Chapter 4
Sentinel Lymph Node Biopsy and Neoadjuvant Chemotherapy in Breast Cancer Patients

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Abstract Patient selection and timing of sentinel lymph node (SLN) biopsy in the context of primary chemotherapy continues to evolve; there is some evidence that primary chemotherapy may modify lymphatic drainage patterns and cause differential downstaging between sentinel and non-sentinel lymph nodes. SLN biopsy undertaken prior to chemotherapy will minimise the risk of a false-negative result, may allow more accurate initial staging and provides important information on prognostication which can guide decisions about adjuvant radiotherapy. However, quantification of regional metastatic load is incomplete, and some advocate SLN biopsy after primary chemotherapy to take advantage of nodal downstaging and avoidance of axillary dissection in up to 40 % of patients. Initial reports on false-negative rates for SLN biopsy after primary chemotherapy in patients who had proven axillary node metastases at presentation based on needle core biopsy were relatively high and a cause for clinical concern. However, more recent data suggest that SLN biopsy is as accurate when performed post- as pre-neoadjuvant chemotherapy, and current practice incorporates both approaches.

Keywords Breast cancer • Neoadjuvant chemotherapy • Post-chemotherapy • Sentinel lymph node biopsy

4.1 Introduction

The technique of sentinel lymph node (SLN) biopsy is now widely practised in many centres around the world and has become standard of care with reduction of upper limb morbidity such as lymphoedema, shoulder stiffness and chronic pain which are commonly linked to axillary lymph node dissection [1, 2]. A review by the American Society of Clinical Oncology Technology Assessment panel reaffirmed that dual localisation techniques with a combination of blue dye and

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isotope maximise identification rates (>90 %) and are associated with high negative predictive values (>95 %) and a short learning curve [3]. Overall false-negative rates are between 5 and 10 % (mean 8.4 %) and are minimised by intraoperative digital examination and removal of nodes which are suspicious but neither hot nor blue. Though there is international consensus that a combination of dye and isotope is optimal for localisation of sentinel node(s), much variation exists in details of methodology, and there is an urgent need for standardisation of techniques to maximise sensitivity and specificity [4]. The NSABP B32 study is the largest of five randomised controlled trials comparing sentinel lymph node biopsy to conventional ALND in clinically node-negative breast cancer patients. With a mean follow-up of 96 months, no significant differences in the primary endpoints of overall survival, disease-free survival and regional control were reported, and SLN biopsy was declared a safe, accurate and effective method for staging clinically node-negative patients [5].

Patient selection and the timing of SLN biopsy in the context of primary chemotherapy continues to evolve as increasing numbers of patients undergo this modality sequence. Before the advent of SLN biopsy, all neoadjuvant chemotherapy patients had an ALND as definitive and standard treatment of regional nodes. The pretreatment status of axillary nodes was unknown, and it was recognised that some node-positive patients became node negative following primary chemotherapy consequent to nodal downstaging. Therefore, neoadjuvant therapy did not influence surgical treatment in terms of the axillary procedure as ALND remained standard of care irrespective of the primary treatment approach.

Following introduction of SLN biopsy, primary surgical patients could potentially avoid ALND, but neoadjuvant patients were obligated to undergo ALND despite a favourable breast tumour response which might render a patient suitable for breast-conserving surgery (BCS). A dichotomy of practice emerged in efforts to define how SLN biopsy should be optimally incorporated into the neoadjuvant setting. Some breast units opted for SLN biopsy in conjunction with completion ALND *after* chemotherapy. This practice was incorporated into prospective trials to assess the safety and accuracy of SLN biopsy following a period of induction chemotherapy which might potentially alter patterns of lymphatic drainage in the axilla and increase false-negative rates. These latter concerns led others to recommend an upfront SLN biopsy performed *prior* to initiation of chemotherapy. The intrinsic accuracy of this technique in terms of parameters such as SLN identification rates and false-negative rates would be no different to patients having primary surgical treatment.

Patients undergoing neoadjuvant chemotherapy now receive less extensive axillary surgery, and this is consistent with a shift in neoadjuvant strategy from inoperable to operable disease. No imaging modality can detect subclinical nodal involvement, but preoperative axillary ultrasound can identify suspicious nodes and in conjunction with percutaneous biopsy (core biopsy or fine needle aspiration) can detect up to 40 % of node-positive cases overall and in 75 % of cases with multiple (>4) involved nodes [6–8]. Neoadjuvant chemotherapy patients are more likely to be clinically node positive or clinically node negative with suspicious nodes

sonographically. Therefore, preoperative axillary ultrasound (with or without node biopsy) is particularly important for this group of patients in terms of deselection for SLN biopsy.

4.2 Sentinel Lymph Node Biopsy Prior to Neoadjuvant Chemotherapy

Advantages – When SLN biopsy is undertaken prior to neoadjuvant chemotherapy, there will be minimal risk of an unacceptably high false-negative result, and information derived from SLN biopsy allows more accurate initial staging of patients [9–12]. Identification rates for an upfront approach are high and range from 98 to 100 % which is consistent with more extensive surgical experience of SLN biopsy pretreatment. Nodal positivity rates are variable (29–67 %) and reflect the heterogeneous nature of the primary tumours within most of these studies which confirm that SLN biopsy has satisfactory performance characteristics for larger tumours [13, 14]. A positive SLN biopsy result would prompt a subsequent ALND following neoadjuvant chemotherapy. By contrast, when the SLN is negative, no further axillary surgery is indicated, and completion ALND can be safely avoided at time of definitive surgery, be this wide local excision, simple mastectomy or mastectomy with immediate breast reconstruction [5]. Upfront SLN biopsy provides important information on prognostication and can guide treatment decisions for adjuvant radiotherapy, systemic therapy and axillary surgery. Although knowledge of the SLN status at presentation may influence decisions on irradiation of regional nodes, precise nodal quantification of axillary metastatic load with an upfront approach is limited; for example, a single positive node only may be retrieved at the time of SLN biopsy, but multiple nodes may be positive despite an innocent ultrasound examination of the axilla. This may be sufficient information alone to justify postmastectomy radiotherapy but not irradiation of the supraclavicular fossa which is presaged on involvement of at least four axillary nodes at presentation [15]. Any non-sentinel nodes containing tumour at the outset may be downstaged by chemotherapy and prior malignant involvement indicated by the presence of fibrosis on subsequent histopathological examination. Some advocate SLN biopsy after induction chemotherapy to take advantage of nodal downstaging and avoidance of ALND in some patients. Knowledge of pretreatment nodal status potentially influences the decision of whether or not to give chemotherapy if the primary tumour is relatively small and may also partly determine the type of chemotherapy and whether to include a taxane-based regimen (with or without an anthracycline). In addition to established clinicopathological factors, molecular tests can assess estimated risk of recurrence in patients with early stage breast cancer. Oncotype DX is one such prognostic test and is approved for clinical usage in many countries. This molecular test measures expression of a 21-gene profile with reverse transcriptase-polymerase chain reaction which does not require

fresh frozen tissue and can be performed on paraffin-embedded tumour tissue [16]. Patients with larger tumours and a confirmed negative SLN biopsy but low score on Oncotype DX could be treated with neoadjuvant hormonal therapy rather than chemotherapy. However, although prognostic tests provide information about risk of recurrence and death, predictive markers are needed to select optimum therapy for individual patients.

Disadvantages – An upfront approach requires an additional operation for all patients undergoing neoadjuvant chemotherapy, irrespective of final nodal status. Nonetheless, it should be noted that selected node-positive patients will also need additional surgery when SLN biopsy follows chemotherapy and facilities for intraoperative node assessment are not available (completion ALND must then be carried out as a delayed procedure at a separate surgical sitting). Concerns have been expressed about possible delays in commencement of chemotherapy treatment when an upfront SLN biopsy policy is employed, with delays consequent to either scheduling issues or wound complications such as seromas and infection. In an audit undertaken in the author's unit of 24 clinically node-negative patients with tumours <5 cm undergoing SLN biopsy prior to chemotherapy, timeframes from diagnosis to SLN biopsy and start of chemotherapy were analysed [17]. The mean time from tissue diagnosis to SLN biopsy was 7.3 days [range 5–22 days], whilst the mean time from SLN biopsy to start of chemotherapy was 9.2 days [range 2–23 days]. The mean time interval from tissue diagnosis to start of chemotherapy was 16.5 days [range 13–25 days]. This time interval in excess of 2 weeks is significantly longer than the average time period of 8.3 days for the group of patients not undergoing SLN biopsy [*t*-Test, $p = 0.00002$]. However, such a delay is unlikely to be detrimental to outcome in the context of patients with clinically and sonographically node-negative disease. Amongst this group of 24 patients, one developed a wound infection subsequent to commencement of chemotherapy within 4 days of SLN biopsy. It may be prudent to wait at least 7 days from the time of SLN biopsy before starting chemotherapy and consider surgical antibiotic prophylaxis in this group of patients.

SLN biopsy undertaken prior to neoadjuvant therapy is helpful if negative as no further axillary treatment is necessary, and such a result can reinforce any decision to withhold subsequent supraclavicular irradiation. However, patients selected for neoadjuvant chemotherapy have a higher chance of nodal involvement and, in the event of a positive SLN biopsy, are then committed to completion ALND with no opportunity for nodal downstaging. An upfront SLN biopsy can be useful in patients who do not require chemotherapy if SLN biopsy negative, but often age, primary tumour size and information from core needle biopsy are sufficient to justify a recommendation for neoadjuvant chemotherapy.

4.3 Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy

Advantages – Some advocate SLN biopsy after primary chemotherapy [18, 19] in order to take advantage of potential nodal downstaging and avoidance of ALND. Thus, rates of node positivity are reduced by 30 % for preoperative adriamycin and cyclophosphamide [18] and by up to 40 % for regimens incorporating a taxane with triple-negative and HER2-positive patients most likely to have a complete pathological nodal response [19]. A 'single' operation has the additional appeal of patient convenience and reduced costs when facilities for intraoperative node assessment are available. Early studies revealed that between 30 and 70 % of patients were committed to ALND with an upfront SLN biopsy. It should be noted however that many of these patients had relatively large primary tumours and few patients had preoperative axillary ultrasound which in conjunction with guided needle biopsy can deselect patients for SLN biopsy (who would then proceed directly to ALND). Hence, reports of higher rates of node positivity are not unexpected within this population of patients. Rates of complete pathological nodal response vary from 20 to 42 % in patients with needle biopsy-confirmed positive nodes pre-chemotherapy [20–23]. Most metastases diagnosed on needle biopsy are macrometastases (>2 mm), and it is conceivable that complete pathological response might be higher for nodes containing micrometastases only, though there is no current evidence to support this. There is a suggestion that knowledge of nodal response to chemotherapy is more relevant in terms of prognostication and decision-making for chest wall/supraclavicular radiotherapy than initial nodal status. In particular, those patients with a complete pathological response in both the breast and axilla appear to have a much better prognosis [24].

Disadvantages – It has been surmised that primary chemotherapy may modify lymphatic drainage patterns within the axilla where there is a degree of plasticity within the lymphatic network of vessels [25]. Distortion of lymphatics may occur secondary to tumour shrinkage with creation of aberrant lymphatic drainage patterns. This together with plugging of lymphatics by tumour emboli could increase false-negative rates. Moreover, induction chemotherapy could lead to differential downstaging between sentinel and non-sentinel nodes [26]. Notwithstanding these theoretical considerations, there is no conclusive evidence that such phenomena occur to any significant extent in neoadjuvant therapy patients, a fact which has encouraged a recent trend away from upfront SLN biopsy in neoadjuvant chemotherapy patients [27]. Interestingly, some have referred to a 'front to back, back to front' phenomenon in which chemotherapy is more likely to eradicate tumour within non-sentinel lymph nodes than the SLN in which the tumour cell burden is likely to be greater. Thus, although cancer cells spread first to the SLN and thereafter to the non-sentinel nodes, the inverse sequence applies to chemotherapy effect [28]. This would increase the negative predictive value of a negative SLN biopsy after chemotherapy. However, if tumour deposits responded earlier in the SLN than non-sentinel nodes, then a false-negative result would ensue.

4.4 Accuracy of Sentinel Lymph Node Biopsy After Chemotherapy

Node-negative patients – Single-institution studies have revealed sensitivity rates of 72–100 % with false-negative rates of 0–33 % when SLN biopsy follows neoadjuvant chemotherapy (NAC) [18, 26, 29–31]. However, most of these studies involved small numbers of patients, and a pooled analysis shows a false-negative rate of about 10 % with an identification rate of 89 %. Rates of identification in the NSABP B-27 study were 85 % using blue dye alone or a combination of blue dye and radioisotope with a reported false-negative rate of 11 % (the false-negative rate was higher for blue dye alone (14 %) compared with radioisotope with or without blue dye (8 %)) [26]. The French GANEA study also detected the SLN in 90 % of cases and reported an overall false-negative rate of 11 % (9.4 % for clinically node-positive cases, 11.6 % for clinically node-positive cases) [32]. An analysis by Hunt and colleagues revealed a false-negative rate of 5.9 % when SLN biopsy followed NAC and 4.1 % for upfront SLN biopsy ($p = 0.39$) [33]. Recent reports have shown false-negative rates in the region of 8–11 %; a meta-analysis of 21 single-institution studies involving more than 1200 patients undergoing post-chemotherapy SLN biopsy with completion ALND reported a pooled false-negative estimate of 12 % when SLN biopsy followed chemotherapy in clinically node-negative patients [34, 35]. A slightly lower figure of 9 % was calculated by Mamounas and Bellon when analysis was confined to studies published in the past 10 years, though values for false negativity ranged from 5 to 25 % [36].

These figures are similar to false-negative rates for primary surgery [3, 5, 37–39], but it should be noted that these two clinical scenarios may not be strictly comparable for several reasons – in the words of Michael Sabel, are we dealing here with 'apples and oranges' [27]. Firstly, only a subset of patients in these neoadjuvant studies had SLN biopsy post-chemotherapy with patient selection and surgeon experience introducing an element of bias. Thus, although standard ALND (level I/II) was a component of the trial protocol, a preliminary SLN biopsy could be undertaken before ALND at the discretion of the surgeon (approximately 20 % of patients) [26]. Secondly, there was much variation in the precise technique used for SLN biopsy (blue dye alone, isotope alone or a combination with dual localisation).

Node-positive patients – There have been mixed reports on false-negative rates when there is needle biopsy (cytology or core biopsy)-proven positive nodes pre-chemotherapy with a limited number of published studies relating specifically to this group of patients (see Table 4.1) [40–42]. Mamounas has recently cited an overall false-negative rate of 11.1 % for SLN biopsy post-neoadjuvant chemotherapy when there is confirmed nodal involvement at presentation [43]. These updated figures are reassuring and have led many experts to conclude that SLN biopsy is as accurate when performed post- as pre-neoadjuvant chemotherapy, but induction chemotherapy has the added advantage of potential downstaging of axillary nodes. However, a note of caution has been sounded by Alvarado and colleagues who

Table 4.1 False negative rates for SLN biopsy following primary chemotherapy in patients with biopsy-proven axillary nodal metastases

Author	No. of patients	False-negative rate (%)
Shen et al. [40]	69	25
Lee et al. [41]	238	5.6
Newman et al. [42]	54	10.7
Alvarado et al. [22]	150	16.1
Boughy et al. [23]	649	12.6

express concerns that false-negative rates can be unacceptably high when SLN biopsy follows neoadjuvant chemotherapy in patients presenting with node-positive disease [22]. They examined 150 patients with biopsy-proven axillary nodal metastases who proceeded to SLN biopsy after primary chemotherapy. Amongst 111 patients in whom ALND was performed, 15 had a false-negative result for an event rate of 20.8 % (15/72), and normalisation of nodes on ultrasound post-chemotherapy reduced this rate to 16.1 % (compared with 27.8 % for those with abnormal node morphology including size and cortical thickness). Furthermore, removal of a single SLN was associated with an even higher false-negative rate as was positivity for the HER2 receptor (33 % versus 18 %). The pathological complete nodal response in this study was 42 %, suggesting that a notable proportion of patients could have been spared the potential morbidity of an ALND [22].

There is a paucity of data on omission of completion ALND in needle biopsy-proven node-positive patients with a subsequent negative SLN biopsy after neoadjuvant chemotherapy (Table 4.1). In particular, it is unclear from some reports whether cited rates relate to patients with positive or negative initial nodal status, and there is confounding of studies due to some patients proceeding to ALND. For example, Hunt and colleagues reported recurrence rates of 1.2 % at a median follow-up of 55 months amongst a group of 575 patients undergoing SLN biopsy after primary chemotherapy, but almost one-third of patients had ALND either for SLN positivity (20.7 %) or as a planned procedure [33]. Further information is needed on rates of regional recurrence specifically in those patients with a negative SLN who did not have ALND. It is conceivable that axillary recurrence is higher when there is residual non-sentinel nodal disease after a false-negative SLN biopsy post-chemotherapy (no further chemotherapy routinely given) [44]. In a combined analysis of the NSABP B-27 and B-18 studies involving 3000 patients undergoing either mastectomy or breast conservation therapy, a total of 356 locoregional recurrence events were documented. The chance of recurrence was related to age, nodal status pre-chemotherapy and the breast/nodal pathological response rates, with low rates of recurrence for those patients achieving a complete pathological response. For those patients who were clinically node negative at the outset, rates of locoregional recurrence were low [45].

Boughy and colleagues have provided important information from the American College of Surgeons Oncology Group (ACOSOG) Z01071 trial which enrolled almost 700 patients and examined false-negative rates for patients with core biopsy-proven node-positive breast cancer (T0–T4, N1–2, M0) who underwent SLN

biopsy and concomitant axillary lymph node dissection (ALND) after primary chemotherapy [23]. The primary endpoint for this study was the false-negative rate for clinically node-positive patients who have at least two SLNs removed for pathological examination. Though dual tracer techniques were recommended, this was not compulsory, and some patients underwent SLN biopsy with single tracer localisation (51 radioisotope only, 13 blue dye only). Rates of identification were 92.5 % overall (>90 % individually for both clinically N1 and N2 patients) with an accuracy of 84 % for assignment of correct nodal status. Forty percent of patients had a complete pathological nodal response with no evidence of any residual tumour on routine H&E staining (metastases >0.2 mm). Moreover, in 40 % of patients with nodal deposits, the sentinel node was the only positive node. Furthermore, the false-negative rate was almost 20 % when only a single tracer agent was employed compared with 12.6 % for dual tracer localisation and harvesting of a minimum of two nodes. It was recommended that at least three nodes be removed in this setting of SLN biopsy post-chemotherapy. Clips may be placed in the node at the time of initial core biopsy, and this will help to ensure that the correct node has been removed and confirm any pathological response to neoadjuvant chemotherapy. Results of this randomised study are consistent with the retrospective study of Alvarado although the latter provided no specific information on the technique of SLN localisation in relation to false-negative rates [22]. Park and colleagues likewise found a relatively high false-negative rate (22 %) when SLN biopsy was performed after neoadjuvant chemotherapy for locally advanced breast cancers. Radioisotope was employed as a sole tracer agent, and interestingly false-negative rates varied significantly between molecular tumour types with improved accuracy and lower false-negative rates for triple-negative breast cancer. These authors concluded that SLN biopsy post-chemotherapy should be restricted to this subgroup of triple-negative breast cancer [46].

On the basis of these Z1071 results, SLN biopsy after neoadjuvant chemotherapy for biopsy-proven nodal involvement at presentation can only be reliably used when dual localisation methods have been employed and at least two nodes have been removed and examined. Notwithstanding these findings on false-negative rates within the Z1071 study, which failed to reach a predefined upper threshold of 10 %, these may not necessarily translate into higher rates of locoregional recurrence. However, in contrast to patients undergoing SLN biopsy prior to any chemotherapy (be this neoadjuvant or adjuvant), this group of post-neoadjuvant patients will not receive any further chemotherapy that might eliminate tumour foci within ‘non-sentinel’ lymph nodes in the setting of false negativity. Longer-term follow-up will determine whether any change in performance parameters for SLN biopsy post-chemotherapy has any impact on clinical outcomes.

There is increasing evidence that decisions for radiotherapy (chest wall/supraclavicular) should be based on tumour response to chemotherapy rather than the status of the regional nodes per se at presentation. Knowledge of sentinel lymph node negativity from downstaging after neoadjuvant chemotherapy (when there were biopsy-confirmed nodal metastases at presentation) is very helpful when estimating benefit from radiotherapy. For clinically node-positive patients who

become negative after neoadjuvant chemotherapy, there appears to be little benefit from radiotherapy. Hence, SLN biopsy after neoadjuvant chemotherapy allows assessment of specific response within the regional nodes to chemotherapy, whereas positive nodes might otherwise be removed with SLN biopsy and preclude any comment on nodal response following formal ALND after neoadjuvant chemotherapy [18, 26].

4.5 NSABP-51/RTOG-1304 Trial

Neoadjuvant chemotherapy can result in a significant downstaging of disease, such that patients presenting with extensive axillary lymph node involvement may have a complete pathological response with no evidence of axillary metastases following induction chemotherapy. Thus, the timing of SLN biopsy (before or after neoadjuvant chemotherapy) may significantly influence decisions concerning adjuvant radiotherapy. For instance, postmastectomy radiotherapy is generally recommended for patients who have metastases in >3 axillary nodes, but it is unclear if this decision should now be based on axillary status *before* or *after* administration of chemotherapy. If this should be based on nodal status at the time of initial presentation, then SLN biopsy prior to neoadjuvant chemotherapy should be urged. On the other hand, if nodal status after neoadjuvant chemotherapy provided sufficient basis for this decision on adjuvant radiotherapy, then SLN biopsy following chemotherapy would be the preferred option.

In an attempt to resolve this issue, a large randomised trial involving 1636 patients has been planned in the United States (NSABP-51/RTOG-1304 trial) [47]. This will be a phase III clinical trial evaluating postmastectomy chest wall and regional nodal radiotherapy and post-lumpectomy regional nodal radiotherapy in patients with positive axillary nodes before neoadjuvant chemotherapy who convert to pathologically negative axillary nodes after neoadjuvant chemotherapy. The study will recruit patients with T1–T3, N1 breast cancer, with documented positive axillary nodes by FNA or core biopsy. Following administration of neoadjuvant chemotherapy, those patients will undergo definitive surgery with histological documentation of negative axillary nodes (either by axillary dissection alone or SLN biopsy with or without axillary dissection). These patients who convert to node-negative status will then be randomised to receive either no regional nodal radiotherapy (and no chest wall radiotherapy for patients treated with mastectomy) or regional nodal radiotherapy (with chest wall radiotherapy for mastectomy patients). Thus, amongst node-positive patients who convert to node-negative status, this trial will determine whether or not decisions concerning adjuvant radiotherapy should be based on nodal status at the time of initial presentation. Ultimately, the results of this trial will be an important consideration in the decision-making process for recommending SLN biopsy either before or after administration of neoadjuvant chemotherapy.

4.6 SENTINA Trial

The German SENTINA trial addressed the role of repeat SLN biopsy in patients who had previously undergone the procedure prior to neoadjuvant chemotherapy [48]. Patients were allocated to one of four arms; initially clinically node-negative patients treated with upfront SLN biopsy were designated arms A and B; if the SLN was negative (arm A, 662 patients), then no further axillary surgery was undertaken. If the SLN was positive before chemotherapy, then repeat SLN biopsy with ALND was performed after chemotherapy (arm B, 360 patients). Patients who were initially clinically node positive were designated arms C and D; those who converted to clinically node-negative status after chemotherapy underwent SLN biopsy with ALND (arm C, 592 patients), whilst those who remained clinically node positive had a standard ALND (arm D, 123 patients). The sentinel node detection rates for arms A and B (pre-chemotherapy) were 99.1 %, 80.1 % for arm C and only 60.8 % for repeat SLN biopsy after chemotherapy (arm B). Moreover, the FNR for repeat SLN biopsy for arm B patients exceeded 50 % (51.6 %, 95 % CI 38.7–64.2 %), and sometimes only a single node was removed. The authors concluded that SLN biopsy is unacceptable as a repeat procedure following neoadjuvant chemotherapy. The FNR was noted to be relatively high for those patients in arm C who converted from clinically node positive to negative after chemotherapy (14.2 %, 95 % CI 9.9–19.4 %).

4.7 Conclusions

SLN biopsy can be performed either as an upfront procedure or following neoadjuvant chemotherapy with advantages and limitations of both approaches. A National Cancer Institute conference recommended SLN biopsy before or after chemotherapy for clinically node-negative disease which underlines the principle of multidisciplinary assessment and no single method applicable to all patients [49]. There is now greater confidence in declaration of a ‘negative’ SLN biopsy after primary chemotherapy for node-positive disease and withholding routine ALND in selected cases. False-negative results can be minimised by taking account of ultrasound characteristics post-chemotherapy and ensuring mandatory ALND when abnormal nodes persist sonographically [50]. Normal-appearing nodes are statistically more likely to be associated with a complete pathological nodal response than those with indeterminate features [22]. Nonetheless, the significance of micrometastases and isolated tumour cells in this setting is uncertain, and these may be of different biological consequence if they represent downstaged macrometastases. Ideally, there should be an ‘all or none’ response of nodes to chemotherapy, but it is conceded that in the ‘post-Z0011 era’, selected patients who are SLN biopsy positive pre-chemotherapy might avoid completion ALND as they will subsequently receive neoadjuvant/adjuvant therapies (including

chemotherapy, hormonal therapy and breast radiotherapy). The use of a nomogram with a limited number of variables may have clinical utility for estimating the probability of residual disease in non-sentinel nodes [51]. This line of reasoning would not apply to SLN biopsy-positive patients *after* neoadjuvant chemotherapy who have residual disease post-chemotherapy and will receive no further chemotherapy (though possibly hormonal therapy/Herceptin). SLN biopsy should be considered post-chemotherapy in those patients for whom pretreatment nodal status would not impact on the choice of chemotherapy or radiotherapy. These recommendations can include selected cases of needle biopsy-proven node-positive cases at presentation that are clinically and sonographically node negative following chemotherapy with evidence of an excellent response in the breast and regional nodes to induction chemotherapy. Any evidence of sentinel node tumour deposits on H&E staining (including isolated tumour cells) should be followed by completion ALND irrespective of the type of breast surgery. Further information must be collected on outcomes in terms of both regional recurrence and overall survival for patients undergoing SLN biopsy after nodal downstaging with induction chemotherapy. In particular, sentinel lymph node-negative patients without completion ALND after neoadjuvant chemotherapy should be carefully monitored, and further axillary surgery for SLN-positive patients in this setting is mandatory at the present time.

Learning Points (Box 4.1)

1. There are advantages and limitations with both approaches to SLN biopsy in the context of neoadjuvant chemotherapy:
   - A National Cancer Institute conference in 2008 sanctioned SLN biopsy *before* or *after* neoadjuvant chemotherapy for clinically node-negative disease.
   - The National Comprehensive Cancer Network in 2011 recommended that SLN biopsy be performed prior to neoadjuvant chemotherapy.
2. There is now greater confidence in declaration of a 'negative' SLN biopsy after primary chemotherapy for node-positive disease and for withholding completion ALND in *selected* cases:
   - Two and possibly three sentinel nodes should be removed.
   - Dual localisation techniques should be employed with blue dye and isotope to minimise FNR.
   - Axillary nodes should be sonographically normal nodes following induction chemotherapy.
3. At the present time, routine SLN biopsy should be undertaken in conjunction with simultaneous completion ALND as a registration study to assess

(continued)

the accuracy of SLN biopsy after primary chemotherapy in terms of false-negative rates.

4. Any evidence of tumour deposits on H&E staining (including isolated tumour cells) should prompt a completion ALND *irrespective* of type of breast surgery.

   SLN biopsy post-chemotherapy should be considered in clinically/sonographically node-negative patients for whom pretreatment nodal status would *not* impact on choice of chemotherapy or radiotherapy.
5. The ongoing NSABP-51 trial is evaluating whether decisions for postmastectomy radiotherapy should be based on axillary status *before* or *after* chemotherapy.
6. If nodal status at presentation is deemed to be important, then upfront SLN biopsy should be urged but otherwise SLN biopsy post-chemotherapy preferred.

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