycles of T then surgery or 3) 4 cycles of preoperative AC, surgery and then 4 cycles of T.[6] While this did show that the addition of docetaxel appeared to increase the number of pathologic complete responses versus AC alone, it did not show an improvement in OS or DFS with the addition of a taxane.[5] Based on the B-18 and B-27 trials, however, neoadjuvant chemotherapy became accepted in a broad population of patients, not just in patients with non-operable tumors.

Neoadjuvant chemotherapy has many additional benefits beyond increased breast conservation rates. The use of preoperative agents allows for in vivo assessment of tumor

response. [3] The ability to monitor tumor response allows the clinician to assess effectiveness of an agent against that particular mass. The tumor response to chemotherapy has important prognostic implications. In the B-18 trial, women who had a pathologic complete response (pCR) had superior outcomes compared with women who did not (OS HR=0.32, *P*<.0001; DFS HR=0.47, *P*<.0001).[5] This was again shown in the B-27 trial with pCR improving OS (HR=0.36, *P*<.0001) and DFS (HR=0.49, *P*<.0001).

Another logical and common use of neoadjuvant chemotherapy is for clinical trials. By assessing the in vivo response, researchers are able to get almost immediate feedback on the effectiveness of novel regimens. Doing this in an adjuvant setting would often require large numbers of patients and years of follow-up. In addition, tumor biopsies taken while on trial allow evaluation of biologic correlates and gene expression changes during therapy.

2. Indications for neoadjuvant chemotherapy

Neoadjuvant chemotherapy continues to be the standard of care for patients with locally advanced and inflammatory breast cancers. Locally advanced tumors include those with skin or chest wall involvement and patients with bulky lymphadenopathy. As described previously this therapy can potentially convert those with unresectable tumors into candidates for mastectomy.

Currently the use of neoadjuvant chemotherapy has been expanded to include patients with large tumors that would typically require mastectomy. In these patients the goal of preoperative chemotherapy is to make breast conservation an option. As previously described, the B-18 trial clearly showed that neoadjuvant chemotherapy leads to an increased rate of lumpectomy (67% *v* 60%).[5]

The standard cutoff for use in the setting of large tumor burden is 4 centimeters or greater. However, use in all T2 (2-5cm) lesions is becoming more commonplace. In a study by Christy et. al. it was determined that neoadjuvant chemotherapy significantly reduced the rate of reoperation for positive margins in patients whose tumors measured between 2-4 cm.[7] This study, which was retrospective, evaluated patients with T2 tumors less than 4 cm in size and compared reoperation rates in the pre and postoperative chemotherapy groups. There was a significantly decreased number of positive margins in the patients who received preoperative chemotherapy (10% *v* 32%, *P*=<0.01). This led to a decreased rate of reoperation (3% *v* 35%, *P*=<0.01) and mastectomy (3% *v* 19%, *P*=<0.01). These findings make a compelling argument for use of preoperative chemotherapy in women with T2 tumors who are interested in breast conservation.

An obvious caveat to this recommendation is that patients considered for neoadjuvant chemotherapy must have a clear indication that they would normally receive adjuvant chemotherapy. In other words, the medications must be oncologically indicated, not used simply to decrease the size of the tumor for breast conservation. Most younger patients with tumors larger than 2 cm or node positive disease would fall into the group where chemotherapy is clearly indicated and therefore may be candidates for preoperative treatment.

Another consideration for preoperative chemotherapy is patient age. In the B-18 trial, women under the age of 50 appeared to have the greatest benefit from preoperative therapy. With 16 years of follow-up, that study shows overall survival in women under the age of 50 was slightly better in the preoperative chemotherapy group (61% *vs* 55% (*P*=0.06)).[5] While this finding did not reach statistical significance, it is certainly a compelling trend. This trend was also seen in DFS for this group at 44% *v* 38% (*P*=0.09). Conversely, women over

the age of 50 appeared to do better with standard, adjuvant chemotherapy, with OS at 50% in the preoperative group versus 55% in the postoperative group (*P*=. 07) Although these results were of borderline statistical significance, we feel that most women under 50 with larger tumors should at least be considered for neoadjuvant therapy.

3. Surgical considerations after neoadjuvant chemotherapy

Tumor localization

It is imperative that a surgeon be involved in the care of a patient undergoing neoadjuvant chemotherapy from the onset. Surgical planning is best done when the surgeon is able to evaluate the tumor prior to any treatment effect. This allows both the surgeon and the patient to have a reasonable understanding of post-therapy surgical options.

It is also imperative that a radiopaque marker be placed with a core biopsy instrument in the tumor at the time of diagnosis. In a study by Oh et. al. a retrospective review was done of 373 patients undergoing preoperative chemotherapy followed by lumpectomy to evaluate the need for marker placement.[8] Of the 373 patients studied, 145 had radiopaque markers placed and 228 did not. With a follow up of approximately 4 years, the patients with marker placement had an improved rate of local control versus those that did not have a marker placed (98.6% *v* 91.7%, *P*=0.02). This improved rate of local control likely represents a much better ability to accurately localize the site where the tumor was prior to treatment.

The increased use of preoperative chemotherapy in breast cancer prompted a National Institute of Health Conference on local-regional treatment following chemotherapy. This conference held in March, 2007 sought to standardize many aspects of regional treatment after preoperative chemotherapy, including pretreatment clip placement.[9] In the statement from this conference the recommendation is: "*Radiopaque clips should be placed within all abnormalities at the time of biopsy to provide localization for subsequent surgical removal and pathologic assessment of the tumor bed if there is a complete clinical and radiologic response.*" Based on this recommendation it is our practice to place a marker whenever possible.

In addition to radio-opaque marker placement, another novel technique for tumor localization has been recommended by Lannin et. al. This technique involves pretreatment tattooing of the margins of the palpable tumor area by the surgeon (Figure 1).[10] By marking the area of involvement prior to chemotherapy, the surgeon is able to remove the entire area once the treatment is done. This method takes into account the possibility that when the tumor shrinks with chemotherapy it may not shrink concentrically but rather in a honeycomb fashion leading to many microscopic islands of disease within the breast (Figure 2).[11] It is theorized that this honeycomb regression, which can be seen in up to 40% of tumors, may lead to the trend for increased rates of local recurrence that were seen in the B-18 trial (13% *v* 10%, *P*=0.21) and other similar trials.[5, 12] Another benefit of this technique is that the tattooing often obviates the need for needle localization at the time of definitive surgery.

4. How much breast tissue needs to be removed following chemotherapy?

Surgery continues to be the standard of care following neoadjuvant chemotherapy. The down-staging of tumors to make them amenable to breast conservation is one of the primary benefits of preoperative treatment. This benefit, however, presents a conundrum for the surgeon; if the patient appears to have had an excellent clinical response how much breast tissue should be removed?

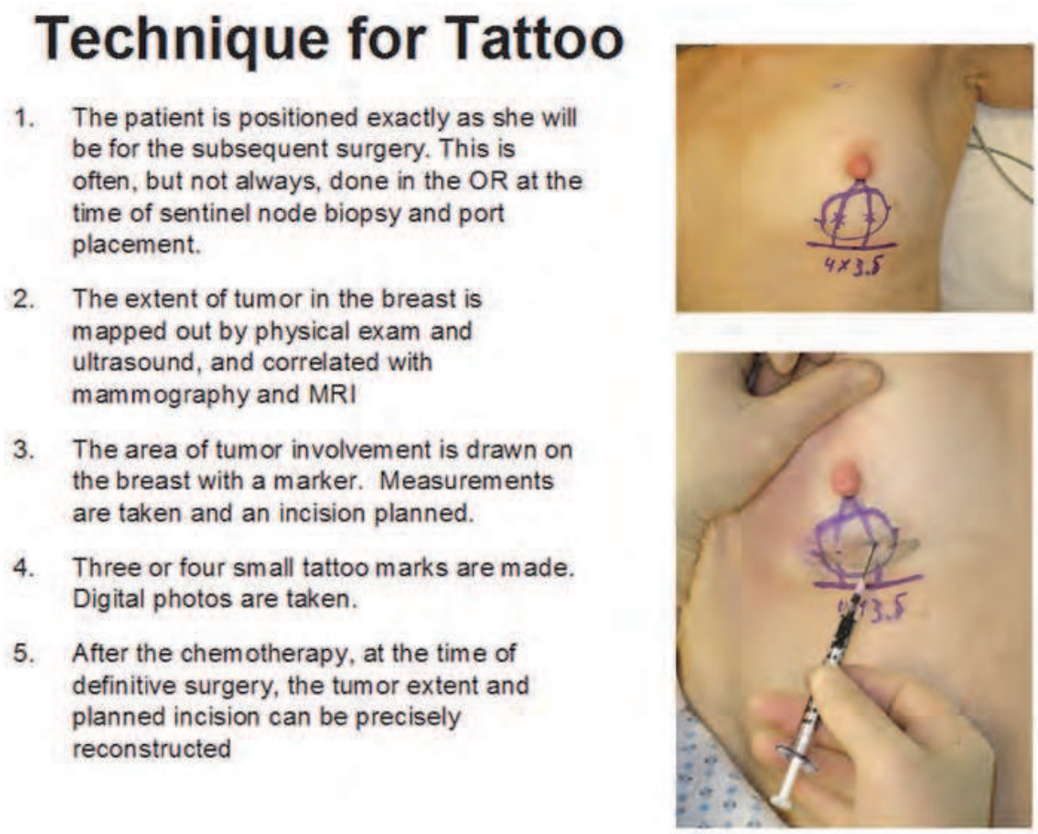


Fig. 1. Technique for placement of tattoos prior to neoadjuvant chemotherapy.

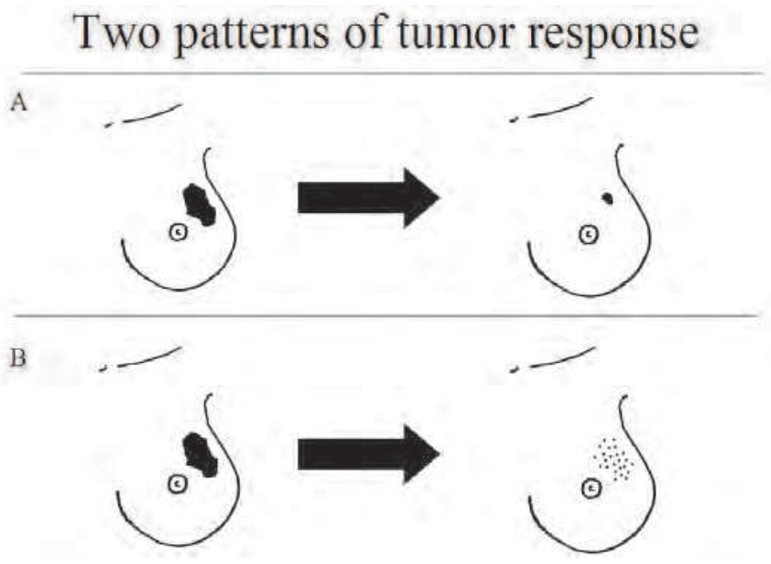


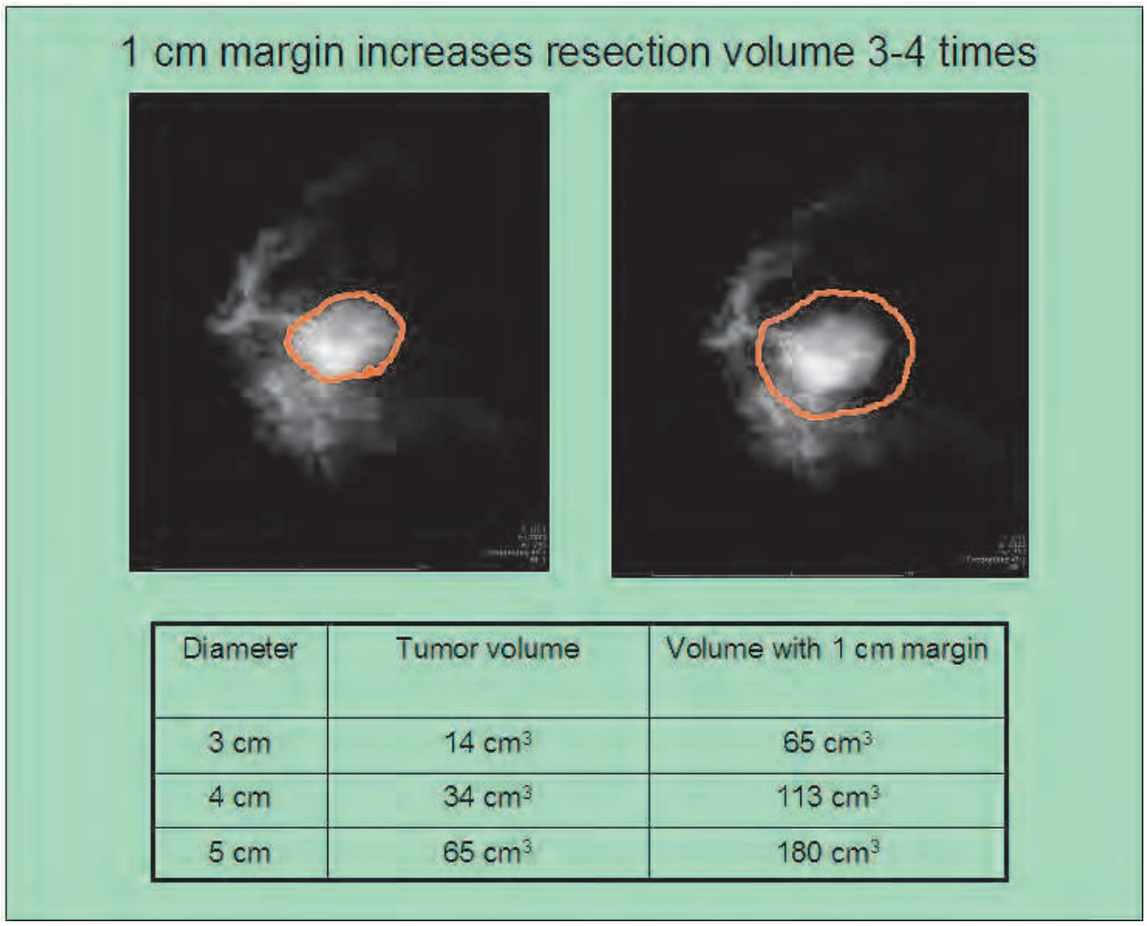
Fig. 2. Types of response to neoadjuvant chemotherapy. Our experience is that about 25% of patients have a complete pathological response and about 5% have no response. The remaining 70% are fairly evenly split between a type A or a type B response, or a combination of both.

This conundrum is exacerbated by the fact that preoperative neoadjuvant chemotherapy followed by breast conservation therapy (BCT) has been found in some studies to lead to an increased rate of local recurrence (LRR). While this was not statistically significant in the B-18 trial, other studies have shown a definitive increase in local recurrence. Mauri et.al. published a meta-analysis of neoadjuvant trials in 2005. This analysis looked at 9 trials comparing adjuvant to neoadjuvant chemotherapy. Encompassing nearly 4000 patients this study showed a 22% increased relative risk of local recurrence in the neoadjuvant treatment arm (P=0.015).[13] While at first blush this number is large enough to make BCT seem implausible, a limitation to this study was the inclusion of trials where radiation was used without surgery. In these trials, as one might expect, there was a substantial increase in LRR. Never the less the trend toward increased LRR does mandate careful surgical planning in order to minimize this risk.

Following chemotherapy, patients need to be evaluated in a multimodal fashion to determine if they are candidates for breast conservation. Breast examination is often done in conjunction with some combination of mammography, ultrasound (US) and magnetic resonance imaging (MRI). Unfortunately there is no one modality that has been shown to have 100% accuracy in the neoadjuvant breast population. In fact, many studies show that each modality is flawed. In a study by Chagpar et. al., 182 patients undergoing neoadjuvant chemotherapy were retrospectively evaluated to assess the accuracy of physical examination, mammography and US for size determination after chemotherapy.[14] Patients were evaluated with all modalities at the time of diagnosis and again prior to surgery, and physical exam and imaging measurements were then compared to the final pathologic measurements. The correlation between pathology and preoperative assessment was moderate at best, with accuracy (+/- 1 cm) at 66% for physical exam, 75% for US and 70% for mammography.

Findings like these have prompted evaluation of MRI in the neoadjuvant population. In a study by Segara et.al., the effectiveness of physical exam and US were compared to MRI at the time of diagnosis and prior to surgery, and again the measurements were compared to final pathology.[15] In this study MRI was slightly superior to the other modalities. They found that the size was accurately predicted (+/- 1cm) in 76% of patients with MRI, 66% with US and 54% with physical exam.

It is clear that no single radiological modality will provide a perfect prediction of residual tumor volume. As a result, it has been suggested that the safest approach following neoadjuvant chemotherapy is to remove the entire volume of breast that was affected by tumor prior to treatment.[16] Advocates of this approach cite the frequency of swiss-cheese-like regression of the tumor and the likelihood of leaving residual tumor cells with lesser resections.[10] While at first glance this appears to negate the benefit of chemotherapy for cytoreduction and breast conservation, this actually is not the case. Figure 3 shows that, for tumors in the 3-5 cm range, the volume of tissue that must be resected to include a 1 cm margin of normal breast tissue around the tumor is actually 3 to 4 times greater than if a very narrow margin is taken. The real value of chemotherapy, therefore, is to allow a pathologically negative margin without removing a wide rim of normal tissue. The goal of surgery after chemotherapy is to resect all of the original tumor and as little as possible of the surrounding normal breast tissue. With the tattoo technique described earlier, the tumor margins are marked and the incision planned prior to the chemotherapy when it can be easily identified by palpation and/or ultrasound. The patient is tattooed and pictures are taken. After the chemotherapy, the original tumor margins can be precisely reconstructed and the exact original tumor volume is resected. (See figure 4)



Diameter	Tumor volume	Volume with 1 cm margin
3 cm	14 cm^3	65 cm^3
4 cm	34 cm^3	113 cm^3
5 cm	65 cm^3	180 cm^3

Fig. 3. Calculated volume of a sphere with and without a 1 cm margin for tumors between 3 and 5 cm. This is the mammogram for the patient shown as case number 1 in Figure 4.

Whatever technique is utilized to determine the area of resection, the surgical tenet of clear margins must be adhered to. It is important that the tissue is sent to a pathologist familiar with tissue changes seen after chemotherapy so that an accurate assessment can be made of margins and response. It is also critically important that the pathologist be informed that the patient had preoperative chemotherapy as it can make interpretation of the specimen more difficult. The tissue after chemotherapy will show varying degrees of fibrosis and cell death.

5. Evaluation of sentinel lymph nodes

The timing of sentinel lymph node biopsy in the neoadjuvant breast patient is one of the most controversial topics in surgical oncology. Initial studies regarding the efficacy of sentinel lymph node biopsy after neoadjuvant chemotherapy showed an unacceptably high rate of false negatives. In one small study, up to 30% of patients undergoing sentinel lymph node procedures after chemotherapy had falsely negative nodes. [17]

As experience with sentinel lymph node biopsy increased, the rate of false negatives decreased. The largest study to date dealing with this topic is the NSABP-B27. In this study 428 women had an attempted sentinel lymph node procedure following neoadjuvant chemotherapy. [18] Of these women, 343 had at least one sentinel node identified followed

by a completion axillary dissection. In this group of women there were 15 women that had a negative sentinel lymph node with metastatic disease found in at least one non-sentinel lymph node. This led to a false negative rate of 10.7% and an overall success rate of 84.8%. This compared favorably to patients undergoing sentinel lymph node procedures without preoperative chemotherapy. In the NSABP B-32 trial, the rate of false negatives was 9.8% with an overall success rate of 97.2%.[19] While this shows that overall identification rates are lower after neoadjuvant therapy, the false negative rate is acceptable.[20]

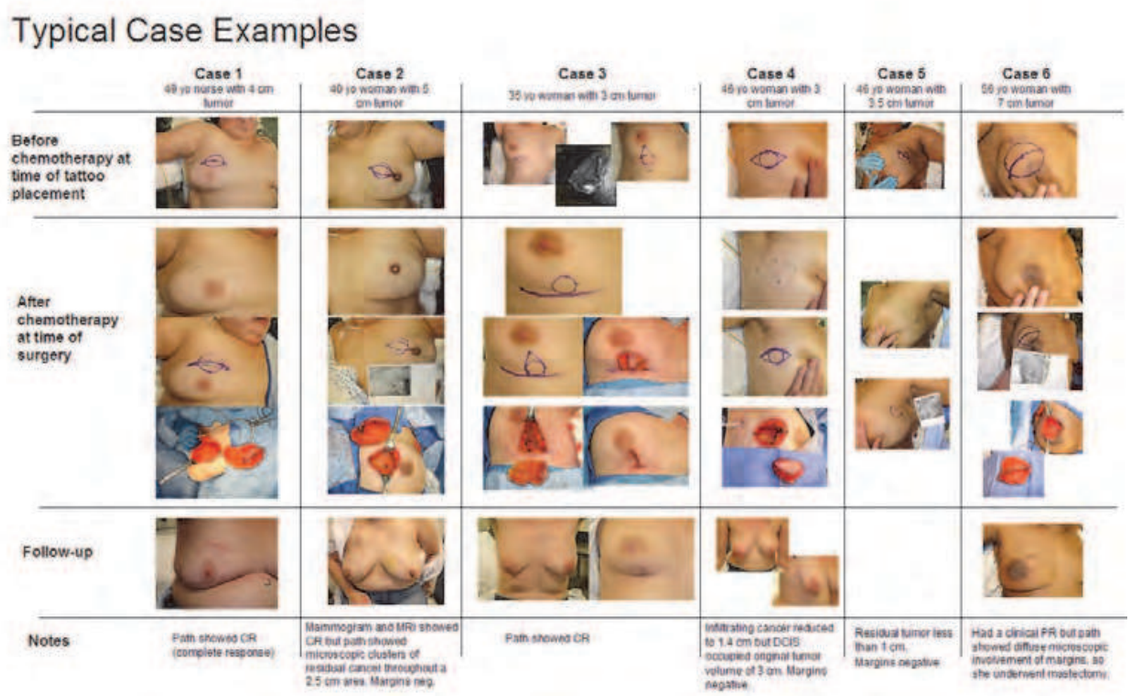


Fig. 4. Representative cases showing pictures before chemotherapy, several months later at the time of surgery, and after several more weeks of follow-up post-operatively.

The advantages and disadvantages of sentinel node biopsy before and after chemotherapy are nicely reviewed in a recent paper by Grube, et al. [21] Sentinel lymph node biopsy performed before chemotherapy has a higher rate of identification (97.2% v 84.8%)[18, 19] This could potentially save a patient from an axillary dissection if a successful sentinel procedure prior to chemotherapy showed a lymph node negative for metastatic disease. While the false negative rates are similar (10.7% v 9.8%) there is a slight advantage in overall accuracy by removing the nodes pre-chemotherapy. The disadvantage of sentinel lymph node biopsy pre-chemotherapy is that up to 30% of patients will have downstaging of their axilla with the preoperative treatment. [22] In these patients, a positive SLNB done before chemotherapy will mandate an unnecessary axillary lymph node dissection after chemotherapy. Doing the sentinel node procedure before chemotherapy also mandates two operations and may delay the onset of chemotherapy.[11]

Advocates of doing the sentinel lymph node procedure after chemotherapy cite the similar false negative rate seen in these patients and feel that this is an oncologically safe procedure.[20] Additionally they cite the potential downstaging of the axilla as a benefit and

feel that this may save patients from axillary dissection. The ability to perform just one surgery is also felt to be an advantage. The possible disadvantages include potentially higher false negative rates and lower rates of identification.

6. Conclusions

Neoadjuvant chemotherapy has become much more common in patients treated for breast cancer. Once performed only in patients with locally advanced or inflammatory breast cancers, it is now used in a much wider population of patients. Current evidence would suggest that preoperative chemotherapy should be considered in women with tumors larger than 2 cm who are interested in breast conservation. It should also be considered in women under the age of 50 as there is a trend for survival benefit. Preoperative treatment may also be considered in women who are interested in participating in a clinical trial testing many of the exciting new drugs that are becoming available.

In patients electing neoadjuvant treatment, it is important that surgical input is elicited from the onset. A radiopaque marker should be placed in the tumor at the time of diagnosis to facilitate localization after tumor regression. Tumor tattooing done prior to chemotherapy may assist in post treatment resection and may obviate the need for needle localization. As always, removal of the tumor to clear margins is imperative. Timing of the sentinel lymph node biopsy continues to be controversial and there is no clear consensus whether a pre- or post- chemotherapy protocol is most advantageous.

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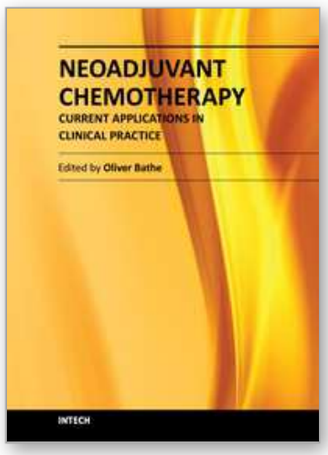

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The most significant advances in cancer therapy in recent years have involved the development of systemic therapeutics. With improvements in response rates in solid tumors, opportunities have arisen to enhance the effectiveness of surgery. Administration of systemic therapy prior to surgery - neoadjuvant chemotherapy - represents one approach by which clinicians have successfully reduced the extent of surgery and, in some instances, positively impacted on clinical outcomes. This collection of works by expert clinicians from a variety of disciplines represents an exploration of the current knowledge of the role of neoadjuvant chemotherapy in diverse tumor types.

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