Management of the Axilla

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15.1 Introduction

Some form of axillary surgery is an integral component in the loco-regional management of early breast cancer. Surgical techniques have become progressively less extensive over the past 30 years in terms of both parenchymal and nodal resection of breast and axillary tissues, respectively. Despite the widespread introduction of breast conservation surgery (BCS), a formal axillary lymph node dissection (ALND) was, until recently, the standard procedure of choice for management of the axilla in the majority of patients irrespective of primary tumour characteristics. Breast screening programmes and heightened public awareness have led to smaller tumour size at presentation and a lower proportion of patients with nodal involvement. Approximately 25–30 % of patients now have nodal disease at the time of diagnosis compared with 50 % two decades ago [1]. For those patients with positive nodes, removal of axillary nodes containing tumour foci minimizes the chance of loco-regional relapse and can provide crucial information for guiding systemic adjuvant treatments. Moreover, axillary nodal status remains the single most important prognostic factor in breast cancer and has yet to be superseded by newer molecular indices [1, 2]. Nonetheless, for node-negative patients with favourable primary tumour parameters, ALND represents over-treatment and can be associated with significant morbidity [3, 4]. Increased rates of node negativity have spurred the investigation of non-invasive methods for imaging the axillary nodes. However, these alone are questionable as a staging modality due to limitations of resolution at the microscopic tumour level. Routine pre-operative axillary ultrasound in combination with percutaneous node biopsy for tissue acquisition provides crucial staging information on regional nodes [5]. The optimum method for managing the axilla in breast cancer patients remains controversial, but there is compulsion to apply surgical methods for purposes of staging in all patients with invasive cancer. The aforementioned stage shift coupled with failure of ALND dissection to confer any clear survival benefit [6, 7] has prompted exploration of less intrusive methods for surgical staging of the axilla. These alternative methods involve either a blind or targeted form of sampling in which a variable, though restricted number of nodes are removed (usually < 4–5 nodes). Non-targetted sampling of the axillary nodes has been championed by a surgical minority for several years, but this technique has now evolved into a targeted form of sampling using blue dye alone, the so-called blue dye-assisted node sampling (BDANS) [8]. Sentinel lymph node biopsy (SLNB) has been embraced around the world as a standard of care for breast cancer patients and ideally incorporates dual localization techniques using both blue dye and radioisotopic localization. Nonetheless, despite SLNB being the dominant method for staging the axilla in clinically node-negative patients, technical aspects await standardization and variations in details of practice persist. Breast cancer is a heterogeneous disease in terms of its pathobiology and this renders any blanket approach to management of the axilla inappropriate. A selective policy based on thresholds of probability for nodal involvement could include not only ALND, but also SLNB, BDANS and observation alone. It should be noted that it is not the absolute incidence of nodal involvement per se which is important, but rather the proportion of these metastases which develop into clinically relevant disease which is determined not only by surgical extirpation but also adjuvant therapies. The latter might be manifest either as loco-regional relapse or as distant metastases which have

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arisen from axillary deposits acting as a source for tertiary spread.

This chapter will address nodal anatomy and patterns of lymphatic dissemination in breast cancer together with underlying biological paradigms. Some basic clinical issues will be discussed including the indications for ALND and optimum axillary management in patients who do not require ALND either as a primary or delayed procedure.

15.2 Anatomy of the Axillary Lymph Nodes

An understanding of nodal anatomy is important in the surgical management of breast cancer. There is often confusion in designation of nodal groupings with classification based on clinical, anatomical or surgical criteria.

1. CLINICAL GROUPINGS—medial, lateral, anterior, posterior, apical
2. ANATOMICAL GROUPINGS—lateral, anterior (pectoral), posterior (subscapular), central, subclavicular, interpectoral (Rotter's)
3. SURGICAL—the axillary lymph nodes can be divided into 3 compartments which are defined in terms of their relationship to the pectoralis minor muscle [9].

LEVEL I—nodes below and lateral to the pectoralis minor muscle

LEVEL II—nodes deep to the muscle and lying posterior to the medial and lateral borders of the pectoralis minor muscle

LEVEL III—nodes above and medial to pectoralis minor

A complete ALND refers to removal of axillary nodes at levels I, II and III, whilst a partial ALND implies a more limited clearance of nodes at levels I and II only. The term sampling describes a blind or targeted resection of a variable number of nodes, usually at level I; the number of nodes removed is generally inversely related to the degree of targeting (Fig. 15.1).

15.3 Lymphatic System of the Breast

Metastases to regional lymph nodes is a common pattern of dissemination for solid epithelial tumours which commonly invade local structures and spread in a progressive and sequential manner from a primary tumour focus. The loco-regional pathways of spread lie in anatomical continuity with lymphatic vessels which act as a link between the index tumour and regional nodes. Metastatic dissemination of breast cancer occurs predominantly via the lymphatic system in accordance with the Halstedian paradigm, though it is acknowledged that a significant proportion of breast cancers are systemic at the outset as a result of tumour cells entering the bloodstream at an early stage of neoplastic development. Furthermore, such haematogenous dissemination is not conditional upon nodal involvement and access to the circulation can occur through both lymphatico-venous communications in regional nodes and the 'leaky' endothelium of the tumour neovasculature.

The lymphatics of the breast form an extensive and complex network of periductal and perilobular vessels which drain principally to the axillary nodes. The mammary gland is derived from ectoderm and develops from anterior thoracic wall structures. As noted by Haagensen [10], the lymphatics of the breast skin and parenchymal tissue are interconnected, and this accounts for preferential drainage of cutaneous malignancies to axillary nodes. Moreover, current practices in SLNB whereby tracer agents are injected intra-dermally are dependent upon the lymphatic system of the breast functioning as a single biological unit. Flow within this network of valveless vessels is passive and this results in a degree of plasticity which is relevant to malignant infiltration; the unidirectional flow of lymph may be diverted due to blockage at proximal sites by tumour emboli. The subepithelial lymphatics of the skin of the breast represent part of the superficial system of the neck, thorax and abdomen. These vessels are confluent over the surface of the body and the subepithelial plexus of lymphatics communicates directly with subdermal vessels to form a cutaneous plexus. Within the region of the nipple-areolar complex, this cutaneous plexus is linked to the Sappey subareolar plexus which receives lymphatics from the glandular tissue of the breast and has a key role in accommodating the dramatic surges of lymph flow occurring during lactation [11, 12]. From this subareolar and a related circumareolar plexus, lymph flows principally to the axillary nodes via a lateral lymphatic trunk. This together with minor inferior and medial lymphatic trunks drains along the surface of the breast to penetrate the cribriform fascia and reach the various groups of axillary nodes (Fig. 15.1).

Although the internal mammary nodes were recognized by Handley as a primary route for lymphatic drainage from medial and central zones of the breast [13], the majority of breast cancers metastasize to the axillary nodes irrespective of the index quadrant [14]. Fewer than 10 % of node-positive tumours exclusively affect the internal mammary nodes, and clinical manifestations of such metastases are rare. Furthermore, the biological significance of internal mammary node involvement is uncertain [15] and substantial morbidity can ensue from surgical extirpation of these nodes with no gains in overall survival from these more aggressive resections [16]. Veronesi examined the impact of extended radical mastectomy in which nodes along the internal mammary chain were excised. Amongst a group of 737 patients, 53.2 % were axillary node positive and an

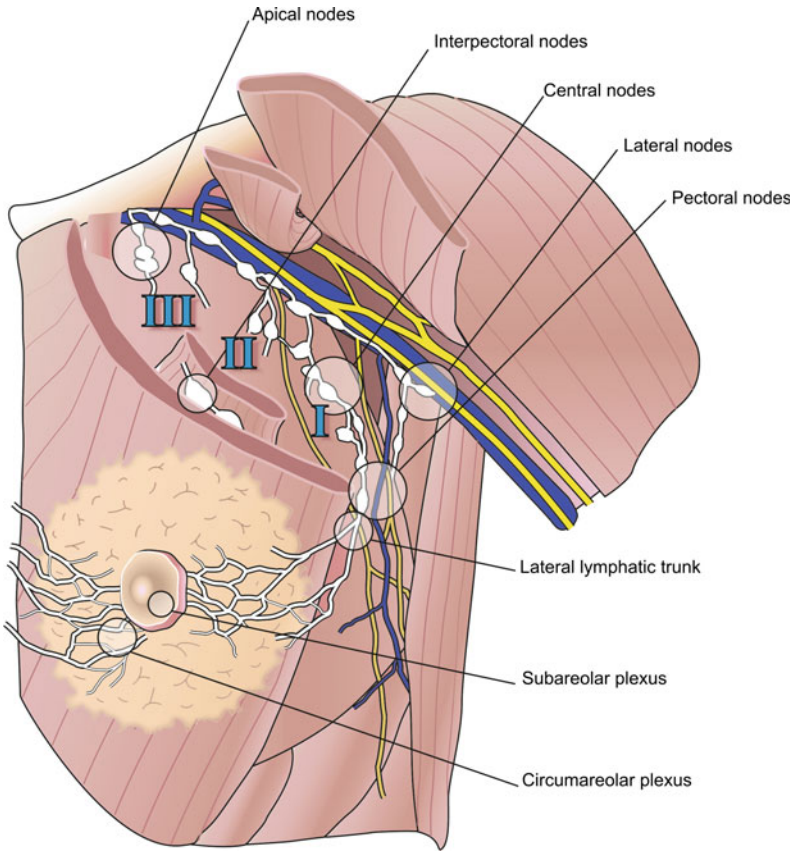

Fig. 15.1 The axillary lymph nodes are located at levels I, II and III; this is a surgical classification and indicating nodes which lie below/lateral, deep/posterior and above/medial to the pectoralis minor muscle, respectively. The lymphatic system of the breast is a complex network of arborizing vessels. A cutaneous plexus is linked to a subareolar plexus which receives lymphatics from the glandular tissue of the breast. From this subareolar and a related circumareolar plexus, lymph flows principally to the axillary nodes via a lateral lymphatic trunk

estimated 20.5 % had positive internal mammary nodes. The comparison group were radical mastectomy patients operated on in the 1960s who received no adjuvant treatment (radiotherapy, chemotherapy or endocrine therapy). No survival benefit was apparent from internal mammary node dissection within this study which was published at the turn of the millennium [17].

The internal mammary chain (IMC) represents one of the accessory drainage pathways of the breast and is considered to receive up to one-quarter of lymphatic flow. However, former estimates based on post-partum injection of colloidal gold suggested that as little as 3 % of the breast lymph flows to the IMC. The IMC is identified on routine lymphoscintigraphy during sentinel node localization in about 15 % of cases [14]. Accessory pathways of lymphatic drainage assume greater importance in more advanced states of disease when the main axillary drainage route has become obstructed [14, 18]. In addition to the IMC, these accessory pathways include the following routes:

1. substernal, crossover (contralateral IMC) [12, 19],
2. pre-sternal crossover (contralateral breast) [20],
3. mediastinal [20],
4. rectus abdominus muscle sheath to subdiaphragmatic and subperitoneal plexus (liver/peritoneal nodes).

Interestingly, with the advent of lymphoscintigraphy as part of sentinel lymph node mapping, drainage to the IMC is more likely when isotope is injected deep within the breast (close to the pectoral fascia) and uncommon when peri-areolar injections are employed [21].

The original definition of the sentinel lymph node was '*the first draining lymph node on the direct pathway from the primary tumour site*' [22]. In its purist form, this definition implied that there was a single node to which cancer cells drain first before proceeding on to higher echelon nodes. The sentinel node hypothesis is 'Halstedian' and presupposes a sequential and orderly spread of cancer cells from the primary tumour to the first draining or sentinel node (usually level I), from whence passage to level II and in turn level III nodes occurs. This hypothesis has proved to be slightly imperfect and does not accord with current understanding of lymphatic drainage patterns from anatomical studies nor the pathophysiology of disordered lymphatic flow [23]. The networks of lymphatic vessels arborize extensively in multiple directions [24] and converge towards a group of 3–5 lymph nodes at level I of the axilla [25] (Fig. 15.2). Detailed anatomical studies undertaken in the 1950s revealed no evidence of a single first or 'sentinel' lymph node at the 'gates of the axilla' towards which all lymphatic channels converge before passing to more distal nodes. As experience with SLNB has

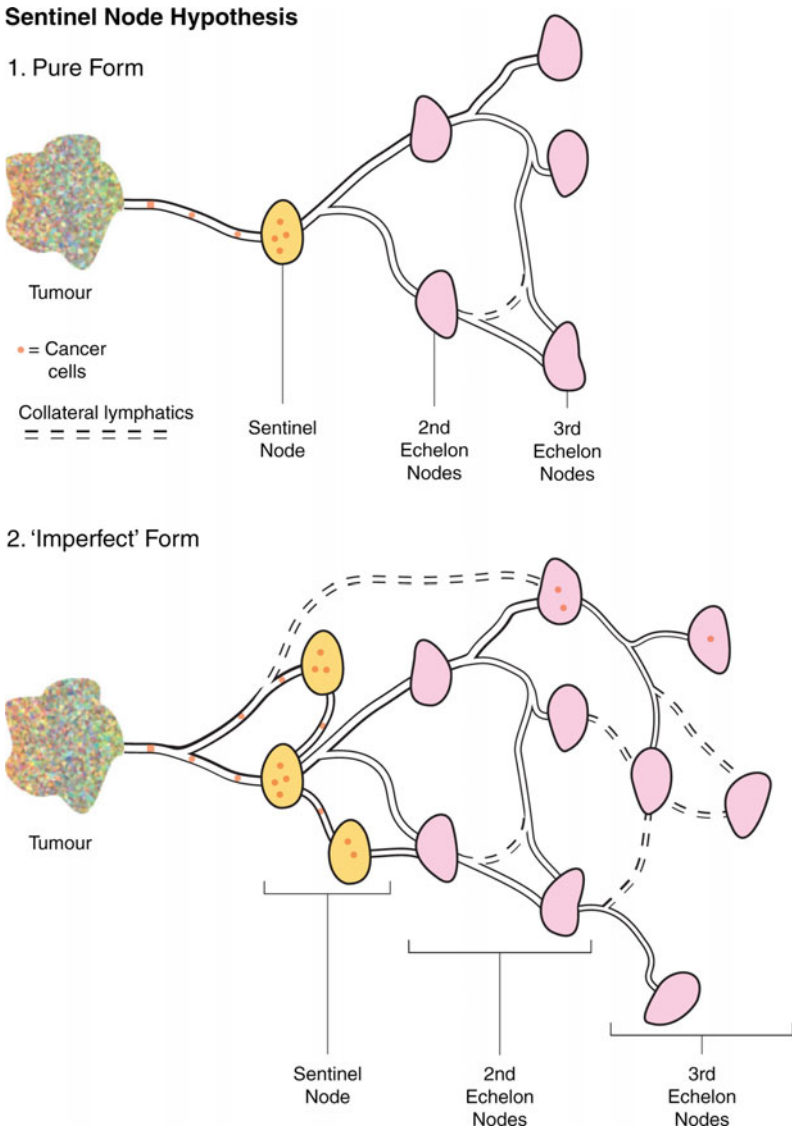

Fig. 15.2 (1) According to the sentinel node hypothesis in its 'pure' form, cancer cells pass from a primary tumour focus to a first draining or sentinel node from where sequential passage to second and third echelon nodes occurs. (2) In reality, cancer cells drain initially to a group of three to five nodes which are all 'sentinel' nodes if they are blue, hot, blue and hot or palpably suspicious. The plasticity of the lymphatic system permits cancer cells to travel via collaterals to non-sentinel nodes. This account for the finite false-negative rate of sentinel node biopsy

accrued using several different methodologies, the average number of nodes removed is between 2 and 3 with false-negative rates being minimized when multiple sentinel nodes are harvested [26]. Indeed, when palpably suspicious nodes are also removed at operation and classified as 'sentinel', many studies report an average of almost 4 nodes [23, 27]. This group of sentinel nodes may therefore correspond to the group of 3–5 nodes at level I from which there is a predictable passage of lymph towards level II and level III nodes. The 'plasticity' of the lymphatic system potentially allows skip metastases to occur in which nodes at levels II and III become involved in the absence of disease affecting level I nodes. In a study of the distribution of nodal metastases in more than 500 patients, Veronesi and colleagues reported skip metastases in only 4 % of cases [28]. In this study, level I nodes alone were found to be involved in 58 %, levels I and II nodes in 22 % and all 3 levels in 16 % of patients. Despite the occurrence of skip lesions, there is generally an orderly passage of lymph from nodes at level I through levels II and III. When nodes at levels I and II are tumour free, the chance of skip metastases at level III is only 2–3 %. For this reason, a standard ALND involves clearance of nodes at levels I and II (partial ALND) only. When at least 10 nodes have been removed during a partial ALND, the axilla should be correctly staged in 96 % of patients with primary breast cancer. When fewer than 10 negative nodes are resected, there is less confidence that the axillary basin is truly negative and involved nodes may have been left behind in a non-targetted dissection. Conversely, when overtly malignant nodes are present at levels I and II, it is customary to undertake a complete ALND which includes level III nodes. The ipsilateral supraclavicular nodes can subsequently be irradiated when extensive nodal involvement is confirmed histologically. More radical resection of axillary nodes is

associated with greater upper limb morbidity including lymphoedema, shoulder stiffness, pain and paraesthesia [3, 4]. The benefits of ALND in terms of regional disease control, staging information and prognostication must be balanced against these potential sequelae of which lymphoedema is the most serious concern. The overall incidence of lymphoedema is cited between 10 and 30 % [4, 29–31]. Rates are generally lower for a level II ALND (10–15 %) compared with a level III ALND (25 %). The combination of a complete ALND with irradiation of the axilla can lead to rates of lymphoedema as high as 40 %. There is rarely any justification for combined axillary dissection and irradiation nowadays. Furthermore, surgeons often loosely refer to level II/III ALND in the literature and this confounds interpretation of data on rates of lymphoedema formation. It has been commented that removal of an additional 3–4 nodes maximum at level III is unlikely to significantly impact on documented rates of lymphoedema [32]. The latter remains a common complication which can lead to major physical and psychological morbidity [33] and in the longer term to the rare complication of lymphangiosarcoma (Stewart-Treves Syndrome) [34]. Though it is often the non-dominant upper limb which is affected (more breast cancers occur on the left side), lymphoedema causes symptoms of heaviness and discomfort with associated functional impairment and an unsightly appearance. The accumulation of protein-rich fluid within the extracellular compartment renders the limb prone to recurrent superficial infection which contributes to more chronic inflammatory changes with fibrosis. Disruption and blockage of the lymphatics raises hydrostatic pressure within other parts of the lymphatic system and promotes further tissue oedema by hampering absorption of excess fluid back into the lymphatic vessels. The precise aetiology of lymphoedema remains unclear, but it is related to the extent of extirpation of axillary nodes. The latter disrupts lymphatic drainage pathways and thus compromised function is more likely when surgical dissection is more extensive [33].

15.4 Axillary Lymph Node Dissection

15.4.1 Surgical Aspects

The axilla is a pyramidal space with an apex directed into the route of the neck and a base bounded infront by the anterior axillary fold (lower border of pectoralis major), behind by the posterior axillary fold (tendons of latissimus dorsi and teres major muscles) and medially by the chest wall [18]. The axillary tissue is composed of adipose and nodal elements. A partial (level II) ALND involves resection of all tissue inferior to the level of the axillary vein with no attempt to skeletonize the latter. All nodal/fatty tissue is cleared from the lateral edge of the latissimus dorsi muscle and to the medial border of pectoralis minor muscle. Wrapping of the arm during surgery permits flexion and adduction of the upper arm with relaxation of the pectoralis major muscle which facilitates dissection towards the apex of the axilla. The pectoralis minor muscle was previously either removed or divided to gain access to higher echelon nodes (namely at level III). The nerves to serratus anterior (long thoracic) and latissimus dorsi (thoracodorsal nerve) muscles are closely applied to the medial and posterior walls of the axilla, respectively. These are important motor nerves and should be preserved during axillary surgery unless encased by tumour. Damage to the long thoracic nerve results in a winged scapula and care should be taken not to inadvertently draw this structure laterally away from the chest wall during dissection of the axillary contents as it lies outside the fascia of serratus anterior. By contrast, the intercostobrachial nerve (ICBN) is purely sensory and crosses the axilla towards its base. It tends to be embedded in fatty/nodal tissue and its anatomical course renders it vulnerable during extirpative surgery. The ICBN has historically been considered a minor sensory nerve whose sacrifice during axillary surgery results in transient sensory loss and paraesthesia with minimal symptoms. In recent years, increasing attention has focused on chronic residual morbidity consequent to nerve division and pathophysiology of the ICBN. Provided the nerve is not encased by infiltrative tissue, oncological clearance is adequate and some surgeons advocate preservation of the ICBN, particularly when there is no macroscopic evidence of nodal involvement. Temple and colleagues found that more than one-third of patients in whom the ICBN was sacrificed reported symptoms of dysaesthesia/paraesthesia and concluded that nerve preservation reduces long-term morbidity [35]. However, the main nerve trunk often divides distally into smaller branches which can preclude preservation. Inadvertent division is not uncommon and the potential benefits of nerve preservation are dubious and poorly documented; nerve preservation does not eliminate potential sensory disturbances. Furthermore, randomized trials investigating preservation of the ICBN reveal no significant reduction in incidence of pain and paraesthesia with longer term follow-up. Nerve division can be associated with relatively normal sensation due to neural anastomoses in the vicinity of the shoulder and upper arm. Conversely, the majority of pain symptoms associated with nerve section are controlled with simple analgesia and resolve after a few months [36, 37]. It has been suggested that maintenance of an intact nerve can increase the chance of subsequent entrapment by scar tissue which can lead to troublesome and persistent symptoms.

A formal ALND is indicated for all patients with early-stage breast cancer who are clinically node positive (i.e. considered to have clinically malignant nodes). In addition, those patients with inflammatory cancers and some with clinically node-negative tumours measuring >5 cm in

maximum diameter should undergo ALND considered at the outset. The chance of nodal involvement is related to tumour size and it is difficult to justify SLNB for larger tumours when there is a high probability of node positivity. Furthermore, there is no clinical trial data on the efficacy of SLNB as a staging procedure for tumours exceeding 5 cm for which false-negative rates are likely to be unacceptably high. Clinical examination of the axilla is notoriously inaccurate with a 30 % error rate either way; that is, 30 % of clinically node-negative patients will prove to have pathological nodal involvement whilst 30 % of clinically node-positive patients will have no evidence of axillary metastases. Pre-operative axillary ultrasound and percutaneous node biopsy is increasingly being used to identify node-positive patients who can then proceed to ALND as either primary surgical treatment or following induction chemotherapy. Percutaneous needle biopsy of lymph nodes will confirm positivity in more than 90 % of women with ≥4 positive nodes and select 40–50 % of node-positive cases overall [5, 38]. Those patients with non-inflammatory tumours ≤5 cm in size are eligible for some form of node sampling as a staging procedure (SLNB, BDANS or blind sampling) [39]. Notwithstanding previous comments, it remains unclear whether all patients with a negative axillary ultrasound and core biopsy are candidates for SLNB when tumour size exceeds 5 cm.

15.4.2 Overall Survival

Axillary metastases are viewed as indicators of risk for distant relapse and do not determine clinical outcome [40]. The majority of studies have not demonstrated any gains in survival from ALND, though the NSABP-B04 trial was confounded by salvage dissection for local recurrence and not powered to detect any benefit smaller in magnitude than 7 % [41]. Others have suggested that some benefit may be derived from more thorough node dissection [42–44]. A large meta-analysis of 3000 cases has claimed a survival benefit of 5.4 % from ALND [45]. Nonetheless, though meta-analyses can partly overcome the problem of under-powering, they cannot readily distinguish between the effects of removing nodal tissue per se and the effect of adjuvant systemic treatments on overall survival.

The issue of whether loco-regional treatment can directly impact on long-term survival was clarified by a milestone publication by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) in 2005 [46]. This showed an overall survival benefit at 15 years from local radiation to either the breast following BCS or the chest wall after mastectomy. For those treatment comparisons where the difference in local recurrence at 5 years was less than 10 %, survival was unaffected. Where differences in local relapse were substantial (>10 %), there were moderate reductions in breast cancer specific and overall mortality. The absolute reductions were 19 % for local recurrence at 5 years and 5 % for breast cancer mortality at 15 years. This represents 1 life saved for every 4 loco-regional recurrences prevented by radiotherapy at 5 years. It is unclear precisely what the proportional contribution of local versus regional reductions in relapse was as absolute nodal recurrence rates were very low [46].

If ALND conferred a clear survival advantage, then this should be the standard of care for all patients with breast cancer. These data from the EBCTCG on longer term follow-up suggest that loco-regional recurrence may act as a determinant of distant disease in a subgroup of women. Loco-regional treatments are potentially curative in the absence of micrometastases when disease is confined to the breast and lymph nodes. Under these circumstances, when loco-regional management is incomplete, cancer cells or even 'oligometastases' may persist within the regional nodes and develop into distant metastases at a later date. For the majority of patients with adequate loco-regional therapy, local recurrence reflects the innate biological features of a tumour and is a marker of risk for distant relapse [47].

15.4.3 Axillary Relapse

Local control of disease is therefore important and can impact on longer term survival of breast cancer patients. The role of ALND in achieving loco-regional control is well established. The NSABP B-04 and King's/Cambridge trials provide key observations on the effect of axillary treatment in clinically node-negative patients and reveal that rates of recurrence are up to 6 fold higher for untreated axillae [41, 48]. In the NSABP B-04 study, rates of axillary recurrence at 10 years follow-up were 17.8 % for patients without axillary treatment (i.e. simple mastectomy only) versus less than 5 % for patients who underwent dissection (1.4 %) or irradiation of the axilla (3.1 %) [41]. Similar results were reported by the Kings/Cambridge trial in which clinically node-negative patients were randomized to the following treatment arms (a) total mastectomy and radiotherapy to the axilla or (b) total mastectomy and observation of the axilla [48]. Thus, treatment of the axilla with either surgery or irradiation will reduce the 5 year risk of relapse by almost 90 %. However, it is the avoidance of uncontrolled axillary relapse which is pertinent; this can cause significant morbidity with invasion of major nerves and blood vessels causing pain and lymphoedema. In the pre-screening era of radical and modified radical mastectomy, axillary recurrence often reflected intrinsically aggressive disease with chest wall infiltration which precluded satisfactory attempts at surgical or radioablation [49]. Most cases of axillary relapse after BCS for smaller tumours

have a more 'benign' phenotype and are salvageable with either surgery or radiotherapy in 70–90 % of cases [50]. Though adequate management of the axilla at the time of initial diagnosis of breast cancer is essential, partial or complete ALND nowadays represents over-treatment for most patients in terms of loco-regional control (including some SLNB-positive patients). The axilla can be accurately staged with more restrictive methods of targeted sampling which identify pathologically node-negative patients who can safely avoid formal ALND. Overall rates of local recurrence following ALND typically vary from 0.8 to 2.5 % at 10 years. The median interval to regional recurrence after ALND is 19 months, and the chance of axillary recurrence is related to number of nodes removed [51].

It is essential that rates of axillary relapse after sampling techniques which deselect patients for ALND remain below those for this 'gold standard' procedure [52–57]. Though previous studies showed that the risk of axillary relapse was inversely related to the extent of ALND and the number of nodes removed [51], targeted approaches to node sampling should minimize false-negative rates and ensure that any residual disease within axillary nodes is low volume. Rates of axillary recurrence for SLNB remain low and range from 0 to 1.4 % with short-term follow-up of <5 years [52–57]. A systematic review of almost 15,000 patients reported an average rate of 0.3 % at a median follow-up of 34 months with most axillary recurrences occurring within 20 months of surgery [58]. Long-term follow-up of a single patient cohort involving more than 1500 patients revealed an axillary recurrence rate of 0.26 % with more than half of recurrences observed beyond 5 years [59] (Table 15.1 [52–59]).

15.5 Methods for Axillary Node Sampling

The recognition that axillary dissection was principally a staging procedure with concomitant morbidity led to investigation of alternative methods for surgical staging of the axilla. These included axillary sampling and more recently SLNB. Both of these methods aim to remove between 3 and 5 biologically relevant nodes compared with 10–20 nodes for a partial ALND [38]. SLNB is a sophisticated form of targeted axillary node sampling, and methods of blind axillary sampling have evolved into BDANS. There is generally an inverse relationship between the average number of nodes sampled and the degree of targeting, i.e. blue dye alone, isotope alone or a combined method. Accurate targeting of nodes reduces the chance of a false-negative result.

15.5.1 Four-Node Axillary Sampling

All methods of sampling are reliant on the sequential involvement of axillary node metastases from level I to level III with a low incidence of skip metastases [27]. Rosen noted that more than 50 % of node-positive T1 tumours involve only 1 or 2 nodes and these are usually within level I territory [60]. Axillary sampling was introduced more than 2 decades ago by Sir Patrick Forrest in Edinburgh and has been widely practiced 'north of the border' but more selectively elsewhere [61]. Initial studies showed that the original technique of a blind 4-node sample from level I could stage the axilla with an estimated accuracy of 97 % [62]. Four-node sampling has been compared with axillary clearance in randomized studies [63, 64] and harvesting of further nodes as part of a completion axillary dissection does not increase rates of node positivity [63]. Blind 4-node sampling is not associated with impaired loco-regional control [62], and there is no evidence to date of any detriment in overall survival [65]. For those patients found to be positive on node sampling, the axilla can either be irradiated (1–2 nodes positive) or surgically cleared (3–4 nodes positive) [62]. Rates of local control are excellent for both approaches and regional recurrence rates are 5 % at 10 years for patients with negative nodes who have been sampled only [62].

15.5.2 Blue Dye-Assisted Node Sampling (BDANS)

A potential problem with standard, or blind forms of sampling is lack of certainty that 4 nodes have been retrieved. It can be difficult to identify nodes amongst the fibro-fatty

Table 15.1 Rates of axillary recurrence following a negative sentinel node biopsy

Author	No. patients	Median follow-up	Axillary recurrences (%)
Chung et al. [54]	206	26 months	3 (1.4 %)
Blanchard et al. [55]	685	29 months	1 (0.1 %)
Naik et al. [53]	2340	31 months	3 (0.13 %)
Veronesi et al. [56]	953	38 months	3 (0.31 %)
Bergkvist et al. [57]	2246	37 months	27 (1.20 %)
Kiluk et al. [59]	1530	59 months	4 (0.26 %)

tissue of the axilla (even when the axillary tail has been mobilized). Blind sampling of axillary nodes requires skill and has been criticized for being too random and unreliable [66]. Standard 4-node axillary sampling has evolved into a blue dye-assisted variant which permits a more targeted sampling and better standardization of technique [8, 38]. A survey undertaken in 1999 revealed that 47 % of British surgeons used axillary sampling (either blind or dye-guided) and this figure increased to 64 % in 2001 [67]. In the absence of nuclear medicine facilities, the standard 4-node sample has been adapted as a 'blue dye-assisted node sample' (BDANS). This is a practical option for identification of 3–4 relevant nodes and avoids use of isotope which may present financial and logistical problems for some breast units. Some surgeons have opted to use BDANS despite availability of radioisotope and with increasing experience of SLNB, removal of 3–4 nodes seems optimal after all! Bleiweiss refers to a 'sentinel node plus' technique in which surgeons remove a similar number of nodes during an otherwise conventional SLNB as for a BDANS [23].

15.6 Sentinel Lymph Node Biopsy

The essence of the sentinel node hypothesis has been discussed above and presupposes a sequential spread of cancer cells to the 'sentinel node' from whence passage to higher echelon nodes occurs. If the sentinel node does not contain metastases, then the remaining non-sentinel lymph nodes (NSLN) are likewise presumed to be tumour free. Conversely, if tumour deposits are found in the sentinel node, then it is implicit that there is a finite probability of NSLN involvement and completion ALND is indicated. A crucial parameter is the false-negative rate which is the proportion of patients incorrectly diagnosed as node negative. The denominator for this calculation should be the number of node-positive patients and not the total number of patients which has been erroneously used in some reports. False-negative rates for SLNB are between 5 and 10 % which are slightly higher than for ALND and considered acceptable.

In practice, it appears that the axilla can be adequately staged by removal of 3–4 relevant nodes—as in sampling. McCarter found that 15 % of patients had 4 or more nodes removed at the time of SLNB and claimed that at least 3 nodes were required to identify 99 % of node-positive patients. False-negative rates are significantly higher when only one SLN is removed (16.5 %), but much lower when multiple nodes are harvested or 'sampled' [68]. Goyal and colleagues reported that amongst node-positive tumours, 99.6 % of metastases were contained within the first 4 nodes, suggesting that removal of more than 4 nodes is unnecessary [26]. It therefore appears that between 2 and 4 nodes should be removed for optimum staging. The sentinel lymph node is subjected to more detailed pathological scrutiny with multiple step-sections and immunohistochemical staining than is the case for routine nodal tissue. This more intense pathological examination of the sentinel lymph node potentially upstages disease and increases rates of node positivity to levels above those expected for standard ALND. Perhaps of more concern is the finding of macrometastases in NSLN when only micrometastases are present in the sentinel lymph node. This suggests that the latter has lower biological priority and that patterns of lymphatic flow exist which preferentially direct tumour cells to these non-sentinel nodes [69]. It has been suggested that when more than 3 'sentinel' nodes are removed, routine pathological processing may be sufficient and compatible with low false-negative rates [70]. Much published data on SLNB comes from validation studies in which clinically node-negative patients have undergone SLNB followed by immediate completion ALND. These studies have provided important information on the success rate and accuracy of SLNB, but have not yielded any comparative data for SLNB alone without concomitant ALND. Furthermore, these single and multi-institutional validation studies have involved relatively small numbers of patients. The NSABP B-32 trial recruited over 5000 women from 80 centres in the USA and Canada and is the largest of 5 randomized controlled trials comparing SLNB to conventional ALND in clinically node-negative patients [71]. Patients were randomized to either SLNB followed by ALND or SLNB alone. Both surgeons and pathologists followed specific protocols and performance audits were periodically done for purposes of quality control and consensual practice. Analysis of secondary endpoints pertaining to accuracy and technical aspects within the context of this trial confirmed SLNB to be a safe and accurate method for staging the axilla with an acceptable false-negative rate (9.8 %) and high negative predictive value. Omission of routine immunohistochemistry (IHC) helped avoid potential upstaging which would remove a subgroup of SLNB-negative patients who might otherwise lead to a decrement in overall survival. It is of crucial importance to ascertain whether the finite proportion of patients with residual disease in non-sentinel nodes suffer impaired overall survival. The NSABP B-32 trial was designed to detect a modest 2 % survival difference at 5 years, thereby acknowledging that any reduction in morbidity must not occur at the expense of impaired survival. At an average follow-up of 96 months, there were no significant differences in the primary endpoints of overall survival, disease-free survival and regional control. Interestingly there was a trend for improved survival in the ALND group with an unadjusted hazard ratio of 1.2 ($p = 0.12$) and an adjusted ratio of 1.19 ($p = 0.13$) which may be attributable to random events favouring the ALND group and positive non-sentinel

lymph node prompting appropriate adjuvant systemic therapy (the unknown non-sentinel node-positive patients in group 2 would be treated as SLNB negative). The conclusions of this trial in terms of the appropriateness, safety and effectiveness of SLNB were justified for this population but may not necessarily apply to patients with larger T2 (2–5 cm) or multifocal tumours who commonly undergo SLNB. Nonetheless, results of NSABP B32 vindicate contemporary SLNB practice and supports a reduction in extent of axillary surgery for the majority of breast cancer patients [71, 72].

15.6.1 Technical Aspects

The technique of SLNB was initially assessed in peer-reviewed pilot studies using blue dye only (patent blue, isosulphan blue and methylene blue). These early studies identified the sentinel node in only two-thirds of cases and a learning curve for the technique was evident as further experience was accrued. Krag and colleagues introduced radioactive tracers (Technetium-99 m colloid) as an alternative method for identification of the sentinel lymph node [73], whilst others have used a dual localization method with detection of 'blue' and 'hot' nodes. Morrow and colleagues randomized patients to SLNB using either blue dye alone or blue dye combined with isotope and showed these to be of similar performance [74]. There is international consensus that dual localization methods are preferable and associated with a short learning curve and optimal performance indicators such as rates of identification and false negativity. In a review by the American Society of Clinical Oncology Expert Panel (ASCO), the overall false-negative rate for the SLNB technique was 8.4 % with a range of 0–29 % [75]. This analysis involved more than 10,000 patients who underwent SLNB followed by completion ALND for validation. Patients were distributed between 69 single and multi-institutional studies and yielded sensitivity rates varying from 71–100 %. The average false-negative rate in these non-randomized studies was comparable to that reported for the NSABP B-32 study (9.8 %) [71, 76]. The NSABP B32 [71], SNAC [77] and European Institute of Oncology (EIO) [78] trials compared SLNB alone with SLNB followed by ALND (A versus A + B), whilst the UK ALMANAC study randomized patients to SLNB versus ALND or node sampling (A versus B) [79] (Table 15.2). Within all trials, SLNB-positive patients underwent completion ALND. Therefore, dual localization with dye and isotope maximizes identification rates (>90 %) and is associated with high negative predictive values (>95 %) [80]. Furthermore, this method is recommended for 'beginners' and use of lymphoscintigraphy has also been advocated as an adjunct during the learning phase, particularly when isotope only is used for localization [81, 82]. However, lymphoscintigraphy does not generally yield additional staging information which influences management and ablative therapy is not routinely directed at extra-axillary nodal sites at the present time. A positive lymphoscintigram can be helpful, especially in the context of an IMC sentinel lymph node [83]. However, a negative lymphoscintigram does not preclude identification of axillary sentinel lymph nodes with standard intra-operative methods. There is probably no advantage in use of lymphoscintigraphy for most patients with tumours in the outer quadrants of the breast and a low likelihood of extra-axillary node involvement [84, 85].

Though intra-tumoral injection of dye/isotope is no longer used, peritumoral, subcutaneous, intra-dermal and subareolar sites are practiced (Fig. 15.3). Based on the evidence that the skin envelop shares a common pattern of lymphatic drainage with the parenchyma of the breast and these converge upon the same sentinel node (s)[10], there is a trend towards subareolar injection which gives less 'shine through' but requires more prolonged massage. The latter may encourage migration of tumour cells to the sentinel node (so-called traumatic metastases or 'traumets') [86]. Benign epithelial cells may be similarly displaced and be interpreted as a false-positive result on immunohistochemistry [87]. A randomized study comparing subareolar with peritumoral injection of blue dye alone for sentinel lymph node identification found a higher nodal yield for the peritumoral compared with the subareolar route (2.33+/−0.7 versus 1.64+/−0.6; $p < 0.001$ [88]. Peri-areolar injections give poorer visualization of the IMC, and when lymphoscintigraphy is employed, it is advisable to inject isotope deeper within the breast parenchyma (closer to the deep fascia). Technetium [99]-labelled nanocolloid or an equivalent radioisotope (20 MBq) is injected at least 2 h before surgery but can be administered on the preceding day if more convenient. It is sensible to use a slightly larger carrier molecule (e.g. sulphur colloid) in these circumstances in order to ensure retention within the lymphatic system up until the time of surgery. A special licence and training is required for handling of radioisotope and injection is best undertaken by nuclear medicine personnel. The dye of choice is injected by the surgeon at the time of surgery, and the breast is massaged for between 2 and 5 min. Some surgeons use 1–2 mls of undiluted dye, whilst others dilute 2 mls of dye with saline up to a final volume of 5 mls. However, larger volumes of injectate cause troublesome staining both of the breast tissues intra-operatively and of the skin post-operatively. Reduced volumes of dye may be appropriate in smaller breasted women and avoids more prolonged staining of the breast skin (of up to 12 months).

There is general consensus that SLNB should aim to remove all nodes which are blue, hot, blue and hot or

Table 15.2 Randomized trials of sentinel lymph node biopsy

Trial	Study population	Study groups
ALMANAC (UK) [79]	Any invasive tumour, Clinical No; (n = 1260)	ALND or ANS vs SLNB (if positive SLN, proceeded to ALND or RT to axilla; if negative SLN, observed)
NSABP-B32 (USA) [71]	Clinical T1–3, N0; (n = 4000)	SLNB + ALND vs SLNB (if positive SLN, proceeded to ALND; if negative SLN, observed)
SNAC (Australia/New Zealand) [77]	≤30 mm invasive tumour Clinical N0; (n = 1060)	SLNB + ALND vs SLNB (if positive SLN, proceeded to ALND; if negative SLN, observed)
European Institute of Oncology (Milan) [78]	T1, N0; (n = 516)	SLNB + ALND vs SLNB (if positive SLN, proceeded to ALND; if negative SLN, observed)
Cambridge [80]	≤30 mm invasive tumour Clinical N0; (n = 1060)	ALND vs SLNB (if positive, proceeded to ALND; if negative SLN, observed)

ANS Axillary node sampling, *RT* radiotherapy, *ALMANAC* Axillary lymphatic mapping against nodal axillary clearance, *SNAC* Sentinel node versus axillary clearance

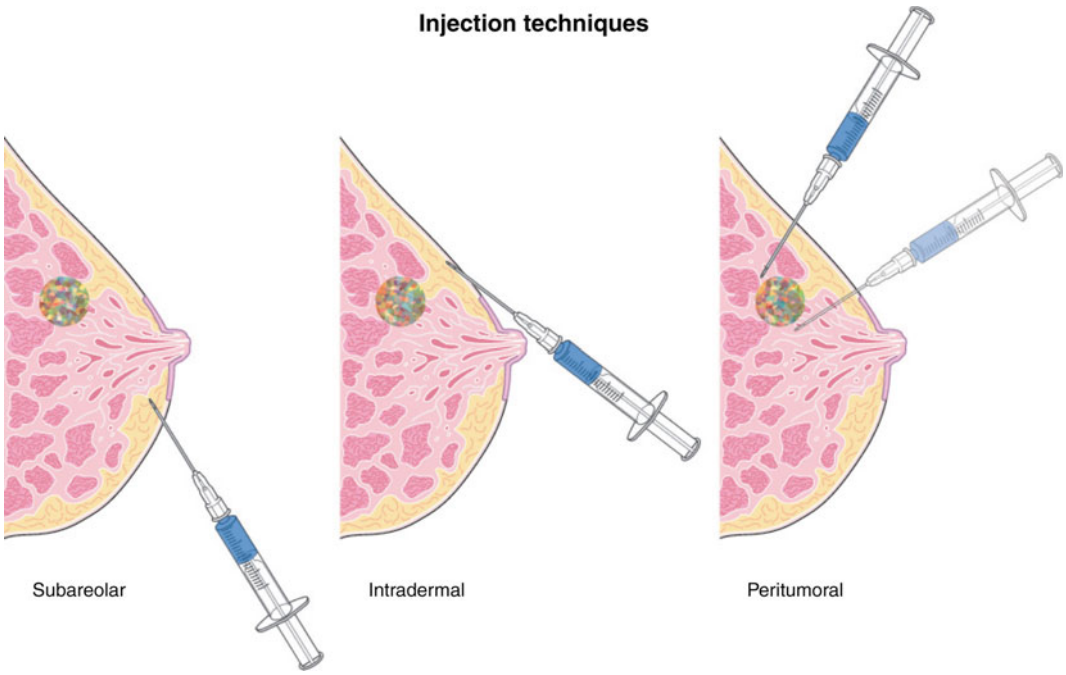

Fig. 15.3 Sites of injection of tracer agents (*blue dye*, *radiocolloid* or *indocyanine green*)

palpably suspicious. Some nodes are blue, but not hot and others are non-blue and hot. Sometimes it can be helpful to trace a blue lymphatic towards a node which may not necessarily be blue (but may be hot and should be removed). The decision when to stop sampling during surgery can be difficult; some surgeons consider any radioactive node to be hot, but use of count ratios can limit the number of nodes excised when activity levels are diffuse and high amongst three or more nodes. It is conventional to designate a node as being hot in terms of either the sentinel node:background count (3:1) or the ex vivo: background count (10:1). In the NSABP B32 trial, all nodes were removed containing at least 10 % of the activity of the hottest node [71]. Potential adverse effects of blue dye include allergic reactions and staining of cutaneous/surgical breast tissue (the latter can be a particular problem during skin-sparing mastectomy with concomitant SLNB). The Medicines and Healthcare Regulatory Authority (MHRA) issued a drug safety update in February 2012 emphasizing that occurrence of allergic reactions to blue dye was not uncommon and estimated to have an incidence of 0.1 % in the ALMANAC trial [79, 89]. Between 1975 and the beginning of 2012, a total of 70 cases of allergic reactions to blue dye had been reported to the MHRA. Of note, 58 of these cases had occurred since 2007 and included 26 serious allergic reactions. These reports of potentially serious allergic reactions have led many surgeons to dispense with routine use of blue dye when there is a strong radioactive signal in the axilla.

Evidence continues to emerge for the efficacy and safety of fluorescence mapping with the fluorochrome indocyanine green (ICG) as an alternative tracer agent for SLNB [90]. This technology relies on generation of molecular fluorescence by contact of ICG with plasma proteins in the lymphovascular system. This fluorochrome absorbs light at a wavelength of approximately 800 nm with the emission of a fluorescent signal when subatomic particles return from an excited to ground state. The illuminated subcutaneous lymphatic channels can be seen on a photodynamic eye (PDE) camera display and ICG tracked as it passes towards the axilla. The fluorescence is scattered by superficial tissues and cannot be detected at a depth of more than 1 cm with current equipment. The visual dimension of fluorescence with high optical sensitivity is a great advantage to radioisotope alone and could be complementary to radioisotope in the absence of blue dye.

Both blue dye and radioisotope have potential drawbacks including allergic reactions, staining of cutaneous and surgical breast tissue, radiation exposure and mandatory licencing. Therefore, problems exist with both tracer agents and exploration of alternative agents is warranted [91]. Identification rates approaching 100% have consistently been reported using ICG in combination with standard tracer agents (either blue dye or radioisotope) [92–95]. There has been a trend away from the use of blue dye for SLNB recently and ICG as a tracer agent may serve as an adjunct to radioisotope in the first instance. There are high levels of concordance (93.5 %) between ICG and radioisotope for sentinel lymph node identification [96] with recent evidence that ICG can outperform both blue dye and radioisotope in terms of detection of positive nodes [97]. Fluorescence imaging provides at least equivalent detection rates but offers an additional dimension of visual guidance and is safe with allergic reactions a rarity. Concerns about excessive nodal yields are not substantiated with average nodal yields of 1.5–3.7 and several recent reports citing nodal counts less than 2 [94, 95, 98]. A combination of radioisotope and ICG could represent a transition phase with ICG eventually becoming a sole tracer at a future stage when more clinical experience with its usage has accrued. It combines many of the advantages of blue dye and radioisotope without the disadvantages —in particular allergic reactions. Use of radioisotope alone can be challenging for less experienced surgeons, and in the longer term, there is a need to explore novel tracer agents such as ICG and magnetic particles [99] (Fig. 15.4).

No formal health economic evaluation of SLNB has yet been undertaken and it may prove to be cost neutral compared with ALND due to the additional costs of equipment, isotope, personnel, etc. Moreover, in some units, patients are now discharged early with drains in situ following ALND and this will reduce the relative cost of the latter procedure [100]. Methods for intra-operative assessment of sentinel lymph nodes obviate the need for delayed ALND in some patients, but reported rates of sensitivity and specificity remain problematic with no single method perceived as having any overall advantage in terms of performance, patient care, logistics and cost [101, 102]. Newer reverse transcriptase polymerase chain reaction (RT-PCR)-based techniques can potentially overcome difficulties of limited pathological sampling of nodes and operating parameters set at a threshold for detection of metastases >2 mm in size (i.e. macro- but not micrometastases nor isolated tumour cells (≤0.2 mm) [103]. Real-time PCR may permit quantitation of tumour load and more accurate differentiation between macro- and micrometastases. It should be appreciated that the definition of nodal micrometastases (>0.2 mm; ≤2 mm) is arbitrary and there is no sudden transition from low risk to high risk. The term staging implies a discontinuous concept, yet in reality there is a continuum in the extent of nodal involvement. Nodal status is the single most important prognostic factor in breast cancer and determines the propensity to form distant metastases. Nonetheless, for women with node-positive disease, a single node is affected in up to 60 % of cases amongst whom up to half contain micrometastases only. These observations are related to the more intensive pathological examination of the sentinel lymph node and were NSLNs to be assessed as thoroughly, some would probably be deemed positive which would otherwise be negative on routine pathological processing without step-sectioning nor immunohistochemistry. A further analysis of patients initially classified as node negative on the basis of H&E staining has confirmed that isolated tumour cells and micrometastases detected with immunohistochemistry only do not impact on survival outcomes. This substudy from the NSABP B32 study has provided further information on the prognostic significance of sentinel lymph node micrometastases detected by immunohistochemistry only [104]. Those patients who were node negative (without isolated tumour cells) had identical disease-free survival to those with micrometastases whereas patients with macrometastatic disease had poorer overall survival compared with node-negative patients or those with micrometastases.

15.6.2 Completion Axillary Lymph Node Dissection

This relatively high incidence of isolated sentinel node positivity with low-volume disease has created management dilemmas in terms of both further (completion) axillary surgery and systemic treatment. The chance of NSLN involvement is related to the volume of disease in the sentinel node. Cserni found on meta-analysis that when macrometastases (>2 mm) were present in the sentinel node, the incidence of

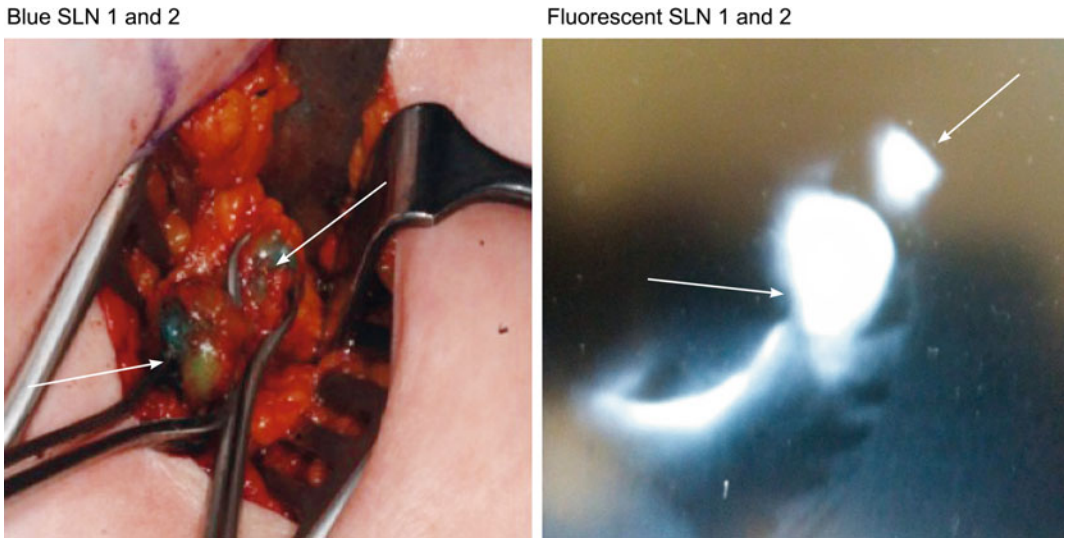

Fig. 15.4 Sentinel lymph nodes (1 and 2) observed in situ with fluorescence imaging using indocyanine green (combined with *blue dye*). An afferent lymphatic can be seen coursing towards the larger lymph node. (Reprinted from European Journal of Surgical Oncology, Volume 38, Wishart GC, Loh S-W, Jones L, Benson JR. A feasibility study (ICG-10) of indocyanine green (ICG) fluorescence mapping for sentinel lymph node detection in early breast cancer. Pages 651–656. Copyright 2012 with permission from Elsevier)

NSLN involvement was 50 %, but only 15 % for micrometastases (>0.2 mm ≤2 mm) and 9 % for isolated tumour cells (≤2 mm) [105]. However, there is much heterogeneity in terminology and definition of isolated tumour cells and micrometastases with lack of reproducibility between categories. The risk of residual NSLN disease for an individual patient can be estimated from a multivariate nomogram which incorporates several factors such as primary tumour size and grade [106]. However, nomograms devised locally for estimation of NSLN involvement may not be transferable to data sets generated from other institutions. Until recently, US guidelines recommend completion ALND for all patients with macro- or micrometastatic deposits in the sentinel lymph node, but not for isolated tumour cells. This includes micrometastases detected either by routine H&E staining or immunohistochemistry alone [75].

There is emerging evidence that selected groups of SLNB-positive patients can safely avoid completion ALND when omitted on a discretionary basis [107, 108]. Axillary ultrasound with core biopsy of nodes according to pre-defined criteria can potentially deselect a subgroup of patients for SLNB who have a positive nodal core biopsy (or fine needle aspirate) or suspicious nodes with a negative needle biopsy. This reduces the axillary tumour burden and the chance of non-sentinel lymph node positivity. Removal of axillary nodes containing foci of tumour provides regional control of disease and may remove a potential source of distant metastases but adjuvant therapies including radiotherapy and systemic treatments are also effective at eliminating residual tumour burden within axillary nodes [109, 110]. Nomograms devised for estimation of non-sentinel lymph node positivity from primary tumour and sentinel node parameters have been difficult to reliably apply in practice and are less accurate when the predicted incidence of non-sentinel lymph node involvement is low [111, 112]. The American College of Surgeons Oncology Group Z0011 trial potentially allows relaxation of informal policies and broadens the scope for omission of completion ALND in sentinel lymph node-positive patients [113]. This phase III non-inferiority trial examined disease-free and overall survival in a group of almost 900 patients undergoing breast conservation surgery for relatively good prognosis T1 and T2 tumours with macro- and micrometastases in 1 or 2 sentinel lymph nodes. Patients were randomized to completion ALND or observation only and all received tangential field whole breast irradiation and systemic therapy (chemotherapy/hormonal therapy). At a median follow-up of 6.3 years, there was no difference in either 5-year rates of loco-regional recurrence [SLNB alone = 1.6 % (95 % CI 0.7–3.3 %) versus ALND group = 3.1 % (95 % CI 1.7–5.2 %); $p = 0.11$] or overall survival [SLNB alone = 92.5 % (95 % CI 90.0–95.1 %) versus ALND group = 91.8 % (95 % CI 89.1–94.5 %)] between the two arms. The unadjusted hazard rate for treatment-related overall survival was 0.79 (90 % CI 0.56–1.11) and when adjusted for age and adjuvant therapy was closer to unity at 0.87 (90% CI 0.62–1.23). Both these values were less than a threshold hazard rate of 1.3 leading the authors to conclude that SLNB alone was *not* inferior to SLNB combined with completion ALND [113]. There have been concerns that this trial failed to accrue its target goal of 1900 patients and was underpowered. However, a lower rate of deaths than expected forced

an early closure of the trial. It should be noted that the stage distribution and treatment context for this Z0011 trial are very different to those of NSAPB B-04 following which ALND prevailed despite equivalence of overall survival for patients with and without axillary treatment [6]. Due to limited follow-up, some breast cancer surgeons consider it premature to assume that results from Z0011 will change routine surgical practice. Nonetheless, more prolonged follow-up is unlikely to witness additional local recurrence which would translate into any meaningful survival decrement and overturn current trial conclusions [113].

The International Breast Cancer Study Group (IBCSG) 23-01 trial specifically aimed to determine whether ALND is necessary in patients with minimal SLN involvement [114]. Patients with micrometastases in ≥1 SLN were randomized to completion ALND or observation only. About 10 % of patients underwent mastectomy and in this respect the trial differed from Z0011 where all patients had breast conserving surgery with breast irradiation. More than 934 patients were randomized and there was also failure to meet the accrual target of 1960 patients, and the trial was likewise closed early due to a low event rate. As for Z0011, the majority of patients received some form of systemic treatment be this hormonal therapy alone, chemotherapy or chemohormonal therapy. At a median follow-up of 5.4 years, a total of 124 disease-free events were reported with no significant difference in the primary endpoint of disease-free survival, thereby satisfying the criteria for non-inferiority. Furthermore, overall survival was almost identical for the observation and completion ALND arms (97.5 and 97.6 %, respectively) and rates of axillary recurrence were very low. These results are potentially practice changing when taken together with those of Z0011.

A delayed ALND can be technically challenging, especially in the context of immediate breast reconstruction, although there is no evidence for increased morbidity with higher rates of lymphoedema for delayed ALND following a positive SLNB compared with a primary procedure [115]. Within the ALMANAC study, there was evidence of clinically significant morbidity from SLNB when analysed on an intention-to-treat basis [79]. This morbidity most likely relates to delayed ALND in sentinel lymph node-positive patients. For some patients, the risk: benefit ratio for detection of non-sentinel lymph node-positive cases may not justify completion ALND. The decision for further axillary surgery should be guided by variables such as primary tumour characteristics and nodal metastatic load together with patient preference. The proportion of retrieved nodes which contain metastases may be a critical factor in determining non-sentinel lymph node involvement [27].

There are several options for immediate change of practice in the aftermath of results from Z0011 and 23-01 trials which suggest that systemic therapies may effectively abort the process whereby circulating tumour cells from loco-regional disease undergo both arrest and proliferation to form viable metastatic foci. For patients with micrometastases (in any number of nodes), it is reasonable to consider omission of completion ALND irrespective of the type of breast surgery (mastectomy or lumpectomy) as there is a low statistical probability of non-sentinel lymph node tumour foci which are dependent on adjuvant treatments for elimination. Omission of completion ALND in the majority of patients who fulfil the criteria for Z0011 would represent a paradigm shift in surgical practice and undoubtedly leave some patients with persistent axillary disease post-operatively. More stringent inclusion criteria could reduce the chance of non-sentinel lymph node involvement even further and allay potential fears about inadequate treatment of residual tumour. This could, for example, take account of the sentinel lymph node metastatic ratio and might stipulate an upper size limit of 3 cm and exclude grade III tumours.

Whatever policy is adopted, it will be mandatory to audit patients carefully and consider establishment of a formal registration system (under the auspices of a formal authority). Furthermore, fully informed consent is essential in view of the above criticisms of the Z0011 trial in terms of accrual, power and limited follow-up. POSNOC (**PO**sitive **S**entinel Lymph **N**ode: **O**bservation vs **C**learance) is a non-inferiority trial which aims to accrue 1900 patients from 50 centres in the UK over a 2.5-year period with primary outcome results at 5.5 years and final trial results at 7.5 years. Pre-operative axillary ultrasound (+/− nodal needle biopsy) is mandatory, and unlike Z0011, this trial will include mastectomy patients and exclude those with sentinel node micrometastases (no further axillary surgery). Patients with 1 or 2 macrometastases in sentinel nodes will be randomized with the primary outcome measure being axillary recurrence [116].

15.7 Intra-operative Node Assessment

The main purpose for intra-operative nodal assessment is avoidance of completion ALND undertaken as a delayed, secondary procedure. Axillary reoperation can be technically challenging due to adhesions and fibrosis, but there is no objective evidence for increased morbidity when ALND follows SLN biopsy and median hospital stay is similar for delayed and primary ALND [115]. When completion ALND is performed as an *isolated* procedure, there are potential benefits from intra-operative assessment in terms of cost

savings, patient convenience and avoidance of further general anaesthesia. When completion ALND rather than radiotherapy is recommended for patients with a positive SLN (tumour deposits >2 mm in size), this is sometimes combined with a breast surgical procedure—hence abrogating some disadvantages relating to cost and inconvenience [102]. For those patients who require a cavity re-excision or completion mastectomy for positive margins following wide excision, further axillary surgery can be done at the same time. The benefits of any intra-operative nodal assessment would be diminished for these patients in whom primary tumour characteristics mandate further surgery. There also exist subgroups of older patients and those with comorbidities for whom a single-stage axillary operation should be recommended at the outset. Similarly, selected women might safely avoid completion ALND with minimal chance of regional relapse or impact on longer term survival. In the 'post-Z0011' era, any decision for selective omission of completion ALND should be based on full histopathological parameters relating to both axillary nodes and primary tumour; ironically some patients may be committed to completion ALND when intra-operative node assessment is available and confirms positivity. Recently published results from the AMAROS trial suggest that axillary radiotherapy can substitute for completion ALND in some patients with low-volume nodal disease for whom intra-operative assessment would not apply [117].

It is appropriate to ask whether intra-operative nodal assessment can be justified for all patients having SLNB as a component of primary surgery in view of the inconsistent and variable sensitivity of both frozen section and touch imprint cytology (TIMC) which have not yet been surpassed by molecular assays based on quantitative reverse transcription polymerase chain reaction (RT-PCR). Both frozen section and TIMC employ rapid H&E staining methods but, like formalin-fixed tissue sections, examine less than 5 % of the node and have other limitations. Interpretation is subjective, and when only clusters of cells are examined, the distinction between micro- and macrometastases may be unclear. This might lead to ALND in some patients with micrometastases only ('false positive'). The reported patient-based sensitivities for both FS and TIMC are highly variable at 36–96 % and specificity of 95–100 % [118–121]. Frozen section examination has a false-negative rate of about 25 % and although TIMC is reported to be more accurate when immunohistochemical staining is used, a 'blinded' trial of a single-section approach using facing halves of a bivalved sentinel lymph node revealed equivalence of accuracy [122]. A meta-analysis reported a sensitivity of 75 % (95 % CI 65–84) and 63 % (95 % CI 57–69) for FS and TIMC, respectively, with TIMC having significantly lower pooled sensitivity for micrometastases (22 %) compared to macrometastases (81 %) [123].

Molecular-based technologies for intra-operative nodal assessment objectively measure expression of genes normally expressed in breast tissue but not lymph nodes such as the cytoskeleton protein CK19 which is expressed in most breast cancer cells [124]. Operating parameters are set such that quantitative RT-PCR detects macrometastases but not micrometastases nor isolated tumour cells. Validation studies suggest these molecular technologies are almost as accurate as conventional histological evaluation but examination of different nodal slabs ultimately prevents complete concordance [125]. Overall concordance levels between RT-PCR scores and permanent H&E sections were 93.7 % for the now extinct GeneSearch Breast lymph node assay (Veridex) and 98.2 % for the one-step nucleic acid assay (OSNA) which typically analyse 50 % of fresh nodal tissue [126]. The remaining commercially available molecular assay (OSNA) takes approximately 30 min to process one node (5 min per additional node) with a mean time saving of 18 min compared to TIMC or frozen section [127]. Though breast resection (wide local excision/mastectomy) is undertaken during this period, in reality intra-operative assessment incurs additional operating time of up to 30 min per case with cumulative delays and cost implications. SLNB-positive patients will subsequently require node clearance which consumes further operating time.

Intra-operative node examination may be more difficult to justify for all patients in the context of contemporary practice which either deselects patients for SLNB or dictates that completion ALND is performed alongside definitive or additional breast surgery. Formal cost analysis is warranted to compare intra-operative node assessment for all cases of SLNB in relation to the small number of cases of isolated completion ALND. Development of non-commercial open access molecular assays ('home recipes') as alternatives may significantly influence cost: benefit analyses of molecular methods for intra-operative assessment compared with TIMC or FS.

15.8 Indications for Sentinel Lymph Node Biopsy

Most of the validatory studies on SLNB were confined to tumours measuring 2 cm or less. With increasing tumour size, there is a greater probability of nodal involvement and gross metastatic disease within a lymph node may prevent uptake of dye and isotope. Lymph flow is passive and will be readily diverted to 'non-sentinel' nodes yielding a false-negative result [23]. A heavily infiltrated node which is non-blue and cold may once have constituted the 'true' sentinel node but subsequently been 'demoted' due to diversion of lymph flow within a complex lymphatic network. Patients with clinically positive nodes are more likely

to have extensive pathological involvement and should not be offered SLNB. Some of these clinically node-positive patients will be found to have innocent nodes on axillary ultrasound and core biopsy/FNAC of a node may be negative. Provided the primary tumour is neither inflammatory nor locally advanced, these patients could be considered for SLNB. Although SLNB is usually contraindicated for tumours over 5 cm in size, Guiliano's group have reported the successful application of SLNB to tumours in excess of 5 cm [128]. Nonetheless, false-negative rates are higher when there is a greater chance of node positivity and current trials are evaluating the accuracy of SLNB for tumours measuring between 3 and 5 cm [77]. The Australian SNAC II trial examined SLNB in tumours exceeding 3 cm in size and includes both multifocal and multicentric tumours. Amongst a group of 100 patients from the SNAC trial database with tumours ≥3 cm (mean size—3.91 cm) almost two-thirds had axillary node metastases. The sentinel node(s) was successfully identified in 93/100 cases with an average yield of 1.75 nodes per case. More than 60 % of patients were SLNB-positive and over 40 % had positive non-sentinel nodes. Notably, the false-negative rate was 5 % which is comparable to outcomes for smaller tumours. However, the high positivity rate for both sentinel and non-sentinel nodes questions the rationale for SLNB in larger tumours—the latter may be more appropriately managed with primary axillary lymph node dissection [129].

15.8.1 Ductal Carcinoma in Situ

The indications for SLNB have broadened in recent years to include patients with widespread ductal carcinoma in situ (DCIS) undergoing mastectomy and even some localized forms of DCIS associated with a clinical or radiological mass lesion [130–132]. Despite earlier arguments against routine SLNB for patients with DCIS [133], there is now consensus that extensive high nuclear-grade (HNG) or intermediate nuclear-grade (ING) DCIS on imaging which mandates mastectomy or DCIS presenting as a palpable lesion are indications for SLNB. Typical cases of screen-detected localized areas of DCIS which represent up to 80 % of cases in a screening programme do not qualify for routine SLNB. An incidental invasive component is found in up to 20 % of cases of DCIS in which mastectomy is the choice of operation and extensive DCIS is a risk factor for invasive malignancy from historical studies [134]. The presence of HNG DCIS, comedo necrosis and mammographic size in excess of 4 cm are independent risk factors for invasion [135, 136]. A significant proportion of those patients with microinvasion (≤1 mm) diagnosed on core biopsy will have further invasive foci on definitive histology. SLNB is advisable for all patients with microinvasion, up to 10 % of whom will be sentinel lymph node positive [130]. Nonetheless, despite reports of node positivity rates approaching 15 % in higher risk DCIS and DCIS with microinvasion [137], many cases involve isolated tumour cells or micrometastases only which are of questionable biological significance and unlikely to be clinically relevant [131]. When the target of biopsy is not microcalcification, there is a greater chance patients will have further invasive foci on definitive histology which mandates some form of axillary staging. Moreover, between 10 and 15 % of lesions diagnosed as DCIS using large bore vacuum devices will show invasion on complete excision [138]. The risk of nodal involvement which is acceptable if left untreated is a subjective judgement and those with very low risk should be spared the minimal but finite morbidity of SLNB with concomitant cost savings.

15.8.2 Multifocal and Multicentric Tumours

Multifocal and multicentric tumours were initially found to be associated with high false-negative rates and were considered a contraindication to SLNB [139]. This was consonant with the misguided assumption that tumours located in different quadrants of the breast drain through mutually exclusive lymphatic pathways, and therefore, SLNB would lead to inaccurate axillary lymph node staging [140]. Subsequent publications have refuted this viewpoint and SLNB is no longer precluded by the presence of multiple tumour foci either within the same (multifocality) or different (multicentricity) quadrants of the ipsilateral breast [140–142]. Furthermore, evidence from lymphoscintigraphy supports the notion that the various quadrants of the breast share common lymphatic drainage channels which converge upon the subareolar region [143]. A meta-analysis evaluated almost one thousand patients with multifocal and multicentric tumours who underwent SLNB followed by ALND. Identification rates exceeded 95 % and the average false-negative rate was 6.3 % when those patients with relative contraindications (e.g. post-chemotherapy or tumours >5 cm) to SLNB were excluded from analysis. Nonetheless, the overall false-negative rate remained less than 10 % when all patients were included but caution is needed when recommending SLNB for multicentric and multifocal tumours where the largest tumour focus is >5 cm or SLNB follows neoadjuvant chemotherapy for such tumours [144]. A recent prospective validation study involving 30 patients with multicentric cancer confirms that SLNB is associated with high rates of identification (100 %) and low false-negative rates when dual localization techniques with blue dye and radioisotope are employed [145]. However, rates of node positivity were relatively high with 66.7 % of patients having axillary nodal metastases (albeit with immediate completion ALND for validation purposes).

15.8.3 Pregnancy

The development of breast cancer during pregnancy presents unique management challenges with a prominent emotional dimension. Though termination may be advocated in the first trimester, surgical treatments can be safely undertaken in any trimester of pregnancy [146]. Adjuvant therapies including radiotherapy and chemohormonal therapies are usually deferred until after delivery though chemotherapy (but *not* tamoxifen) can be safely administered in the second trimester when organogenesis is complete and teratogenic effects are minimal [147, 148]. Radiotherapy is absolutely contraindicated in the gravid state but interestingly the dose of radiation from exposure to technetium radiocolloid in SLNB is only 20 MBq. This is well below the safe upper limit for pregnant women, and therefore, SLNB using isotopic localization only could be employed; note that blue dye can stain placental and foetal tissue and should be avoided. If there are concerns about use of radioisotope during pregnancy, then axillary staging could be carried out as a delayed procedure (if ALND at the outset is deemed inappropriate) or blind sampling undertaken.

15.8.4 Elderly Patients

SLNB should be employed in most elderly patients with clinically node-negative breast cancer, but might be avoided in some older patients who have a low probability of nodal involvement. Perhaps a more pertinent issue is whether completion ALND should be undertaken for a positive sentinel lymph node in older patients. Even before publication of the ACOSOG Z0011 trial, completion ALND was selectively omitted in certain older patients, particularly those with only micrometastases in the sentinel lymph node. A publication from the Memorial Sloan-Kettering Cancer Centre reported that rates of axillary relapse in patients with a positive sentinel lymph node who for various reasons had no further axillary surgery are very low (2 % at 3 years) [149]. Some elderly patients will decline completion ALND when fully informed of risks and benefits of this procedure; this group of patients are very unlikely to have residual disease which would develop into any troublesome regional recurrence or compromise longer term survival in the setting of competing mortality risks.

15.8.5 Repeat Sentinel Lymph Node Biopsy

A particular challenge in contemporary breast cancer surgery is optimal management of the axilla in patients who develop IBTR following previous breast conservation therapy with a negative SLNB. Until recently, ALND was the default option for most SLNB-negative patients with local recurrence after BCS [150]. However, early reports suggested that SLNB was feasible in patients who had undergone axillary surgery for non-malignant conditions [151]. Several studies including a meta-analysis have now confirmed that repeat SLNB for this category of patients is associated with acceptable rates of identification and an inverse relationship is discernible between rates of successful repeat SLNB and the number of nodes previously removed at first surgery [152–154]. Hence, patients who had undergone ALND initially had failure rates exceeding 50 % which were more than twice those for patients having undergone prior SLNB only. An important concept when considering repeat SLNB is restoration of the lymphatic network following disruption from previous SLNB surgery. Although fibrosis occurs in this setting, there is collateralization of lymphatic vessels and connections are re-established between an area of breast tissue which harbours recurrent tumour and a 'new' sentinel lymph node within the territory of the operated axilla. Hence, rather than the adage 'one sentinel node forever' there is now recognition of 'always a new sentinel node' [152, 153]. Intra and colleagues reported their experience of repeat SLNB in patients with IBTR after BCS and a prior negative SLNB. They successfully performed SLNB in 196 out of 207 patients, all of whom had undergone lymphoscintigraphy prior to surgery (with identification of at least one node in 206 patients). Only 9 patients were node positive with micrometastases in 8 and isolated tumour cells in 1 patient. These and other authors have recommended repeat SLNB in selected patients based on results of lymphoscintigraphy; where facilities for the latter are not available, patients should undergo ALND rather than attempts at repeat SLNB which has a higher failure rate when not directed by pre-operative visualization of sentinel nodes on lymphoscintigraphy [155].

15.9 Neoadjuvant Chemotherapy

A dichotomy of practice has emerged in efforts to define how SLNB should be optimally incorporated into the neoadjuvant setting. Some breast units have opted for SLNB in conjunction with completion ALND *after* chemotherapy. This was practiced in prospective trials to assess the safety and accuracy of SLNB 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 upfront SLNB performed *prior to* initiation of chemotherapy. The intrinsic accuracy of this technique in terms of parameters such as sentinel lymph node identification rates and false-negative rates would be no different to patients having primary surgical treatment.

15.9.1 Sentinel Lymph Node Biopsy Prior to Neoadjuvant Chemotherapy

Advantages—there will be minimal risk of an unacceptably high false-negative result and information derived from SLNB allows more accurate initial staging of patients when SLNB is undertaken prior to neoadjuvant chemotherapy [156, 157]. Identification rates for upfront SLNB are high and range from 98 to 100 % which is consistent with more extensive surgical experience of routine SLNB pre-treatment. It should be noted that nodal positivity rates are variable (29–67 %) within this patient population and reflect the heterogeneous nature of primary tumours within and between studies which nonetheless confirm that SLN biopsy has satisfactory performance characteristics for larger tumours [129]. A positive SLNB result would prompt a subsequent ALND following neoadjuvant chemotherapy, but otherwise 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 [70]. Upfront SLNB provides important information on prognostication and can guide treatment decisions for adjuvant radiotherapy, systemic therapy and axillary surgery. Although knowledge of the sentinel lymph node 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 SLNB, but multiple nodes may be positive despite an innocent ultrasound examination of the axilla. In addition to established clinicopathological factors, molecular tests such as Oncotype DX (Genomic Health, Redwood, California) can assess estimated risk of recurrence in patients with early-stage breast cancer. Patients with larger tumours and a confirmed negative SLNB 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—upfront SLNB requires an additional operation for all neoadjuvant chemotherapy patients, irrespective of final nodal status. Nonetheless, selected node-positive patients will need additional surgery when SLNB follows chemotherapy and facilities for intra-operative node assessment are not available. Concerns have been expressed about possible delays in commencement of chemotherapy treatment when an upfront SLNB policy is employed, with delays consequent to either scheduling issues or wound complications such as seromas and infection. It may be prudent to wait at least 7 days from the time of SLNB before starting chemotherapy to minimize potential wound problems and consider surgical antibiotic prophylaxis in this group of patients.

A negative SLNB result prior to neoadjuvant therapy can be helpful as no further axillary treatment is necessary, and such information 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 SLNB, are then committed to completion ALND with no opportunity for nodal downstaging. An upfront SLNB 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.

15.9.2 Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy

Advantages—when SLNB is undertaken after primary chemotherapy, it is possible to take advantage of potential nodal downstaging and avoidance of ALND [158]. A 'single' operation has the additional appeal of patient convenience and reduced costs when facilities for intra-operative node assessment are available. Rates of complete pathological nodal response vary from 20 to 36 % in patients with needle biopsy-confirmed positive-node pre-chemotherapy [159]. 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 [160].

Disadvantages—primary chemotherapy may modify lymphatic drainage patterns within the axilla where there is a degree of plasticity within the lymphatic network of vessels [161]. Distortion of lymphatics may occur secondary to tumour shrinkage with creation of aberrant lymphatic drainage patterns which together with plugging of lymphatics by tumour emboli could increase false-negative rates. Notwithstanding these theoretical considerations, there is no conclusive evidence that such phenomena occur to any significant extent in neoadjuvant therapy patients and this may have encouraged a recent trend away from upfront SLNB in neoadjuvant chemotherapy patients [162]. Interestingly, chemotherapy is more likely to eradicate tumour within non-sentinel lymph nodes than the sentinel lymph

Table 15.3 Accuracy of sentinel lymph node biopsy after neoadjuvant chemotherapy

Study/author	Identification rate (%)	False-negative rate
NSAPB B-27 [169] (428 patients)	85	11 % (8 % [dye + RI]; 14 % [dye alone])
GANEA (French) [166] (195 patients)	90	11 % (9.4 % [node −ve]; 11.6 % [node +ve])
MD Anderson [164] (575 patients)	97.4	5.9 % (4.1 % [pre-chemotherapy]; p = 0.39)

node in which the tumour cell burden is likely to be greater. Thus although cancer cells spread first to the sentinel lymph node and thereafter to the non-sentinel nodes, the inverse sequence applies to chemotherapy effect and some have referred to a 'front to back, back to front' phenomenon in which chemotherapy is more likely to eradicate tumour within NSLN then the SLN in which the tumour cell burden is usually greater. Thus although cancer cells spread first to the sentinel node and thereafter to NSLNs, the inverse sequence applies to chemotherapy [163]. This would increase the negative predictive value of a negative SLNB after chemotherapy. However, if tumour deposits responded earlier in the sentinel than non-sentinel nodes, then a false-negative result would ensue.

An analysis by Hunt and colleagues revealed a false-negative rate of 5.9 % when SLNB followed neoadjuvant chemotherapy and 4.1 % for upfront SLNB [164]. 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 SLNB with completion ALND reported a pooled false-negative estimate of 12 % when SLNB followed chemotherapy in clinically node-negative patients (Table 15.3) [165]. These figures are similar to false-negative rates for primary surgery, but it should be noted that these two clinical scenarios may not be strictly comparable as only a subset of patients in these neoadjuvant studies had SLNB post-chemotherapy with patient selection and surgeon experience introducing an element of bias [163]. 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 (Table 15.4) [167–169]. Mamounas cited an overall false-negative rate of 11.1 % for SLNB post-neoadjuvant chemotherapy when there is confirmed nodal involvement at presentation [170]. These updated figures are reassuring but a note of caution has been sounded by Alvarado and colleagues who express concerns that false-negative rates can be unacceptably high when SLNB follows neoadjuvant chemotherapy in patients presenting with node-positive disease [171]. They reported an overall false-negative rate of 20.8 % although normalization 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).

There is a paucity of data on omission of completion ALND in needle biopsy-proven node-positive patients with a subsequent negative SLNB after neoadjuvant chemotherapy. 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. Further information is needed on rates of regional recurrence specifically in those patients with a negative sentinel lymph node 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 SLNB post-chemotherapy (no further chemotherapy routinely given) [172].

Boughy and colleagues have provided important information from the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial which examined false-negative rates for patients with core biopsy-proven node-positive breast cancer who underwent SLNB and concomitant ALND after primary chemotherapy [173]. The primary endpoint for this study was the false-negative rate for clinically node-positive patients who have at least 3 sentinel lymph nodes removed for pathological examination. Rates of identification were 92.5 % overall with an accuracy of 84 % for assignment of correct nodal status. Forty percentage of patients had a complete pathological nodal response with no

Table 15.4 False-negative rates for cytologically/core biopsy-proven positive nodes pre-chemotherapy

Author	No. patients	False-negative rate (%)
Shen et al. [167]	69	25
Lee et al. [168][a]	238	5.6
Newman et al. [169]	54	10.7
Alvarado et al. [171]	150	16.1
Boughy et al. [173]	649	12.6

[a]In this study, some patients were classified as node positive on the basis of suspicious nodes on ultrasound/PET scan

evidence of any residual tumour on routine H&E staining (metastases >0.2 mm). The false-negative rate was almost 20 % when only a single tracer agent was employed compared with 10.2 % for dual tracer localization and harvesting of a minimum of 2 nodes. It was recommended that at least 3 nodes be removed in this setting of SLNB post-chemotherapy. On the basis of these Z1071 results, SLNB after neoadjuvant chemotherapy for biopsy-proven nodal involvement at presentation can only be reliably used when dual localization methods have been employed and at least 2 nodes have been removed and examined.

The German SENTINA trial addressed the role of repeat SLNB in patients who had previously undergone the procedure prior to neoadjuvant chemotherapy [174]. Patients were allocated to one of four arms; initially clinically node-negative patients treated with upfront SLNB were designated arms A and B; if the sentinel lymph node was negative (arm A—662 patients), then no further axillary surgery was undertaken. If the sentinel lymph node was positive before chemotherapy, then repeat SLNB 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 SLNB with ALND (arm C—592 patients) whilst those who remained clinically node positive had a standard ALND (arm D—123 patients). The false-negative rate for repeat SLNB patients (arm B) exceeded 50 % (51.6 %; 95 % CI 38.7–64.2 %) and sometimes only a single node was removed. It was concluded that SLNB is unacceptable as a repeat procedure following neoadjuvant chemotherapy. The false-negative rate was also 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 %).

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, SLNB after neoadjuvant chemotherapy allows assessment of specific response within the regional nodes to chemotherapy whereas positive nodes might otherwise be removed with SLNB and preclude any comment on nodal response following formal ALND after neoadjuvant chemotherapy [158, 170].

A large randomized phase III trial (NSABP-51/RTOG-1304 trial) will evaluate post-mastectomy 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 [175]. 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 SLNB either before or after administration of neoadjuvant chemotherapy.

There is now greater confidence in declaration of a 'negative' SLNB after primary chemotherapy for node-positive disease and withholding routine ALND in selected cases. 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. 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.

15.10 Internal Mammary Node Biopsy

Substantial surgical morbidity can result from removal of internal mammary nodes with no demonstration of any gains in overall survival [16, 17]. It is uncommon for the internal mammary nodes to be involved in the absence of metastases in the axillary nodes, which undermines its value as additional staging information. The biological significance of internal mammary chain disease remains uncertain, and the use of adjuvant therapies is often prompted by concomitant axillary nodal disease. Thus, the necessity for internal mammary node biopsy is controversial; it is acknowledged that microscopic involvement of the internal mammary nodes may be significant for medially placed tumours with positive axillary nodes. It should be noted that trials of post-mastectomy radiotherapy which have shown an improvement of about 10 % in overall survival included irradiation of the internal mammary chain [176, 177]. The EORTC trial recruited axillary node-positive and node-negative patients with medial/central tumours. A total of 50 Gy was delivered in 25 fractions with a mixed technique of 6MV photons (26 Gy in 13 fractions) and 12 meV electrons (24 Gy in 12 fractions) [178]. A small improvement in overall survival at 5 years was noted which just reached statistical significance (HR 0.87; 95 % CI 0.76–1.00; $p = 0.056$). A meta-analysis of all three trials investigating irradiation of the internal mammary nodes (French, MA-20 and EORTC) reveals a benefit for overall and metastases-free survival (HR 0.88; 95 % CI 0.8–0.97; $p = 0.012$). Nonetheless, clinical manifestation of internal mammary node recurrence is rare. The indications for

irradiation of the internal mammary nodes is unclear at the present time, but CT-based simulation with new planning techniques may minimize the volume of the heart and lungs exposed to radiation and hence related morbidities such as pericarditis and coronary artery disease. Internal mammary nodal irradiation is associated with low lung toxicity and a slight excess of cardiac deaths was noted in the French study, but numbers were small and not statistically significant. There is a delicate balance between cardiac versus breast cancer deaths, particularly for right-sided tumours. Patient selection is a major challenge and only a minority of stage 2 patients will have malignant involvement of internal mammary nodes. The odds of internal mammary nodal involvement increases from 2 to 20 % when lymphovascular invasion is present but nodes are negative. What are the implications of these findings for SLNB and how should sentinel node-positive patients be treated in the meantime? Some would argue that the main criterion for administration of internal mammary node irradiation should be a positive internal mammary node biopsy, although PET imaging may offer an alternative basis for declaring internal mammary node positivity. By implication, internal mammary node biopsy as a standard of care warrants consideration. There is likely to be a statistically significant benefit in overall survival from internal mammary node irradiation for internal mammary node-positive patients and high risk pN0 patients. Nonetheless, the role of internal mammary node irradiation in the era of SLNB remains unclear—especially bearing in mind that axillary lymph node dissection does not confer a survival advantage—so why should treatment of the internal mammary nodes be associated with any survival gain?

15.11 Conclusion

Approaches to management of the axilla have become more complex and present clinical decision-making challenges in terms of indications for SLNB and extent of surgery for SLNB-positive patients with limited axillary tumour burden. Axillary surgery encompasses both staging and therapeutic procedures, and it is important to select patients appropriately to avoid under- and over-treatment of patients, respectively. SLNB is now the dominant and preferred method for staging the axilla, but several questions remain unanswered. These relate to methodology, interpretation and the clinical significance of nodal metastases when SLNB is undertaken as a primary surgical procedure or following neoadjuvant chemotherapy. There has been a trend towards abandonment of blue dye for routine SLNB in recent years, but false-negative rates are minimized when dual localization techniques are used post-chemotherapy for needle biopsy-proven node-positive disease. For some patients, completion ALND may not be justified whilst for others any form of surgical axillary staging might be safely omitted. Collective results from the Z0011 and IBCSG 23-01 trials are considered practice changing in the USA, although a more cautious approach has been adopted in many European countries with a related POSNOC trial currently recruiting patients in the UK. Data from local audits suggest that results of Z0011 may not be applicable to practices in other units worldwide and pertain to a minority of SLNB-positive patients. Ironically, most patients with needle biopsy-proven nodal metastases at presentation are committed to an ALND, but some of these patients might be adequately treated with a SLNB which removes any positive nodes. Nonetheless, node-positive patients with larger, locally advanced or inflammatory cancers should undergo primary ALND. Individualized recommendations based on the risk of relapse in conjunction with benefits and cost of treatment is the ideal approach to management of the axilla. This strategy should incorporate a spectrum of options including ALND, targeted sampling and observation alone.

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