Management of the Axilla

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26.1 Introduction

For much of the twentieth century, Halsted mastectomy was the standard treatment for operable breast cancer [1]. The operation included dissection of the axillary lymph nodes, which was reasonable since the nodes were metastatic in most patients [2]. From the early 1980s, breast-conserving surgery, flanked by irradiation of the residual breast, became an acceptable alternative to mastectomy, and by 1990, breast-conserving surgery was the preferred treatment for early breast cancer [3]. Early breast-conserving protocols included axillary lymph node dissection (AD) since most patients still presented with axillary node involvement. However there was much debate as to the utility of this procedure in patients with a clinically uninvolved axilla. As early as 1977, 5-year results of the NSABP B04 trial had shown that mastectomy patients with no clinically evident axillary disease who did not undergo AD were at no greater risk of distant disease or death than those who did receive AD [4]. Furthermore many surgeons were anxious to avoid AD if possible because of its sequelae: permanent lymphedema was relatively common [5], and pain, arm weakness, loss of arm movement, and limitation of hand movements were not infrequent [6].

On the other hand, axillary node status was recognized as a prognostic indicator in breast cancer [7], and this was important since, at that time (1980s), the only other widely used prognostic factor was the size of the primary.

In the final decade of the twentieth century, sentinel node biopsy (SNB) was introduced as a means of determining axillary status in patients with clinically node-negative disease. This proved to be a major turning point in axillary management and remains the axillary staging procedure of choice today for most women with a clinically negative axilla [8]. For a time, the introduction of SNB muted the debate on the utility of AD in patients with a clinically negative axilla, as it proved to be an accurate but minimally invasive staging procedure, yet permitted avoidance of AD in the growing proportion of patients with a pathologically negative sentinel node (SN).

However the debate on the utility of AD soon reignited as understanding of breast cancer biology increased and systemic treatments improved: in selected patients with limited axillary involvement determined by SNB, AD seems to confer no advantage, while total avoidance of axillary surgery may be justified in selected patients with an uninvolved axilla as determined by palpation, ultrasound or other presurgical investigations. In what follows current indications for axillary management will be presented in detail, followed by an outline of expected future developments.

26.2 Management of the Clinically Uninvolved Axilla

SNB is the standard approach [8] to a clinically uninvolved axilla in all patients except those with T4 disease (including inflammatory breast cancer) and those with a clinically involved axilla prior to neoadjuvant treatment. SNB was validated by a series of trials [9–14], and it is now clear that SNs can be detected in over 97% of patients, that their status predicts axillary status with about 90% accuracy, and that the axilla is site of first failure in less than 1% of cases [15].

26.2.1 SNB Technique

Several methods have been developed to identify SNs. The commonest involve peritumoral or periareolar injection of either blue dye or colloid labeled with the short-lived gamma emitter ^{99m}Tc. If blue dye is used, the surgeon searches visually for blue lymph ducts leading to blue nodes after making an incision in the axilla [16]. If the radiotracer method is used, the surgeon uses a gamma-detecting probe to guide the axillary incision and also find and remove the SNs.

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Scintigraphy may be used to identify axillary hotspots prior to surgery [17]. Some advocate use of both blue dye and radiotracer to ensure that at least one SN is always found [18]. Experience at the European Institute of Oncology is that an SN is identified in over 99% of cases using radiotracer alone [19]. Only if an axillary hotspot is not seen on scintigraphy after two radiotracer injections is the blue dye method used [20]. Recently the dye indocyanine green which fluoresces in the infrared has been used as an alternative to radiotracer [21]. It has a closely similar SN identification rate to radiotracer (≈99%) and is recommended for centers not equipped to handle unsealed radioactive materials. After indocyanine injection, fluorescence is elicited and detected by a "photodynamic eye" camera: the lymphatic drainage thus made evident is visualized in real time on a monitor. The fluorescence is followed from the injection site to the axilla, and an incision is made where the fluorescence disappears into the axilla. The fluorescent nodes are localized and excised [21].

Another recently developed SN detection technique, called SentiMag, involves injection of magnetic particles (Sienna+) and their detection with magnetic sensor. The system comprises a mains-powered base unit, a handheld probe connected to the base unit by flexible cable, and an air-operated footswitch for balancing [22]. The particles move in the lymph ducts to accumulate in the SN. The probe emits an alternating magnetic field which is absorbed by the Sienna+ particles. In turn these particles emit a magnetic field detected by the probe. Results using this method appear comparable to the radiotracer method [22].

26.2.2 Surgical Removal and Pathological Examination of SNs

If the radiotracer method is used, the gamma-detecting probe is used in the operating room to verify the presence of one or more axillary hotspots. SNB begins after the primary tumor has been removed with a 2–3-cm incision made over the hotspot (loudest audio signal on the counter connected to the probe). The isolated SNs are removed and tagged separately for frozen section examination. The axilla is then checked any for residual activity, which if present is removed. While waiting for the result of the frozen section examination, the surgeon closes the breast. If the SNs are disease-free or contain only micrometastases, the axilla is closed and not further axillary treatment given. If one or more SNs harbor metastases, complete (three-Berg-level) AD is performed (see below).

Examination of three to six SN sections is insufficient to ensure a low false-negative rate and consequently high probability that SN status reflects axillary status, so a more extensive examination of all SNs is necessary. The method used at the European Institute of Oncology is to bisect each node along its major axis and cut 15 pairs of 4-μm thick sections 50–100-μm intervals in each half node (60 sections per node). If any residual tissue is left, additional pairs of sections are cut at 100-μm intervals to completely sample the node. One section of each pair is stained with hematoxylin and eosin and examined. Only is there is any doubt as to the presence of metastasis is the second section of a pair stained by a rapid immunohistochemical method to reveal cytokeratins. SN status is then communicated to the surgeon, and depending on the result AD is performed or not performed.

26.2.3 One-Step Nucleic Acid Amplification

One-step nucleic acid amplification (OSNA) is a relatively new technique for the intraoperative analysis of SNs in breast cancer. The removed SNs are homogenized, and the number of copies of cytokeratin-19 (CK19) mRNA is determined by a rapid quantitative method shown to accurately reflect SN status as determined by pathological analysis of SN sections [23]. The number of mRNA copies correlates with extent of SN involvement (absent, micrometastatic, or macrometastatic) and permits no further axillary treatment when the copy number is low. The method has the advantage that it is reproducible and standardized and does not depend on the expertise of the pathologist, so it is particularly suited to institutes that cannot spare a pathologist for intraoperative SN examinations.

26.2.4 SNB After Breast Surgery

Previous breast-conserving surgery does not contraindicate SNB when a woman presents with disease recurrence in the breast and a clinically negative axilla. It was initially thought that surgery would disrupt the lymphatic drainage so that a new SN would be less likely to be found and would probably not receive lymph from the tumor. The European Institute of Oncology carried out 543 SNBs with radiotracer in women who had received prior breast surgery (excisional biopsy or quadrantectomy). The radiotracer was injected between the breast scar and the axilla, and the presence of an axillary initially verified with lymphoscintigraphy. An SN was identified intraoperatively in 99% of cases and was negative in 70% of them. Among the 161 patients with a positive SN, it was the only positive node in 61.5% of cases. After a median of 2 years, four cases developed axillary failure, two of which had received complete AD [24].

Even a previous mastectomy does not seem an absolute contraindication for SNB. Four patients treated at the European Institute of Oncology with total mastectomy and breast reconstruction with prosthesis developed an isolated

subcutaneous recurrence, with a clinically negative axilla. Subdermal injection of radiotracer has permitted to identify SNs [25]. Preoperative lymphoscintigraphy showed one axillary SN in three patients and two SNs in the fourth patient: SNs were positive in two patients who received AD, negative in the other two who received no further axillary treatment. Follow-up is too brief to suggest conclusions. Nevertheless it is difficult to decide where to inject radiotracer in mastectomied patients since scar tissue and fibrosis surrounding the scar are likely to impede lymphatic drainage and hence SN identification.

26.2.5 SNB After SNB and Radiotherapy

When disease reappears in the operated breast (recurrence or second cancer) after breast-conserving surgery and SNB, a new SNB is indicated if the axilla is clinically clear. Although the lymphatic system is disrupted by breast and axillary surgery, lymphatic drainage subsequently re-forms to allow identification of a new SN [26]. Even after radiotherapy the lymphatic drainage system re-forms, allowing SN identification in most patients [27]. In recurring patients, as in those treated for the first time, the prognostic information provided by SN examination is important; and the patient should be spared AD if possible. From May 2001 to December 2011, 212 patients treated at the European Institute of Oncology by breast-conserving surgery plus SNB with a pathologically clear SN experienced local reoperable recurrence. Preoperative lymphoscintigraphy demonstrated at least one new SN in 207 patients (97.7%), whereas no drainage was observed in five patients (2.3%). One or more SNs were surgically removed from 196 of the 207 patients. SNs were not isolated from the remaining 11 patients. The success SNB rate was 92.5%. Extra-axillary drainage pathways were visualized in 17 (8%) patients. The annual axillary recurrence rate after a median follow-up period of 48 months was 0.8%, and the cumulative incidence of axillary recurrence at 5 years was 3.9%. These data indicate that second SNB should be considered for patients who underwent conservative surgery and had a negative axilla and subsequently recurred locally [28].

26.2.6 SNB After Neoadjuvant Treatment

The 2014 ASCO guidelines indicate that most women with breast cancer should have SNB and reported "intermediate level evidence" that the benefits of SNB after neoadjuvant treatment outweighed the harms. However the guidelines did not recommend SNB in women with an involved axilla prior to neoadjuvant treatment, even if they became cN0 afterward. The reason given was that the false-negative rate (FNR) may range from 10 to 30%, and this was considered unacceptably high [8]. Several studies in fact found FNRs above 10% [29–32]; others however found FNRs below 10% [33–36]. Furthermore the clinical significance of a high FNR is unclear, since the early randomized trials on SNB found that while the FNR was of the order of 10% (control arms), the axillary failure rate in the SNB-only arms was of the order of 1% [10, 14].

To address this issue, a retrospective study from the European Institute of Oncology investigated outcomes in a consecutive series of patients treated between 2000 and 2010. One group of 147 patient was cN1/2 before neoadjuvant treatment and became cN0 afterward and received SNB with AD if the SN was positive. These were compared with to those in a consecutive series of 247 patients, treated over the same period, who were cN0 before neoadjuvant treatment and remained so afterward. After a median follow-up of 61 months, just one patient in each group developed axillary failure as first event; one other patient in each group developed simultaneous local plus regional failure suggesting that SNB is acceptable in cN1/2 patients who become cN0 after neoadjuvant therapy. Furthermore survival outcomes were closely similar in the two groups [37]. The 2015 St. Gallen Conference Panel [38] considered that SNB was appropriate in patients with a clinically positive axilla at presentation who downstaged after neoadjuvant chemotherapy, but that AD was required if even one SN was positive. Nevertheless FNRs remain high unless three or more SNs are examined.

26.2.7 SNB in Multicentric Disease

In multicentric breast cancer, the different disease foci may drain to different axillary nodes so a negative SN has a greater probability of being a false negative (and not reflecting the true state of the axilla). At the European Institute of Oncology, two techniques are adopted to minimize this possibility: (a) if there are two cancer foci, two subdermal injections of radiotracer are given; (b) if there are several tumor foci, a single sub-areolar injection is given, since there is evidence that the axillary nodes receive lymph from a periareolar network of superficially located lymph ducts [39]. Between June and December 2007, 337 patients with multicentric breast cancer and a clinically negative axilla underwent SNB at the European Institute of Oncology. In 100% of cases, at least one SN (median 1.7, range 1–7) was identified. A total of 138 patients with either negative SNs ($n = 134$) or isolated tumor cells in the SN ($n = 4$) did not undergo AD. There were 27 (19.5%) events in the latter group, but only three (2.2%) developed axillary disease after a median follow-up of 5 years (range 17–134 months) providing evidence that SNB is acceptable in patients with multicentric disease [40].

26.2.8 SNB in Pregnancy

Results of a dosimetry study carried out at the European Institute of Oncology indicate that the use of radiotracer to identify the SN in pregnant women is unlikely to have any adverse effects on the fetus. The study recruited 26 premenopausal, nonobese, nonpregnant breast cancer patients of median age 36.7 years scheduled for SNB with radiotracer. Scintigraphy revealed radiation (gamma rays) coming only from the injection site and the axilla. Skin dosimeters (thermoluminescent detectors) were placed on the epigastric, umbilical, and hypogastric regions to measure radioactivity that might be received by the fetus. In 23 of these patients, the absorbed dose was below that detectable by the detectors; in the remaining three patients, minimal doses (about 1000 times lower than the threshold for deterministic effects) were recorded. These findings suggest that use of the standard amount of radioactivity (12 MBq di ^{99m}Tc) to perform SNB is safe at all stages of pregnancy [41].

26.2.9 SNB in Male Breast Cancer

Only about 1% all breast cancers occur in men. Breast cancer is generally diagnosed later in men than women, and around 60% of male cases have axillary involvement at diagnosis, when SNB is not indicated. However, tumor biology, prognostic factors, and prognoses seem closely similar in the two sexes [42] (even though trials to define optimal treatments in men have not been conducted), and men with a clinically clear axilla should therefore be candidates for SNB. SNB is particularly indicated because the sequelae of AD may be more incapacitating in men as their job or lifestyle may be physically demanding [43]. Between April 1999 and January 2005, 75 men were treated at the European Institute of Oncology for breast cancer. Thirty-two with a clinically negative axilla underwent SNB, and at least one SN was found in all cases (mean 1.5, range 1–3). In six cases the SN was metastatic: micrometastatic in two, only one involved axillary node in the other four. After a median follow-up of 30 months (range 1–63), there were no recurrences or axillary failures [23].

26.2.10 SNB in Ductal Intraepithelial Neoplasia

Since ductal intraepithelial neoplasia (DIN) does not metastasize by definition [44], SNB does not seem appropriate. This is supported by a study from the European Institute of Oncology [45] which found that, in 854 cases of pure DIN (no microinvasive foci identified on definitive pathological examination), SN involvement occurred in only 1.9% of cases, decreasing to 1.4% if SNs with only isolated tumor cells were excluded. This finding and others [46] justify not performing SNB in patients with "pure" DIN.

Nevertheless there is always the possibility that DIN may harbor foci of invasive or microinvasive disease not found by preoperative biopsy. The review by Shapiro-Wright et al. [47] found that the risk of a metastatic SN was relatively high in the presence of high-risk DIN (characterized by high grade, comedo necrosis, or large size) and also when the lesion was palpable. In such cases DIN was frequently (10–38%) upstaged to microinvasive or invasive breast cancer on pathological examination. This study also found that in DIN patients scheduled for mastectomy, the SN was involved in a high proportion of cases. In fact contraindication for breast conservation is a risk factor for the presence of invasive cancer or progression to invasive cancer. Tunon-de-Lara et al. [48] also found that invasive disease was frequently underestimated by vacuum-assisted biopsy of DIN patients scheduled for mastectomy.

These findings indicate that SNB should be performed in DIN patients only when biopsy indicates invasive disease; when mastectomy is indicated; when the lesion is palpable; and when the lesion is large. These recommendations are essentially the same as those of ASCO 2014 [8].

The question remains, however: should axillary dissection be performed in DIN patients with a positive SN?

Since the Z0011 trial showed that AD is not necessary in patients with invasive breast cancer and fewer than two positive SNs treated by conservative surgery and systemic therapy [49], it would seem that AD is overtreatment in DIN patients with or without micro-invasion, provided they are scheduled for conservative breast surgery. In fact, in only 0.39–13.7% of such cases are other axillary nodes involved [49, 50]. It is therefore recommended that immediate AD not be performed if the SN is positive during intraoperative examination, in DIN patients undergoing conservative breast surgery.

26.3 Management of the Metastatic Axilla

AD remains the standard treatment if the axilla is metastatic, irrespective of whether breast-conserving surgery or mastectomy is scheduled. If an SN is positive, the AD procedure initially involves enlargement of the excision to access the SNs. If the patient has clinically palpable axillary lymph nodes, increasingly, they are confirmed as positive prior to surgery by needle biopsy, ultrasound, or both, and the surgeon proceeds to AD after removing the primary tumor. The excision is made in continuity with the breast incision when the cancer is in the upper-outer quadrant and is separate when the tumor is located elsewhere. A small lateral cutaneous flap is then prepared to allow access to the lateral margin of the

latissimus dorsi, its insertion in the humerus, the coracobrachialis muscle, and the lateral portion of the vasculonervous tract. The margin of the latissimus dorsi is isolated along its length so as to identify and prepare the blood vessels and the thoracodorsal nerve. The adipose tissue between the internal fascia of the latissimus dorsi and the surface of the chest wall is detached. At this point the long thoracic nerve (Bell's nerve) adherent to the chest wall may be observed under the muscle fascia and whose pathway runs from the high portion of the latissimus dorsi vasculonervous tract to the lower part of the serratus muscle. The medial cutaneous flap is now prepared to access the lateral margin of the pectoralis major and to identify the surface between this and the underlying pectoralis minor. By introducing a retractor, the pectoralis minor may be accessed. The adipose tissue between the two muscles, which includes the Rotter lymph nodes, is thus carefully explored, and if nodes are palpable they are removed, sparing always the thoracic acromial peduncle and the interpectoralis vessels. The coracoclavicular pectoralis ligament is now located and is displaced medial to the vasculonervous thoracic acromial fascia. The margins of the pectoralis minor muscle are identified, and, medially and laterally to the coracoclavicular pectoralis fascia, the index finger is introduced under the venter musculi. Dissection of the adipose tissue continues by uncovering the plexus brachialis and the axillary vein—the anterior surface of which is isolated. By following the vein medially, the tendon of the subclavius muscle becomes visible, thus reaching the apex of the axilla (third level) where the highest axillary lymph nodes and lymphatic vessels are located. These should be isolated carefully, excising the adipose tissue from the tendon of the subclavius muscle and pulling it downward. The lateral limit of each lymph node level should be marked by metal disks or different colored threads to facilitate pathological examination. Performed in this way, so as to spare all vascular and nervous tracts of the muscles, including the intercostal nerves, AD causes side effects in less than 6% of cases yet provides maximum possible prognostic information [51]. By contrast random biopsy of one axillary node, sampling, or removal of the first level only does not ensure disease removal, does not completely obviate the risk of lymphedema, and ignores the possibility of skip metastases, which are may occur in up to 12% of cases.

26.4 Future Developments

In a sense, the future of axillary management is already here. Trials have shown that AD does not confer any benefit in selected patients with a metastatic SN. Perhaps the most important of these was the Z0011 trial [49] which recruited 891 patients with T1-T2 disease, non-palpable axillary nodes, and macrometastases in no more than two SNs, who underwent breast-conserving surgery and whole breast irradiation. They were randomized to either AD (at least ten nodes removed) or no further treatment to the axilla. Most patients also received systemic adjuvant therapy. Overall 5-year survival was 91.8% (95% CI, 89.1–94.5%) in the AD group and 92.5% (95% CI, 90.0–95.1%) in the SNB only group. Axillary failure rates were low in both groups.

The IBCSG 23-01 trial [52] assessed whether omitting AD in patients in whom one or more SNs contained only micrometastases (foci ≤2 mm) had any effect on outcomes. Patients with a non-palpable axilla and tumor up to 5 cm in diameter were eligible; they could also be scheduled for mastectomy. They were randomized to AD versus no further axillary treatment, and after 5 years, there were no significant differences in outcomes between the groups, with axillary failure rates low in both groups.

The AMAROS trial investigated whether axillary irradiation could serve as an alternative to AD in patients with clinically node-negative disease found to have a positive SN. After a median follow-up of 6.1 years, survival outcomes did not differ between the two arms, and regional control rates were high (99.5% and 99.0%) although there were fewer side effects in axillary irradiation arm (lymphedema in 28% of AD arm vs. 14% of axillary irradiation arm patients; $p < 0.0001$) [53, 54].

Further evidence was provided by long-term results of the INT09/98 trial [55], which started the pre-SNB era. The trial randomized patients, age 30–65 years, with T1N0 disease to quadrantectomy with or without AD. A total of 517 patients were evaluated. After a median follow-up of nearly 11 years (127.5 months; interquartile range 113–141 months), neither overall nor disease-free survival differed between the AD and no AD arms. Although overt axillary disease occurred in 22/245 (9.0%) of no AD arm patients (a median of 30 months after surgery), this had no effect on survival outcomes. The authors noted that the biological characteristics of primary were an adequate guide to adjuvant treatment.

Based on the findings of these studies, the 2014 ASCO guidelines [8] and 2015 St. Gallen Conference guidelines [38] recommended that most women scheduled for breast-conserving surgery and whole-breast radiotherapy, and found to have just one to two metastatic SNs, should not undergo AD, although it might be preferable if they were given some form of systemic therapy.

The question obviously arises: if AD can be omitted in many patients with a positive SN, why should we bother to perform SNB? The ongoing SOUND trial was designed to answer this question. Patients with a clinically negative axilla but positive SN are randomized either to AD or to no further surgical treatment of the axilla. To be eligible, patients must be candidates for breast-conserving surgery and have a lesion of ≤2 cm; furthermore axillary negativity must be ascertained by palpation plus axillary ultrasound, with ultrasound-guided fine needle aspiration if a single doubtful lymph node is identified on ultrasound [56].

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