Chapter 6
Ultrasound for Axillary Staging

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Abstract Ultrasound examination of the axillary lymph node has been demonstrated to be a useful tool in evaluating axilla lymph node status. Axillary ultrasound (AUS) was first used to identify positive lymph nodes preoperatively, so that patients could undergo axillary lymph node dissection (ALND) directly and be spared from sentinel lymph node biopsy (SLNB). Recent studies also focus on the application of AUS in surgical planning when AUS reveals negative nodal status. When AUS is negative, the chance of having more than three positive nodes is low. Therefore, when AUS is negative, one can plan immediate reconstruction after mastectomy, and there is no need of intraoperative SLN examination for breast-conserving surgery. If AUS reveals suspicious lymph node and ultrasound-guided biopsy proves the node to be metastatic, SLNB can be spared if mastectomy is planned. Axillary ultrasound is also helpful in guiding whether SLNB should be done before or after neoadjuvant chemotherapy. If AUS is negative, the chance of having positive SLN is relatively low, and it would be reasonable to proceed with SLNB. If AUS or ultrasound-guided biopsy is positive, one may consider SLNB after neoadjuvant chemotherapy. For node-positive patients undergoing neoadjuvant chemotherapy first, patients with negative AUS before SLNB can be considered to undergo SLNB alone after neoadjuvant chemotherapy.

Keywords Axillary staging • Sentinel lymph node biopsy • Axillary ultrasound • Neoadjuvant chemotherapy

6.1 Current Status of Sentinel Lymph Node Biopsy and Axillary Ultrasound in Axillary Staging

Sentinel lymph node biopsy (SLNB) is widely accepted by physicians and patients as an option of axillary staging due to its low incidence of morbidity. In its recent SLNB clinical practice guideline update, the American Society of Clinical Oncology made several recommendations, which include that clinicians should not

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recommend axillary lymph node dissection (ALND) for women with early-stage breast cancer who do not have nodal metastases and clinicians should not recommend ALND for women with early breast cancer who have one or two sentinel lymph node metastases and will receive breast-conserving surgery with conventionally fractionated whole-breast radiotherapy [1].

During the advent of SLNB, ultrasound examination of the axillary lymph node has also been demonstrated to be a useful tool in evaluating axilla lymph node status. Axillary ultrasound (AUS) was first used to identify positive lymph nodes preoperatively, so that patients could undergo ALND directly and be spared from SLNB. Recent studies also focus on the application of AUS in treatment decision-making when AUS reveals negative axillary lymph node status. The applications of ultrasound in axillary staging in conjunction with SLNB are reviewed in the following.

6.2 Axillary Ultrasound Can Identify Metastatic Lymph Node

Among different studies of different incidences of lymph node involvement in axillae, metastases were detected preoperatively by ultrasound-guided fine-needle aspiration cytology (US-FNAC), and 1.4–45 % of SLNB could be avoided [2–13]. In one large series of 726 patients (consisting of 732 axillae) with 67 % of T1 tumor, 30 % of T2 tumors, and 2.7 % of T3 or T4 tumors reported by van Rijk et al., about one-quarter of axillae were found to have suspicious lymph node by AUS, and about one-third of these axillae with suspicious ultrasound were proved by US-FNAC to have metastatic lymph node involvement by SLNB [9]. Those patients with normal AUS did not receive US-FNAC. The sensitivity and specificity were 35 % and 82 %, respectively, for AUS, and 21 % and 99.8 %, respectively, for US-FNAC. In this series, 58 of 732 (8 %) of axillae were diagnosed preoperatively to have lymph node metastasis. Therefore, 8 % of patients can be saved from SLNB and receive ALND directly.

Among the earlier studies, the percentage of metastatic lymph nodes diagnosed preoperatively by ultrasound-guided biopsy ranged from 5.7 to 80 %, and the percentage of SLNB avoided ranged from 1.4 to 45% [2–13]. In addition to the different incidences of metastatic lymph nodes among these studies, the explanation for the wide variation of rates could also be due to differences in the following factors: the percentage of lymph nodes visualized, the criteria of suspicious nodes detected by AUS, biopsied only the suspicious nodes or all nodes visualized, and the biopsy method (core needle biopsy (CNB) or FNAC).

The specificity of US-FNAC is higher than that of AUS, but the sensitivity of AUS is higher than that of US-FNAC, which implies that the false-negative rates of US-FNAC may be due to FNAC but not due to ultrasound. Two studies reported the use of CNB in biopsy of the lymph node [2, 3]. Complications associated with the

CNB procedure seem acceptable. Just like in the diagnosis of primary tumor, the false-negative rate is expected to be lower with CNB than with FNAC.

6.3 Ultrasound Evaluation Decreases False-Negative Rate of SLNB

Pre-SLNB evaluation of the axillary lymph node by AUS will help to decrease the false-negative rate of SLNB. As demonstrated in the study by Sato et al., the SLN identification rate for 262 total patients and 208 patients with negative AUS was 88.2 % and 98.6 %, respectively, while for 23 patients with T3 tumors and 6 patients with T3 tumors but negative AUS, the identification rate was 65.2 % and 100 %, respectively [14]. The false-negative rate of SLNB for all 262 patients and 208 patients with negative AUS was 10.8 % and 1.7 %, respectively, while for 23 patients with T3 tumors and 6 patients with T3 tumors but negative AUS, the false-negative rate was 35.7 % and 0 %, respectively.

6.4 Axillary Ultrasound Is Helpful in Large Tumor Staging

The incidence of lymph node metastasis demonstrated by ALND in breast cancer patients for different tumor sizes as reported by Silverstein et al. was 5 %, 16 %, 28 %, 47 %, 68 %, and 86 % in T1a, T1b, T1c, T2, T3, and T4 tumors, respectively [15]. Since the chance of lymph node involvement is low in small tumors, which makes the complications associated with ALND more undesirable, SLNB was first applied in small tumors to replace ALND [16–18]. In daily practice, SLNB generally has been applied to invasive breast cancers not larger than 3 cm and without clinical evidence of lymph node involvement [18–20]. Tumor size is limited to 3 cm or smaller for several reasons: first, nearly half of the T2 tumor may develop lymph node metastasis, which would necessitate a second procedure of ALND after SLNB and make SLND unnecessary; second is the incorrect perception that false-negative rate of SLNB could be high in a large tumor, due to a higher chance of the complete occupancy of cancer in the lymph node, which prevents the radiotracer entering the lymph node.

The recent ASCO SLNB guideline recommends that clinicians should not perform SNB for women who have large or locally advanced invasive breast cancers (tumor size T3/T4) [1]. Only one study of 64 patients with locally advanced breast cancers was found by the panels. The FNRs were 5.1 % for patients with locally advanced breast cancer and 5.8 % for those with early-stage breast cancer enrolled in different randomized trial comparing SLNB with ALND [21].

Actually, several studies, also non-randomized trials, have focused on the accuracy of SLNB in large breast cancer. In a prospective multi-institutional

study of 2,085 breast cancer patients, the identification rate of SLN and false-negative rate were not significantly different in patients with T1, T2, and T3 tumors [22]. All patients received SLNB using dual tracer with radioactive colloid and blue dye, followed by ALND. The identification rate of SLN was 93.2 % and 97.8 % for T2 and T3 tumors, respectively, compared with that of 92.1 % for T1 tumors, and the false-negative rate was 6.8 % and 3.0 % for T2 and T3 tumors, respectively, compared with 9.2 % for T1 tumors. When the tumor size was categorized into a 1-cm difference, the SLN identification rate tended to be higher and false-negative rate lower in patients with larger tumors. Generally speaking, the identification rates of SLN (93–100 %) and false-negative rates of SLNB (3–6.8 %) were not worse in T2 and T3 tumors than those of T1 tumors [22–25]. In one study of 218 patients with T2 and T3 tumors and in the other study of 48 patients with tumor larger than 3 cm, both with negative SLN and not receiving ALND, none of the patients developed isolated axillary recurrence at a median follow-up of 31 months and 43 months, respectively [26, 27]. Based on the findings in these studies, it seems that SLNB is as accurate an axillary staging procedure in T2 and T3 breast cancers as in T1 cancers.

In addition, the sensitivity of AUS in detecting lymph node metastasis has been shown to increase as the tumor size increases. Koelliker et al. reported the sensitivity of ultrasound for T1, T2, T3, and T4 tumor was 56 %, 64–73 %, 82 %, and 100 %, respectively, and Somasundar et al. reported 35 % and 67 % for T1 and T2 tumors, respectively [11, 28]. This could be explained by larger metastasis depositing in lymph nodes of larger cancer, which make it easier to be detected by AUS [10, 13]. As mentioned previously, pre-SLNB evaluation of the axillary lymph node by ultrasound will help to decrease the false-negative rate of SLNB. The study by Sato et al. demonstrated that the false-negative rate of SLNB for all 262 patients and 208 patients with negative ultrasound was 10.8 % and 1.7 %, respectively, while for 23 patients with T3 tumors and 6 patients with T3 tumors but negative ultrasound, the false-negative rate was 35.7 % and 0 %, respectively [14]. Therefore, AUS is helpful for axillary staging in large tumor. Either the metastatic lymph node can be identified preoperatively, or accuracy of SLNB can be ensured by negative AUS.

6.5 Negative Ultrasound Indicates Fewer Nodal Metastases

Reports also suggest that when AUS or US-FNAC reveals negative axillary lymph node status, the chance of having more than three positive lymph nodes or tumor deposits in the lymph node >5 mm is low. The study by van Rijk et al. demonstrated that patients, whose axillary lymph node involvement was diagnosed by preoperative US-FNAC, had more positive nodes than patients whose axillary lymph node involvement could not be detected by US-FNAC (mean 4.3 vs. 2.2, median 3 vs.1.5; $p < 0.001$) [9]. The study by Bonnema et al. also demonstrated that the chance to

detect metastatic lymph nodes by US-FNAC was higher when there were four or more positive nodes compared with when there was only one positive node [4]. In Swinson et al.'s series, none of 14 cases with micrometastasis (0.2–2 mm) of the lymph node were detected by US-FNAC, but 38 of 102 (37 %) cases with lymph node metastasis larger than or equal to 2 mm were detected by US-FNAC [13]. Fifty percent of cases with more than three positive nodes were detected preoperatively by US-FNAC, while only 15 % of cases with one positive node were diagnosed by US-FNAC. In this series, 278 of 369 (75 %) breast cancers were detected by screening. In a series of 286 patients having negative AUS before SLNB, 32 % of patients have positive SLNs of macrometastasis or micrometastasis and 9.2 % of 286 patients might have positive non-SLNs. The mean and median numbers of positive nodes (SLNs plus non-SLNs) were 1.7 and 1, respectively [29].

6.6 How to Find the Lymph Node in Axillary Ultrasound

To increase the percentage of metastatic lymph nodes diagnosed preoperatively, one needs to know how to visualize a lymph node. In the early reports, the percentage of the lymph node visualized in axillae was only 35–37 % [5, 8], while in more recent reports, it was 100 % [9]. A normal lymph node has a central fatty hilum and thin cortex, which sometimes is hard to detect from the surrounding fatty tissue of the axilla (Fig. 6.2). To find a lymph node, or even an SLN, in the axilla, one also needs to be aware of the frequent location of an SLN. In 98.4 % of our 974 patients, the hotspot detected on the axilla skin before SLNB was located in the area demarcated by the four landmarks of the hairline, a line tangential to and 2 cm below the center of the hairline, the lateral border of the pectoralis major muscle, and the midaxillary line (Fig. 6.1) [30].

6.7 Ultrasound Criteria of Metastatic Lymph Nodes

The diagnostic criteria of a metastatic lymph node by ultrasound vary among reports [2–4, 7–9, 11, 12, 31]. The following characteristics may suggest that a lymph node could be metastasized: the absence of or narrow fatty hilum, an eccentrically or concentrically increased thickness of cortex (more than 2 mm), an atypical cortex appearance (echo poor, inhomogeneous), and the ratio of longitudinal to transverse axis less than two (Fig. 6.2). In addition, if ultrasound examination is done after excisional biopsy, a benign axillary lymph node may look suspicious (with increased thickening of cortex) [7].

In one study using ultrasound alone without biopsy to evaluate axillary status, Sato et al. chose the absence of the hilum as the criteria of lymph node involvement

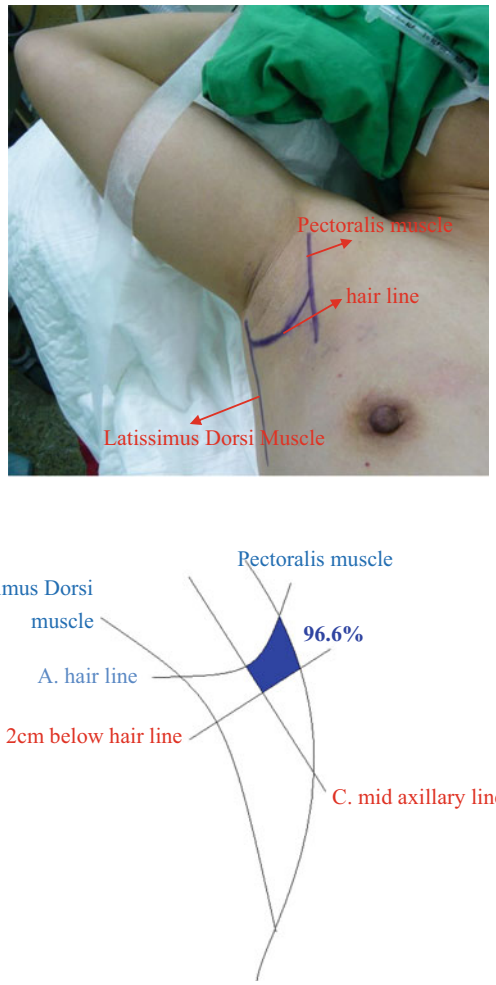

Fig. 6.1 Frequent locations of axillary sentinel lymph node

[14]. In 54 patients with abnormal ultrasound, 50 had lymph node metastasis and in 208 patients with normal ultrasound; only 62 had lymph node involvement. The PPV, sensitivity, and specificity calculated from these data were 93 %, 45 %, and 97 %, respectively. Maximum cortex thickness was the most significant feature in the study by Deurloo et al. to predict lymph node metastasis [8]. To obtain a high sensitivity at 95 %, and a low specificity at 44 %, a maximum cortex thickness of 2.3 mm was shown to be the most important criteria for biopsy. In a recent study by Koelliker et al., the PPV for the absence of the hilum, eccentric hilum, hypoechoic

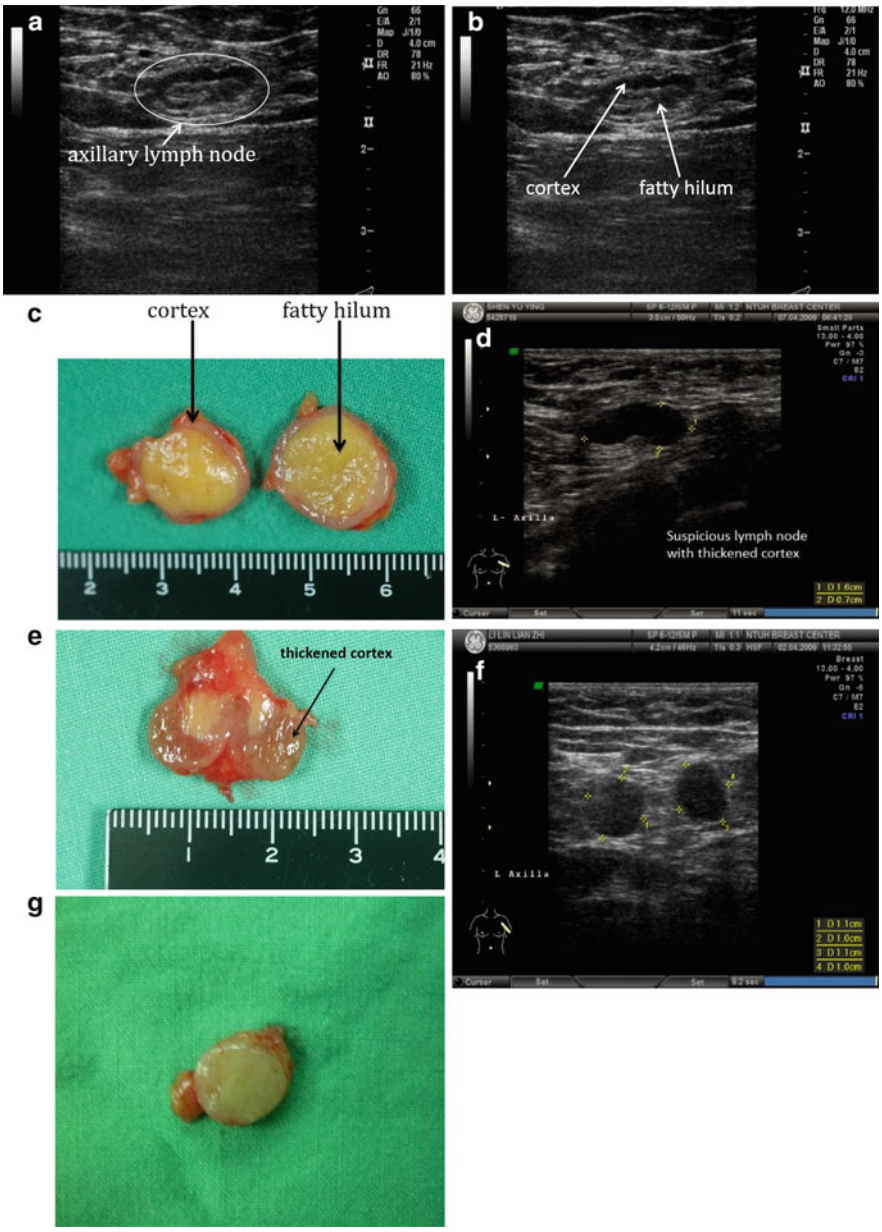

Fig. 6.2 Ultrasound images and photos of benign and suspicious axillary lymph nodes (**a**) A benign lymph node on AUS with thin cortex (**b**) Benign lymph node on AUS (**c**) Cut surface of a benign lymph node (**d**) A suspicious lymph node with thickened cortex (7 mm) (**e**) Cut surface of a lymph node with thickened cortex (**f**) A metastatic lymph node characterized by loss of the fatty hilum with rounding appearance (**g**) Cut surface of a metastatic lymph node

cortex, and thick or lobular cortex was 100 %, 94 %, 97 %, and 73 %, respectively [11].

In a study using ultrasound-guided CNB, the sensitivity of ultrasound to diagnose a metastatic lymph node based on the cortical thickening, the absence of the fatty hilum, and the nonhilar blood flow was 79 %, 33 %, and 65 %, respectively, and the PPV was 73 %, 93 %, and 78 %, respectively [3]. With the cortical thickness cutoff point set at 3 mm, the sensitivity and specificity of this parameter for the detection of metastatic nodes were 95 % (61 of 64 patients) and 6 % (2 of 36 patients), respectively. If 4 mm was used as the cutoff point, sensitivity decreased slightly to 88 % (56 of 64 patients) and specificity increased to 42 % (15 of 36 patients). Of the 191 needle-localized nodes, Cho et al. used a cutoff point of a cortical thickness of 2.5 mm and achieved a sensitivity of 85 % and specificity of 78 %. When AUS is negative, the chance of having positive node was about 11% [32].

6.8 Application of Axillary Ultrasound If Neoadjuvant Chemotherapy Is Not Planned

Based on the above studies, loss of the fatty hilum has the highest PPV in predicting positive lymph node. While different thickness of cortex will yield different values of sensitivity, specificity, NPV, and PPV, one may choose different criteria depending on how to apply AUS. For example, if a metastatic lymph node needs to be ruled out, a lymph node with loss of the fatty hilum or a cortical thickness more than 2 mm will receive US-FNAC. If the cytology is negative, SLNB will be done to confirm the status of axillary lymph node. With these criteria, the NPV will be the highest and the chance of having a metastatic lymph node will be the lowest. Hence, when AUS is negative and neoadjuvant chemotherapy is not planned, one can plan immediate reconstruction after mastectomy, and there is no need of intraoperative SLN examination (no unanticipated ALND, which is helpful for scheduling surgery) if breast-conserving treatment is planned and will be more comfortable to follow Z0011 conclusion to omit ALND when there are no more than two positive SLNs (Fig. 6.3a). If AUS reveals a suspicious lymph node and US-FNAC proves the node to be metastatic, SLNB can be spared if mastectomy is planned. If breast-conserving surgery is planned in a patient with suspicious AUS or positive US-FNAC but the lymph node is not palpable before US-FNAC, some people still think ALND can be spared if positive SLNs are not more than two, since only patients with palpable axillary nodes, but not patients with positive AUS, were excluded in Z0011 trial.

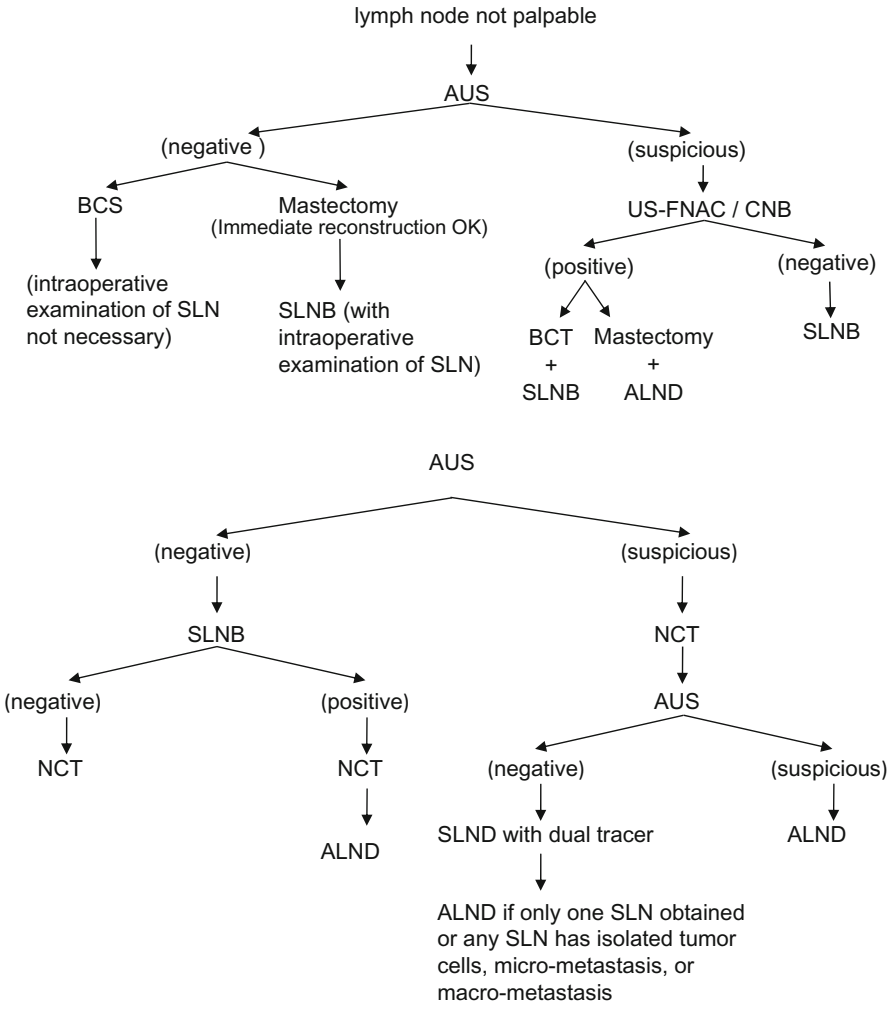

Fig. 6.3 Flowchart of proposed algorithm using ultrasound in conjunction with SLNB for axillary staging among patients receiving primary surgery or neoadjuvant chemotherapy (**a**) Neoadjuvant chemotherapy (NCT) not considered. *AUS* axillary ultrasound, *BCS* breast-conserving surgery, *US-FNAC* ultrasound-guided fine-needle aspiration cytology, *CNB* core needle biopsy, *SCNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection (**b**) Neoadjuvant chemotherapy (NCT) considered

6.9 Axillary Ultrasound for Guiding SLND Before or After Neoadjuvant Chemotherapy

The 2014 American Society of Clinical Oncology (ASCO) SLNB guideline recommends that SLNB may be offered before or after neoadjuvant systemic therapy but states that SLNB seems less accurate after neoadjuvant systemic therapy [1]. In

general, when SLNB is done before neoadjuvant chemotherapy and SLN is negative, axillary staging is not necessary after neoadjuvant chemotherapy; while if SLN is positive, ALND is usually recommended after chemotherapy. The rationale of doing SLND after neoadjuvant chemotherapy is that about one-third of positive nodal status before chemotherapy will be converted to negative nodal status after chemotherapy. SLND done after neoadjuvant chemotherapy may save these patients from ALND.

Axillary ultrasound is helpful in guiding whether SLNB should be done before or after neoadjuvant chemotherapy. If AUS is negative, the chance of having positive SLNs is relatively low, and it would be reasonable to proceed with SLNB. Even there are positive SLNs, if the number of positive nodes is not more than two and breast-conserving treatment is planned after neoadjuvant chemotherapy, ALND may still be waived according to the conclusion of Z0011 study [33]. If AUS or ultrasound-guided biopsy is positive before neoadjuvant chemotherapy, one may consider SLNB after neoadjuvant chemotherapy.

The SENTINA study investigated the feasibility of SLNB before and after neoadjuvant chemotherapy [34]. It included 1,737 patients undergoing at least six cycles of an anthracycline-based chemotherapy. Among them, 76 % had T2 tumor, 6.4 % had T3 tumor, and 14.2 % had unknown tumor size; 1,022 patients were clinically node negative and 715 patients were clinically node positive. Clinical lymph node status was evaluated preoperatively by palpation and ultrasound. Palpable nodes were considered as negative nodal status if ultrasound showed benign-look lymph nodes. Basically, clinically node-negative status means negative AUS in SENTINA study. No uniformly standard for sonographic lymph node assessment is described in SENTINA. Lymph nodes were classified as suspicious if the hilum/cortex ratio $>2{:}1$ or total loss of the hilum.

Immunohistochemical staining of SLN was not required in SENTINA. Only 25 % of patients had FNA cytology or core needle biopsy confirmation for their positive nodal status. Of the 1,022 patients, who had negative AUS and underwent SLNB before neoadjuvant chemotherapy, 65 % had negative SLN. The IDR of second SLNB in patients who had positive sentinel nodes before neoadjuvant chemotherapy and had a second SLNB procedure after neoadjuvant chemotherapy was 76.2 % or 52.9 % with dual tracers (isotope and blue dye) or isotope only, respectively. Although 70.8 % had negative node revealed by second SLNB, the FNR of second SLNB was as high as 51.6 %.

Some previous studies support that SLNB alone seems feasible after neoadjuvant chemotherapy [35–40]. However, the identification rates and false-negative rates vary widely among different studies due to inclusion of patients of different stages and different nodal status before neoadjuvant chemotherapy. Three recent studies reported the application of AUS related to SLNB after neoadjuvant chemotherapy in patients presenting with positive axillary nodes.

Among the 715 patients presenting with initially suspicious nodes on AUS in SENTINA study, 17 % had persistent suspicious nodes after neoadjuvant chemotherapy and underwent ALND directly after neoadjuvant chemotherapy. AUS converted from positive to negative after neoadjuvant chemotherapy in 83 %

(592/715) of patients. The IDR of SLNB was 80 % (474/592) and FNR was 14.2 % (32/226) in these 474 patients who had successful SLNB. Of the 474 patients, 248 (52.3 %) had negative node and 226 (47.7 %) were node positive.

The FNR of SLND is significantly related to the number of resected sentinel lymph nodes in these patients who converted from node-positive to node-negative status on AUS after neoadjuvant chemotherapy and then underwent SLNB. The false-negative rate was 24.3 % for patients who had only one sentinel node removed, 18.5 % for patients who had two removed, and less than 10 % for patients who had three or more sentinel lymph nodes removed (9.6 % for patients who had at least two SLNs removed). The false-negative rate was also lower, although not significant in multivariate analysis, for 389 patients who underwent SLNB with dual tracers (isotope and blue dye) compared with 164 patients who received isotope alone (8.6 % vs. 16.0 %). But dual tracer was associated with a significant increase in the IDR (87.8 % vs. 77.4 %).

ACOSOG Z1071 trial included 701 eligible patients with cN1 (disease in movable axillary lymph nodes, 663 patients, T1 and T2 69 %, T3 and T4 30 %) or cN2 (disease in fixed or matted axillary lymph nodes, 38 patients) at presentation documented by fine-needle aspiration biopsy or core needle biopsy [41]. Seventy-four percent of patients received neoadjuvant chemotherapy with both anthracycline and taxane. The FNR of SLNB after neoadjuvant chemotherapy was 12.6 %. FNR significantly decreased when dual tracers (isotope and blue dye) were used for mapping ($P = 0.05$; FNR, 10.8 % dual tracer vs. 20.3 % single tracer) and when at least three SLNs were obtained ($P = 0.007$; FNR, 9.1 % for ≥ 3 SLNs vs. 21.1 % for 2). Multivariate analysis revealed that no other factors, such as chemotherapy duration, dual or single mapping agents, single or multiple injection sites, pre-chemotherapy tumor size, and lymph node status after chemotherapy, would affect the FNR of SLNB, once the number of SLNs harvested (2 vs. ≥ 3) was accounted for.

In Z1071 trial, 611 patients had an AUS examination before SLNB after neoadjuvant chemotherapy [42]. The AUS images were submitted for central review by a single radiologist. A lymph node was considered suspicious if the cortex was either focally or diffusely thickened (>3 mm thick) and the fatty hilum was deformed or absent, which is not quite different from the criteria of suspicious node in SENTINA. In the 470 cN1 patients with a post-chemotherapy AUS (negative or positive nodal status) and at least two SLNs removed, FNR of SLNB was 12.6 %. If only patients with post-chemotherapy normal AUS would have been selected for SLNB surgery with resection of at least two SLNs, the FNR would be 9.8 %.

There were no difference of clinical N stage at presentation, completion of all chemotherapy, the number of SLNs removed, and the number of additional axillary lymph nodes removed between patients with normal lymph nodes and those with suspicious nodes on AUS. Patients with post-chemotherapy suspicious nodal status on AUS were more likely to have positive nodes after neoadjuvant chemotherapy, two or more positive SLNs, additional positive nodes, greater number of involved nodes, and larger median SLN metastasis size, than patients with normal AUS

findings. In patients with a normal AUS, 8.6 % had more than two positive SLNs. In patients with a normal AUS but positive SLNs, 62.6 % had no additional positive nodes in the ALND specimen.

SN FNAC study enrolled patients with T0-T3, N1-2, and M0-X breast cancer and biopsy-proven node-positive status receiving neoadjuvant chemotherapy [43]. Among them, 50 % were T2, 40 % were T3, 96 % received both anthracycline and taxane, and 57 % were ER or PR positive and Her2 negative. AUS before and after neoadjuvant chemotherapy was performed. Immunohistochemical staining of SLN was included in pathological examination of SLN, and SLN metastases of any size, including isolated tumor cells, were considered positive. The SLN identification rate was 87.6 %, and the FNR was 8.4 %. If isolated tumor cells in SLN had been considered negative nodal status, the FNR would have increased to 13.3 %. The average number of SLNs removed was 2.7. Although the size of SLN metastases did not correlate directly with the rate of positive non-SLNs, but the average number of residual positive nodes in the ALND after positive SLNs with isolated tumor cells, micrometastasis or macrometastasis after neoadjuvant chemotherapy was 0.7, 0.5, and 2.8, respectively. If only one SLN was obtained, the FNR increased to 18.2 %. In the presence of two or more than two SLNs, the FNR of SLNB decreased to 4.9 %. The FNR of SLNB mapping with dual tracers (isotope and blue dye) and single tracer (radiocolloid) was 5.2 % and 16.0 %, respectively, but the difference was not significant. AUS was also done before and after neoadjuvant chemotherapy. Its impact was not reported.

Based on the above three trials, harvesting only one SN is associated with a high FNR (SN FNAC, 18.2 %; ACOSOG Z1071, 31.5 %; SENTINA, 24.3 %) of SLNB done after neoadjuvant chemotherapy in patients with node-positive breast cancer. In the above three trials, 20–31 % of patients had only one SLN harvested [33, 41, 43]. As there is probably no way to increase the number of harvested SLNs, patients with only one SLN harvested after neoadjuvant chemotherapy better proceed to ALND. The FNR for patients with two or more than two SLNs and SN metastases >0.2 mm was 11.5 % in SN FNAC study, which is close to the FNR of 12.6 % reported in the ACOSOG Z1071 trial but much lower than the 18.5 % in SENTINA patients who had two removed (less than 10 % for patients who had three or more sentinel lymph nodes removed in SENTINA).

By applying immunohistochemical staining in the pathologic evaluation of the SLNs and considering SLN metastases of any size as positive, FNR becomes 8.4 % in SN FNAC trial. While immunohistochemical staining of SLN decreased the FNR in the SN FNAC study, it was not mandatory in both SENTINA and Z1071 trials.

The FNR of SLNB with resection of at least two SLNs in node-positive patients with negative AUS after neoadjuvant chemotherapy was 9.6 % in SENTINA trial and 9.8 % in Z1071 trial. In both trials, AUS was done after neoadjuvant chemotherapy but before SLNB. Patients with suspicious nodal status on AUS in SENTINA trial will undergo ALND directly without SLNB. The percentage of patients with positive nodes revealed by ALND was not reported in SENTINA trial. In this situation, one would use stricter criteria of AUS to select patients with positive nodal status for ALND. Although the AUS criteria of the suspicious node

used in SENTINA trial (criteria of suspicious lymph node: hilum/cortex ratio >2:1 or total loss of the hilum) and Z1071 trial (criteria of suspicious node: the cortex was either focally or diffusely thickened (>3 mm thick) and the fatty hilum was deformed or absent) seem not very different, the central review by single radiologist would probably still use a stricter criteria, e.g., a thinner cortex, to define a negative nodal status [34, 42]. In SN FNAC study, AUS nodal status was also evaluated but not considered in the calculation of FNR of SLNB.

In summary, for patients with positive nodal status undergoing neoadjuvant chemotherapy, AUS should be performed before SLNB after neoadjuvant chemotherapy. Only patients with negative AUS can be considered to undergo SLNB alone after neoadjuvant chemotherapy. ALND should be considered not only for patients with micrometastatic or macrometastatic SLNs but also in patients with isolated tumor cells in SLN. Patients with only one SLN harvested after neoadjuvant chemotherapy better proceed to ALND. Dual tracer with isotope and blue dye should be used for SLNB mapping (Fig. 6.3b).

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