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Management of the axilla

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Introduction

Since the days of Halsted, management of the axilla has been a key aspect of care of breast cancer patients. It is well established from randomised controlled trials, such as the NSABP B-04, that axillary dissection does not improve survival,[1] yet evaluation of the axilla remains a cornerstone of breast cancer surgery. The status of the axillary lymph nodes remains a key prognostic factor and a critical component of the American Joint Committee on Cancer (AJCC) staging system. Furthermore, removal of lymph nodes harbouring disease can provide an element of local control, even though survival may not be affected. Local control, however, is only an issue for node-positive patients, and given that the majority of patients in the current era present with mammographically detected node-negative disease, there has been considerable interest in techniques that stage the axilla in breast cancer patients while minimising the considerable morbidity associated with axillary clearance.

Axillary node clearance

Technique

The contents of the axilla lie deep to the clavipectoral fascia, and are divided into three levels, based on their relationship to the pectoralis minor muscle (see Anatomy, Chapter 1). Level I is lateral to the muscle and contains the most lymph nodes, and usually the sentinel lymph node(s). Level II nodes lie behind the pectoralis minor, and Level III is medial to it. Axillary dissection aims to remove the lymph nodes and surrounding axillary fat from at least levels I and II. Level III nodes should be removed if there is any suspicion that these are involved.

Axillary clearance typically involves making a separate incision when breast conservation or nipple-sparing mastectomy is performed, but can be done through the mastectomy incision in most cases. After raising skin flaps, the clavipectoral fascia is incised to enter the axilla proper. The axillary contents are typically mobilised off the chest wall lateral to the pectoralis major muscle using a combination of blunt dissection and ligation of small lymphatics and veins with electrocautery. It can be helpful to have an assistant retract the pectoralis muscle medially. Larger veins and lymphatics should generally be clipped and ligated. The medial pectoral nerve wraps around the lateral edge of the pectoralis major muscle and should be preserved when possible. Other important structures to identify and preserve include the thoracodorsal bundle, which contains an artery, vein and nerve and lies anterior to the latissimus muscle, which they supply. The long thoracic nerve runs along the chest wall and innervates the serratus anterior muscle. Intercostobrachial nerves are located in a more anterior position and run obliquely, providing sensation to the upper inner arm. Finally, the axillary vein is at the top of the field, and is the superior limit for most axillary dissections. At the conclusion of the dissection, one should generally re-examine the cavity for any residual palpable adenopathy, and examine the space between the pectoralis major and minor adjacent to thoraco-acromial vessels for any palpable nodes and remove them.

It is generally advisable to leave a drain in the axilla after the axillary dissection is completed, to prevent accumulation of serous fluid and blood postoperatively. Patients can be discharged with the drain, and it can usually be removed when the output is 50 mL or less or after 24 hours if there is support for seroma drainage available.

Complications

Axillary dissection has several known complications, including lymphoedema, limitations in postoperative shoulder and arm mobility, prolonged postoperative pain, cording (Mondor's disease) and paraesthesia.[2–4] Inadvertent injury to the long thoracic nerve causes winged scapula due to weakness of the serratus anterior muscle. In the case of damage to the thoracodorsal bundle, weakness of the latissimus muscle ensues, with weakness of the arm with respect to extension, adduction and medial rotation. Injury to the intercostobrachial nerve results in sensory deficit in the upper inner arm.

For many patients, lymphoedema is the most dreaded complication, and efforts to reduce the risk and/or modify the course and progression of the disease continue. Generally speaking, the incidence of self-reported lymphoedema after axillary dissection is about 15%.[5] This risk is higher if axillary radiation is administered postoperatively. Several recent studies suggest that subclinical lymphoedema is far more common among patients undergoing axillary surgery than once appreciated.[6] Data from the ALMANAC trial reported 12-month incidence of lymphoedema of 5% with sentinel lymph node biopsy alone versus 13% with axillary clearance.[7] Exercise is not harmful,[8] and treatment for lymphoedema is generally supportive, with physical therapy, arm strengthening, stretching; and compression garments for the arm and hand can be helpful.

Mondor's disease or syndrome, or cording of the axilla and upper arm, is a self-limited, harmless condition.[9] It is typically observed within a couple of months after surgery of the breast and/or axilla. It is believed to be caused by thrombosis in subcutaneous veins and ligation of veins after axillary dissection. Patients may experience pain and/or tenderness in the area, but can be reassured that the condition will subside with time. Warm compresses and non-steroidal anti-inflammatory drugs can be helpful.

Shoulder dysfunction and limitations in range of motion may also be observed after axillary dissection.[10,11] Rehabilitation with physical therapy, stretching, strengthening, etc. are the mainstay of treatment, although symptoms may persist for at least a year after surgery. The presence of positive axillary nodes and higher body mass index appear to place women at higher risk for dysfunction,[12] and early intervention for those at high risk should be considered.

Less invasive techniques for axillary staging

While axillary clearance, also known as axillary dissection, is clearly efficacious in accurately staging the axilla, it is also associated with significant

Table 10.1 • Comparison of morbidity between axillary surgery techniques

			Rate of complications		
Study	**Arm**	**No.**	**Lymphoedema**	**Numbness**	**↓ ROM**
Lumachi et al.[64]	SLNB	54	3.7%		
	AS	48	4.2%		
	ALND	50	16%		
Fleissig et al.[2]	SLNB	424	7%	8.7%	6.2%
	ALND	405	14%	19%	8.4%
Aitken et al.[65]	AS + XRT	28	32%		57%
	AS	26	8%		8%
	ALND	40	20%		15%
Galimberti et al.[28]	SLNB	453	3%	12%	3%
	ALND	447	13%	18%	8%
Kootstra et al.[66]	SLNB	34	0%		18%*
	ALND	76	28%		26%
Ashikaga et al.[67]	SLNB	2008	16.7%	7.5%	13.2%*
	ALND	1975	27.6%	30.5%	19.0%

*Decreased range of motion for abduction.

ALND, axillary lymph node dissection; AS, axillary sampling; ROM, range of motion; SLNB, sentinel node biopsy; XRT, radiation therapy.

morbidity (Table 10.1). The technique of axillary sampling, in which surgeons remove four palpable nodes in Level I of the axilla, was pioneered in the early 1980s in Edinburgh. This technique successfully identified nodal status and avoided axillary dissection in those with negative nodes. Many of those with positive nodes at sampling were treated by regional radiotherapy rather than further surgery. In a pooled analysis of two randomised controlled trials comparing axillary dissection versus axillary sampling and radiotherapy, the latter was found to result in higher rates of axillary recurrence, both in the node-positive (HR = 2.64, 95% CI: 1.00–6.95, $P = 0.049$) and node-negative (HR = 3.53; 95% CI: 1.29–9.63, $P = 0.014$) cohorts, albeit this did not impact breast cancer-specific distant disease-free survival.[13]

Although the technique of sentinel node biopsy had been described decades earlier and popularised in the staging of melanoma, it was not until the mid-1990s that the technique began to be employed for the staging of breast cancer.[14] The concept was simple – by injecting a radioactive tracer and/or blue dye into the lymphatics draining the breast, one could identify the first (or 'sentinel') lymph nodes of the axilla, such that if the tumour would have metastasised to the axillary lymph nodes, these nodes would be affected first. If the sentinel nodes were negative, the likelihood of further axillary disease would be low and the benefit of axillary clearance minimal. Hence, the technique of sentinel node biopsy could provide an accurate means of staging the axilla, while minimising the morbidity of axillary dissection. Table 10.2 shows data from several large studies in which sentinel node biopsy was followed by axillary dissection. In general, these data demonstrate that sentinel node identification rates have improved over time; the procedure is highly accurate, with false-negative rates predominantly under 10%. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial randomised patients who underwent sentinel node biopsy to routine axillary dissection versus axillary node dissection only if the sentinel node was positive. This study found no difference in overall survival, disease-free survival and locoregional recurrence between the two arms.[15]

Table 10.2 • Sentinel node biopsy identification, accuracy and false-negative rates

Study	No.	SLN ID (%)	Accuracy (%)	False-negative (%)
Giuliano et al. (1996)[16]	174	65	96	12
Giuliano et al. (1997)[68]	107	66	100	0
Guenther et al. (1997)[69]	145	71	88	12
Veronesi et al. (1997)[70]	163	98	98	5
Borgstein et al. (1997)[71]	130	94	99	2
Krag et al. (1998)[17]	443	93	97	11
Nwariaku et al. (1998)[72]	119	81	99	4
Bass et al. (1999)[73]	186	93	99	2
Veronesi et al. (1999)[18]	376	99	96	7
Viale et al. (1999)[74]	155	100	97	7
Schlag et al. (2000)[75]	146	81	93	8
Molland et al. (2000)[76]	103	85	98	5
Haigh et al. (2000)[77]	283	81	99	3
Doting et al. (2000)[78]	136	93	98	5
Tafra et al. (2001)[19]	535	87	96	13
Bergkvist et al. (2001)[79]	498	90	n/a	11
McMasters et al. (2001)[20]	2206	93	97	8
Krag et al. (2001)[80]	145	98	98	4
Quan et al. (2002)[81]	152	93	100	0
Nano et al. (2002)[82]	328	87	94	8
Shivers et al. (2002)[83]	426	86	99	4
Bergkvist et al. (2005)[84]	675	95	n/a	8
Krag et al. (2007)[85]	2807	97	97	10

Sentinel node biopsy technique

Choice of dye

Since the origins of this technique, there has been controversy surrounding the optimal agent to use for sentinel node mapping. Blue dye alone and radioactive colloid agents are generally used. They are used singly, mostly for logistical reasons, but most opt for a combination of the two as there are data to suggest that while the false-negative rates are similar for either technique,[16–20] sentinel node identification is optimised with use of dual tracers.[21,22]

In terms of types of blue dye, there are three agents that are commonly used: isosulfan blue, patent blue and methylene blue dyes. The sentinel node identification rate is similar between them (93–94%), but they vary significantly in side-effects and cost.[23] Isosulfan blue is known to have a 1–3% risk of allergic reaction, and is considerably more expensive than methylene blue. If an allergic reaction occurs which produces hypotension then consideration should be given to abandoning the surgical procedure, supporting the patient and planning any subsequent surgery without the use of blue dye. Methylene blue also carries a risk of skin necrosis, particularly if an intradermal injection technique is used, and isolated cases of pulmonary oedema have also been reported. An awareness of the effect of blue dye on skin colour is necessary to avoid concern over postoperative appearance of the patient in recovery and of undermined breast skin flaps.

Injection site

Another area of controversy has been where to inject. Based on experience in sentinel node biopsy for melanoma, initially many surgeons injected tracers in a peritumoral location. Given data that injecting into the subareolar (Sappey's) plexus can identify the same sentinel node as peritumoral injection,[24,25] many surgeons have moved towards this technique, which allows for a uniform injection site regardless of where the tumour is situated, or whether there is more than one tumour in the breast. In addition, the subareolar technique has been found to be associated with a high sentinel node identification rate, and the same false-negative rate as other injection techniques.[22,26] Subareolar injection, however, always results in nodes in the axilla being highlighted and thus there is no need for preoperative lymphoscintigraphy. It is estimated that up to 10% of breast cancers drain to the internal mammary nodes which will not be identified by subareolar injection. The issue with internal mammary nodes is that drainage to these nodes relates to a range of factors, including breast size and the depth of injection. Furthermore, the clinical impact of not chasing possible involved internal mammary nodes is negligible.

Intraoperative evaluation

While sentinel lymph nodes were often sent for intraoperative evaluation when the technique was first pioneered, this was based on the premise that a positive sentinel node would lead to a full axillary dissection. There has now been movement away from this practice for a number of reasons. First, it is clear that axillary radiotherapy provides good control in those with positive nodes at sentinel node biopsy.[27] Second, data from trials such as the American College of Surgeons Oncology Group (ACOSOG) Z-0011[28] and the International Breast Cancer Study Group (IBCSG) 23-01[29] suggest that, for patients with limited axillary nodal disease, axillary node dissection may not be warranted.

In terms of techniques that can be employed for intraoperative evaluation, there are three main approaches: frozen section, imprint cytology and molecular analysis. The accuracy of frozen section ranges from 83 to 91% in studies, and has been associated with a specificity of 99–100%, and a sensitivity of 57–74%.[30] The specificity and sensitivity of touch imprint cytology ranges from 94 to 100% and 34 to 95%, respectively.[31] Comparing the two techniques, the sensitivity of touch imprint cytology is lower than frozen section (62%; 95% CI 53–70% vs 76%; 95% CI 65–84%), while specificity was comparable for both (99%).[32] Molecular analysis has also been evaluated for its utility in the intraoperative evaluation of sentinel nodes. There are several platforms for this. In a meta-analysis of one-step nucleic acid amplification (OSNA), the sensitivity and specificity of this test were found to be 84.5% (95% CI 74.7–91.0%), and 91.8% (95% CI 87.8–94.6%), respectively.[32] In a large multicentre study, the Metasin assay was found to have a sensitivity of 92% (95% CI 88–94%) and specificity of 97% (95% CI 95–97%).[33]The GeneSearch™ Breast Lymph Node study similarly was found to have a sensitivity and specificity of 82% and 97%, respectively.[34] Studies comparing molecular tests to touch imprint cytology have found that both OSNA and BLN are more sensitive than touch imprint cytology, but less specific.[34,35] In their systematic review and economic evaluation of these techniques, Huxley et al. found that OSNA was not cost-effective compared to histopathology for intraoperative evaluation of sentinel lymph nodes in breast cancer; data for Metasin were thought to be insufficient for analysis in that study.[32] There are also other issues with these techniques in relation to their accuracy in

differentiating micro from macrometastases. Given the concerns and the move away from intraoperative assessment these techniques offer few advantages to physicians or patients.

Preoperative imaging and evaluation of lymph nodes

Axillary ultrasound and fine-needle aspiration (FNA) of suspicious nodes had once been thought to be a means of streamlining care, allowing node-positive patients to proceed directly to axillary node dissection. Ultrasound and needling of radiologically suspicious axillary nodes has a sensitivity of 21–86% for the detection of metastatic disease.[36] Given the ACOSOG Z-11 and IBCSG 23-01 trial data suggesting not all sentinel node-positive patients require an axillary dissection, some have argued that sentinel node biopsy may be a more appropriate method of axillary staging to reduce the morbidity of axillary dissection as patients with a positive ultrasound and FNA would otherwise be forced to have a complete dissection.[37] However, there is evidence that those with nodal disease detected preoperatively have a higher disease burden. In addition, the imaging and FNA data may be helpful in determining whether patients would benefit from neoadjuvant chemotherapy, and that by placing a clip in the biopsied node at the time of FNA or core biopsy, one can reduce the false-negative rate of sentinel node biopsy after neoadjuvant therapy.[38]

Controversial situations

Ductal carcinoma in situ (DCIS)

DCIS, by definition, is non-invasive, and therefore axillary node evaluation should not be required. However, the risk of upstaging patients who were diagnosed as having DCIS on core biopsy has been reported to be up to 47%.[39,40] Given this, some have advocated sentinel node biopsy in young patients with high-grade or comedo DCIS who present with a palpable mass or larger tumour size on imaging, as all of these factors increase the risk of concomitant invasive disease.[41,42] In contrast, many have argued that since a sentinel node biopsy can be done after breast-conserving surgery or excisional biopsy with good identification and low-false negative rates,[43] one could always return to the operating room for a sentinel node biopsy if invasive disease is found on final pathology. Given that sentinel node biopsy cannot be performed after mastectomy and that mastectomy performed for DCIS implies a large area of involvement, sentinel node biopsy is usually performed at mastectomy for DCIS but is not recommended for patients having breast-conserving surgery.[44]

Prophylactic Mastectomy

The rationale that one could not return to the operating room to perform a sentinel node biopsy if an occult invasive cancer is found on final pathology is not as persuasive in the setting of prophylactic mastectomy as it is for DCIS. The risk of occult disease and a positive lymph node in patients undergoing prophylactic mastectomy is less than 2%.[45] Some argue that this is a minimally invasive procedure that does not increase lymphoedema rates over those who do not have axillary surgery,[46] but most would not perform sentinel node biopsy in this circumstance.[45,47]

Axillary dissection in node-positive patients vs radiotherapy

While axillary dissection was long considered the gold standard among patients found to have a positive sentinel lymph node, management is evolving in favour of less surgery.

It is also possible that axillary radiation instead of axillary dissection should and could be considered for a broad group of patients, including those undergoing mastectomy, those with less favourable tumour biology, those with only micrometastatic disease and those who receive neoadjuvant chemotherapy. In the EORTC 10981-22023 AMAROS trial, patients who had 1–2 positive nodes at the time of sentinel lymph node biopsy were randomly assigned to receive axillary radiation ($n=2404$) or axillary lymph node dissection ($n=2402$).[27] In this study, approximately 18% underwent mastectomy in both arms. After a median follow-up of 6.1 years, axillary recurrences were observed in 0.43% in the surgery group and 1.19% in the radiation group, but lymphoedema was seen significantly more often in the surgery group at 1, 3 and 5 years. Interestingly, in the NSABP B-04 study, which was performed before the use of sentinel lymph node biopsy, where clinically node-negative patients were randomised either to modified radical mastectomy or simple mastectomy and radiation, data at 25-year follow-up demonstrated axillary recurrence rates of 4% in both treatment groups.[48] There was also no difference in disease-free survival or overall survival between the two groups.

The ACOSOG Z0011 trial was designed to evaluate risk of recurrence and overall survival among patients undergoing breast conservation therapy who were found to have a positive lymph

node at the time of surgery.[28] In this trial patients with T1 and T2, cN0 breast cancer who were undergoing breast conservation and sentinel lymph node biopsy were randomised if a positive sentinel lymph node was identified intraoperatively. 445 patients were randomised to completion axillary dissection and 446 patients were randomised to observation alone. All patients received adjuvant whole-breast radiation therapy. After a median follow-up of 6.3 years, there were no statistically significant differences with respect to either local recurrence or survival. In the United States, axillary management of this select group of patients has changed dramatically based on these results. Post-hoc analysis of the Z0011 data did reveal that 19% of patients received a third field to the supraclavicular region, 8% had a posterior axillary boost, and almost 50% received high tangents.[49] Because of this and other methodological issues, the European POSNOC and BOOG 2013-07 trials are underway to evaluate outcomes for node-positive patients at sentinel node biopsy undergoing breast conservation and mastectomy with or without further axillary therapy.[50,51]

There are two retrospective, single institution studies from the USA evaluating recurrence among node-positive patients who underwent mastectomy without radiation therapy or axillary dissection. Importantly, patients were carefully selected in both for small tumour size, small size of nodal metastases and low predicted rate of additional non-sentinel nodal disease. A 2012 study of 210 selected patients with a positive sentinel lymph node who underwent mastectomy found low rates of regional nodal recurrence at 5 years (1.2%)[52] and a second study of 58 patients with 5.5 years of follow-up demonstrated a regional nodal recurrence rate of 3%.

The International Breast Cancer Study Group (IBCSG) 23-01 performed a prospective analysis of patients with micrometastatic (0.2–2 mm) disease in the sentinel node(s).[29] Similar to Z0011, these were patients with T1 and T2 tumours, and clinically negative axillae, who were randomised to either sentinel lymph node biopsy alone versus sentinel node biopsy plus axillary dissection. Not surprisingly, axillary recurrence was observed in 1% of patients at 5 years in the group that received no axillary dissection, and additional non-sentinel axillary disease was observed in 13% of those who underwent axillary dissection.

Future results of the ongoing SOUND trial (Sentinel node vs Observation after axillary Ultras-souND) are anticipated. In this prospective study, patients with small breast tumours and negative preoperative axillary ultrasound will be randomised to either sentinel node biopsy or no axillary staging.

Other trials have evaluated whether the addition of regional node irradiation to standard whole-breast radiation for selected patients has any effect on survival. The MA.20 study compared whole-breast radiotherapy alone to whole-breast radiotherapy plus lower axillary, supraclavicular and internal mammary lymph node (regional) radiation in women with early-stage breast cancer who underwent breast conservation and adjuvant systemic therapy.[53] Women were either node-positive or high-risk node-negative. High-risk was defined as tumours larger than 5 cm, or 2 cm or more with fewer than 10 axillary nodes removed and at least one of the following: grade 3 histology, ER-negative, or with lymphovascular invasion. There were a total of 916 women in each group, and the median follow-up was 9.5 years. There was no significant difference in survival between the groups: 82.8% in the nodal irradiation group vs 81.8% in the control group, HR 0.91, $P = 0.38$. Although disease-free survival was 82.0% in the nodal-irradiation group and 77.0% in the control group, the former had higher rates of grade 2 or higher acute pneumonitis and lymphoedema, (1.2% vs 0.2%, $P = 0.01$ and 8.4% vs 4.5%, $P = 0.001$, respectively). Further discussion of axillary radiation can be found in the radiotherapy chapter.

Management of the axilla after neoadjuvant chemotherapy

Historically, patients who were considered for neoadjuvant chemotherapy underwent sentinel lymph node biopsy as a separate procedure prior to the start of systemic treatment. The reasons for this were to stage the axilla before chemotherapy to know the 'true' nodal status and to determine whether complete axillary dissection was needed after chemotherapy at the time of definitive surgery. More recently, however, several studies have demonstrated that patients with a clinically negative axilla at presentation can be staged with sentinel lymph node biopsy after systemic treatment. A more controversial topic is whether patients who convert from node-positive to node-negative after chemotherapy may be able to avoid axillary dissection without increase in risk of axillary recurrence. This issue is also discussed in the neoadjuvant therapy chapter. Since 2010, several large, prospective randomised trials have been undertaken to address questions regarding the successful identification of sentinel lymph nodes after chemotherapy, the false-negative rate and long-term outcomes for these patients. Overall, the management appears to be shifting in favour of less aggressive axillary surgery.

Three meta-analyses and a systemic review have been published evaluating the identification rates and false-negative rates of sentinel node biopsy after neoadjuvant chemotherapy.[54–57] These studies show that the identification rate is approximately 90% and the false-negative rate is approximately 9% (Table 10.3).

The SENTINA trial was undertaken to address the question of timing of sentinel node biopsy in patients undergoing neoadjuvant chemotherapy and whether sentinel node biopsy can accurately be performed twice. The primary endpoint was to assess the false negative rate of sentinel lymph node biopsy after chemotherapy for patients who converted from clinically node-positive (cN+) to clinically node negative (cN0). The secondary endpoints included detection rates before vs after chemotherapy and false-negative rates after a second sentinel lymph node biopsy. In this four arm trial of 1737 patients who received at least six cycles of anthracycline-based neoadjuvant chemotherapy, all cN0 patients underwent sentinel lymph node biopsy prior to chemotherapy. Node-negative patients constituted group A ($n=662$) and received no further axillary surgery, while Group B was comprised of node-positive patients who underwent a second sentinel lymph node biopsy followed by completion axillary dissection after chemotherapy ($n=360$). The cN+ patients all received neoadjuvant chemotherapy. Those who converted to cN0 ($n=592$) underwent sentinel node biopsy followed by axillary dissection (Group C), and those who remained clinically node-positive after chemotherapy comprised Group D ($n=123$), and underwent axillary dissection without sentinel lymph node biopsy. Among patients in Group B, for those who underwent a second sentinel node procedure, both the detection rate was low (60.8%) and the false-negative rate (51.6%) was unacceptably high. However, cN+ patients in group C who converted to cN0 and underwent their first sentinel lymph node biopsy after neoadjuvant chemotherapy demonstrated higher rates of detection (80.1%) and a lower false-negative rate (14.2%).[58] When dual isotope and blue dye was used and more than two nodes removed, the false-negative rate was less than 10%.

A second reported trial, the ACOSOG Z1071, evaluated several questions. First, the feasibility and accuracy of sentinel lymph node biopsy was investigated after neoadjuvant chemotherapy in patients who presented with positive axillary nodes confirmed by needle biopsy. In this trial of 689 patients with clinical T0–T4, N1–N2, M0 breast cancer in whom sentinel node biopsy was attempted, the identification rate was 92.7% when at least one sentinel node was identified, with mapping technique found to be the only factor that affected identification of the sentinel node. The use of blue dye alone increased the likelihood of failure, with an identification rate of 78%.[58] Among 649 patients who underwent sentinel node biopsy followed by axillary lymph node dissection, the identification rate was 92.9%, and the false-negative rate was 12.6% overall. However, this rate fell to 10.8% when dual mapping agents were used and at least three nodes were examined.[59]

A recent addition to management of the involved axilla post neoadjvuant chemotherapy is the targeted axillary surgery pioneered at the MD Anderson Cancer Center. This is discussed in Chapter 16 on neoadjuvant therapy. By performing sentinel node biopsy together with removal of the node clipped at diagnosis, the false-negative rate falls to below 5%. In the meantime, a selective policy is encouraged, with sentinel node biopsy (using two agents and taking at least three nodes) including the clipped node (if present) considered adequate sampling for those with an apparent complete response to chemotherapy in the axilla; subsequent surgical clearance should be performed if there is residual malignancy in the sampled nodes.

Table 10.3 • Identification rate and false-negative rates for sentinel lymph node biopsy after neoadjuvant chemotherapy

Trial	No.	SLN ID (%)	False-negative (%)
Van Deurzen et al.[56]	2148	90.9%	10.5%
Tan et al.[57]	449	94%	7%
Xing et al.[54]	1273	90%	9%
Kelly et al.[55]	1799	90%	8.4%

Management of patients presenting with axillary lymph node metastases and an unknown primary

Occult primary breast cancer represents less than 1% of all operable breast cancer. Patients presenting with a positive axillary lymph node should undergo a thorough imaging work-up of the breast to identify the primary tumour, including mammography and ultrasound, and if both are negative, breast MRI. Several studies have demonstrated that screening breast ultrasound can identify small, mammographically occult tumours, particularly in women with dense breast tissue.[60] Patients are typically evaluated for distant disease and other primary sources with chest and abdominal CT scan. In cases where mammography and ultrasound are

negative, MRI can be useful as disease can be found in the breast in up to 70% of these patients.[61]

Patients with axillary metastases and an unknown primary should undergo axillary lymph node dissection, and be considered for whole-breast radiotherapy. A 2010 study of the SEER database that analysed 750 cases from 1983 to 2006 evaluated cause-specific survival and overall survival among women with T0N+M0 breast cancer. Of these, 596 patients (79.5%) underwent axillary dissection. Compared to those who underwent axillary dissection alone, patients who also had mastectomy or radiation therapy to the breast had improved 10-year overall survival (64.9% vs 58.5%, $P=0.02$). Those who had observation alone had overall survival of 47.5% at 10 years.[62] The risk of local recurrence is also reduced with radiotherapy. A retrospective study from 2011 demonstrated rates of ipsilateral breast tumour recurrence in patients who received radiation therapy to the breast to be 16% and 23% at 5 and 10 years, respectively, compared to 36% and 52% for patients who did not receive radiation therapy.[63]

Conclusion

The management of the axilla for breast cancer has evolved, sparing many patients the morbidity of axillary dissection while maintaining the ability to stage the axilla with low recurrence rates. Whereas axillary dissection was once routine for all invasive breast cancer patients, it is now performed selectively. Improvements in systemic therapy and selected use of axillary radiation in addition to and/or instead of axillary dissection are likely to decrease future rates of axillary dissection further. While there continue to be a number of controversies to be addressed as this trajectory continues, several clinical trials are ongoing to answer important questions pertaining to axillary management, particularly in the neoadjuvant setting.

Key points

- The status of the axilla is a key prognostic factor and an important component for staging.
- Axillary clearance does not improve survival from breast cancer for node-positive patients, but can decrease rates of local recurrence. Axillary dissection has several known complications, including lymphoedema, limitations in postoperative shoulder and arm mobility, prolonged postoperative pain, cording (Mondor's disease) and paraesthesia.
- Sentinel node biopsy is an accurate procedure, with a false-negative rate under 10%, and should be performed for clinically and radiologically node-negative patients to avoid the morbidity associated with axillary clearance.
- While axillary dissection was long considered the gold standard among patients found to have a positive sentinel lymph node, management is evolving in favour of less surgery.
- Trials evaluating radiotherapy instead of axillary clearance for node-positive patients suggest that selected patients may avoid the morbidity associated with axillary clearance with similar outcomes.
- The role of axillary clearance for node-positive patients who receive preoperative systemic therapy is evolving toward less surgery in cases where the nodes are sterilised.

Full references available at **http://expertconsult.inkling.com**

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The ACOSOG Z-0011 trial demonstrating that for patients with 1–2 positive nodes undergoing partial mastectomy with whole-breast radiation therapy, local recurrence rates are low even without completion axillary dissection.

27. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15(12):1303–10. PMID: 25439688.

Patients who had 1–2 positive nodes at the time of sentinel lymph node biopsy were randomly assigned to receive axillary radiation ($n = 2404$) or axillary lymph node dissection ($n = 2402$). After a median follow-up of 6.1 years, axillary recurrences were observed in 0.43% in the surgery group and 1.19% in the radiation group, but lymphoedema was seen significantly more often in the surgery group at 1, 3, and 5 years.

29. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol 2013;14(4):297–305. PMID: 23491275.

Findings of the IBCSG 23-01 trial which found, similar to the ACOSOG Z-0011 trial, that completion axillary dissection may not be required in patients who have micrometastases in their sentinel node.

59. Boughey JC, Suman VJ, Mittendorf EA, et al. Factors affecting sentinel lymph node identification rate after neoadjuvant chemotherapy for breast cancer patients enrolled in ACOSOG Z1071 (Alliance). Ann Surg 2015;261(3):547–52. PMID: 25664534.

Among 649 patients who underwent sentinel node biopsy followed by axillary lymph node dissection, the identification rate was 92.9%, and the false-negative rate was 12.6% overall. However, this rate fell to 10.8% when dual mapping agents were used and at least three nodes were examined.