Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy for Breast Cancer

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Breast cancer is the second most common cancer worldwide, affecting nearly one in eight women [1]. Accurate cancer staging is essential for determining the patient’s prognosis and for choosing the appropriate treatment. The staging system most often used is the American Joint Committee on Cancer (AJCC) TNM system, where T refers to the size of the tumor, N refers to spread of the primary cancer to nearby lymph nodes, and M refers to the spread of metastasis to distant sites in the body [2]. While the prognosis of patients with breast cancer is known to depend on many factors, one of the most important prognostic indicators is the extent of axillary lymph nodal involvement [3]; metastasis to these lymph nodes has been shown to decrease the 5-year survival rate by 28-40% [4]. Therefore, determining lymph node involvement is of great importance, as it is one of the main factors that guides local, regional, and systemic treatment decisions [5].

Axillary management for patients with breast cancer has significantly evolved over the past decade. Recent trends have shifted from axillary lymph node dissection (ALND) to a less invasive sentinel lymph node biopsy (SLNB) in patients presenting with clinically node-negative disease (cNo) [6]. SLNB can accurately spare node-negative patients an operation from which they cannot benefit. While patients with node positive disease may undergo ALND, it is preferable for patients with clinically node-negative disease to undergo SLNB as this procedure avoids the complications that often follow ALND such as upper extremity lymphedema and paresthesia. [7-9]. Sentinel lymph node surgery allows the surgeon to identify the first lymph node(s) that the primary tumor drains into. Therefore, if there are no metastases in the sentinel lymph node(s), it is predictive of non-sentinel axillary lymph nodes [10].

During a sentinel lymph node biopsy, single or dual tracer (radiolabeled colloid and blue dye) is injected into the breast either peri-tumorally or periaereolar and taken up by the breast lymphatics. Lymph nodes that are blue, radioactive, or palpably abnormal are resected and undergo further pathological analysis. Blue dye was first used to identify the SLN in melanoma in 1992. Soon after, Krag et al. and Giuliano et al. were the first to use radioisotope and blue dye tracers, respectively, to locate the SLN in patients with breast cancer [11,12]. In 1996, Albertini was the first to report the technique of combining the two methods [13]. Despite success with each method individually, we support the use of combined tracer. Combination dye and isotope technique has been shown to best identify the SLN with the lowest false negative rate (FNR) when compared to either tracer alone [14]. The median number of SLNs in the non-neoadjuvant setting is two. Histological examination of lymph nodes is the most accurate way to identify metastasis in the lymph nodes [15].

The relevance of metastases in the SLN has been questioned over recent decades with regard to predicted risk for non-sentinel node metastases. Various groups set out to determine which patients with SLN metastases would actually benefit from additional ALND (i.e., which patients were likely to have non-sentinel metastases). In 2014, Koca et al. validated 14 existing models for prediction of non-sentinel node metastases, and they found that tumor size, presence of lymphovascular invasion, extranodal extension of SLN, large size of metastatic SLN, number of negative SLNs, and multifocality were independent predictive factors for non-SLN metastases [16]. These findings may be used to guide decisions regarding adjuvant therapy and need for further axillary surgery.

Though it is well-established that SLNB predicts axillary nodal status with high accuracy, it has recently come into question whether SLNB following neoadjuvant...

chemotherapy (NAC) is as reliable. In the 1970s, neoadjuvant chemotherapy was first introduced for the treatment of patients with locally advanced breast cancer [17]. Neoadjuvant chemotherapy not only allows tumor response to be assessed in situ, but it also downstages tumor burden in the breast or axilla. The latter is particularly beneficial as it allows for less extensive surgery, i.e., ALND [15]. SLNB after chemotherapy provides information about residual nodal disease in order to guide regional therapy. It is important to determine whether there is residual tumor in the axillary lymph nodes after preoperative chemotherapy in patients with breast cancer so that they can be removed to improve local control and because the finding of residual disease is an independent prognostic factor [18].

One potential downfall of chemotherapy is that it leads to shrinkage and fibrosis, while also inducing emboli and debris to deposit in lymphatic channels [19]. As a result, lymphatic drainage routes may be altered, thus decreasing identification rates of the SLN following preoperative chemotherapy. The sentinel node concept is most reliable when primary organ lymphatic channels are free from malignant obstruction. Further, there is concern that chemotherapy may cause histological changes of metastases and lymph nodes, thereby interfering with the accuracy of N staging via SLNB [20]. Because the reliability and accuracy of SLNB following chemotherapy is unknown, many groups sought to assess the FNR of SLNB following NAC. False-negatives occur when metastases are not identified in the SLN but are found in non-sentinel axillary lymph nodes. False negative rates have varied historically across the board, ranging from 0 [21] to 19.4% [22]. In studies on SLNB in clinically node-negative patients who underwent surgery without any prior chemotherapy, FNRs < 10% have been deemed oncologically acceptable [23].

In lieu of randomized trials to guide practice, Xing et al. conducted a meta-analysis in 2006 to assess the use of SLNB after NAC [24]. The authors concluded that SLNB following preoperative chemotherapy appears to be an accurate and reliable technique for determining the need for axillary treatment in patients who are clinically node-negative. This group estimated the sensitivity of SLNB after preoperative chemotherapy to be 88% with a false negative rate of 12%. Thus, it was demonstrated that SLNB is a reliable technique for identifying or ruling out lymph node metastases in patients who underwent neoadjuvant chemotherapy.

More recently, in 2016, Geng et al. published a systematic review and meta-analysis on the accuracy of SLNB after NAC for initially clinically node-negative breast cancer [25]. They included 16 studies that were published from 2000 to 2015. In 2019, Shirzadi et al. published a meta-analysis that assessed SLNB after NAC in two cohorts: patients who were initially node negative (n=23 studies) and patients who were initially node positive and converted to node negative (n=13 studies) [19]. Geng et al. calculated a pooled FNR of 6%, with a 95% confidence interval (CI) of 3-8%. Similarly, Shirzadi et al. calculated a pooled FNR of 7% in the cohort that was initially node negative, and a pooled FNR of 13% in the cohort that was node-positive converted to node-negative.

How many lymph nodes should be sampled to increase the identification rate (IR) and decrease the FNR in patients who undergo SLNB after NAC? Most studies argue identification of 2-3 SLNs is preferred over one SLN. The SENTINA and Alliance trials put forward that in order to achieve a FNR < 10%, at least 3 SLNs should be harvested [5,26]. Similarly, the SN-FNAC study, as well as the meta-analysis by Shirzadi et al., state that ≥2 sentinel lymph nodes should be harvested [14,23]. Wong et al. assessed FNRs in a cohort in which only 1 SLN was biopsied compared vs. 2 or more, and they found a much higher FNR rate in the former group (14.3% vs. 4.3%) [27].

Various studies also looked at whether the type of tracer mapping agent used during the procedure impacts the IR and FNR. While the meta-analysis by Geng et al. did not find any difference in outcomes amongst the different types of tracer, most studies concluded that using either radioisotope alone or a combination of two tracers was beneficial, as it increased the IR and decreased the FNR [5,23,26,27]. Moreover, a recent study from Japan discussed the use of a novel triple tracer technique that resulted in an IR of 100% and a FNR of 0% [28]. With respect to these studies, dual or triple tracer seem to be the better choices.

Over the past few decades, an increasing number of studies have assessed the accuracy and efficacy of SLNB after NAC in patients being treated for breast cancer. Two recent meta-analyses reported pooled FNRs of < 10% for patients who were initially clinically node-negative, concluding that SLNB following NAC is acceptable for this group of patients. Therefore, these patients may be able to avoid ALND and the morbidities that often follow. Although, less is known regarding FNRs in patients who were initially node-positive and then converted to node-negative. Based on the ACOSOG 1071 study, it is reasonable to consider SLNB in patients with a C1 or C2 disease at presentation and good clinical response to neoadjuvant chemotherapy [5]. SLNB should be performed with dual tracer and effort made to remove any positive lymph nodes and all sentinel nodes. At least two, and ideally three SLNs should be removed as the FNR is lower and reliably predicts axillary status. When residual disease is identified in the SLN following neoadjuvant treatment, the current standard of care is to perform a completion ALND given the high risk of additional disease in non-sentinel nodes. The goal of
axillary staging is to avoid a false-negative biopsy in which a patient would be understaged and perhaps undertreated.

In regards to sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer, the current standard of care for management of viable tumor cells, including micrometastatic disease in the SLN in this group of pretreated patients is ALND [29]. Axillary radiotherapy could although yield comparable outcomes with fewer adverse side effects [30]. Nonetheless, in patients with cN1 disease, SLNB is accurate with an acceptable FNR using dual tracer mapping and removal of > 2 sentinel nodes.

References


