Management of the Axilla in Early Breast Cancer

4

Monica G. Valero and Mehra Golshan

Contents

M. G. Valero · M. Golshan (✉)
Department of Surgery, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA
e-mail: mgolshan@bwh.harvard.edu

M. G. Valero
e-mail: mvalero@partners.org

M. Golshan
Breast Oncology Program, Susan F. Smith Center for Women's Cancer, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA, USA

W. J. Gradishar (ed.), *Optimizing Breast Cancer Management*, Cancer Treatment and Research 173, https://doi.org/10.1007/978-3-319-70197-4_4

Abstract

Management of the axilla in early breast cancer patients has significantly evolved in the last several decades. With the arrival of the sentinel lymph node biopsy, surgical practice for axillary staging in patients with early breast cancer has become gradually less invasive and formal axillary lymph node dissection has been confined to selected patients. Over the last two decades, evidence from randomized clinical trials have allowed for the de-escalation of axillary surgery in the management of early stage breast cancer. Advances in the staging and treatment of the axilla constitute a key component in determining initial surgical planning and therapeutic strategies in the treatment of early breast cancer. This chapter provides an updated review on the history, evolution, and current practices for axillary management in patients with early breast cancer, with particular attention to the surgical recommendations and controversial scenarios of the evolving management of the axilla.

Keywords

Sentinel lymph node biopsy · Axillary staging

4.1 Introduction

Significant advances over the last several decades have been reported in the multidisciplinary management of patients with breast cancer. Advances such as screening mammography, the development of targeted and less toxic systemic therapy, improved radiation therapy planning and dosing, the adoption of breast-conserving surgery (BCS), and the use of sentinel lymph node biopsy (SLNB) have influenced and improved the care and outcomes of patients with breast cancer.

The surgical treatment of the breast and the axilla has evolved from the radical axillary lymph node dissection (ALND) to the less invasive SLNB, and in some cases, even forgoing axillary staging altogether. SLNB has become the standard approach for axillary staging in patients with early-stage breast cancer, providing accurate staging with decreased rates of lymphedema and morbidity, and improved quality of life when compared to an ALND [1]. Dr. Donald Morton first introduced the concept for SLNB in 1992, which consisted of a minimally invasive procedure for detection of occult lymph node metastasis in melanoma surgery. Since this development, the importance of regional lymph nodes status and the use of SLNB in early breast cancer became an area of significant debate for providers in the field. Despite this early discovery, ALND continued as the standard of care until the twenty-first century when SLNB was validated and incorporated into practice for surgical management of the axilla [1].

4.2 History of Axillary Surgery

There have been significant advances in the surgical and clinical management of axillary dissection in breast cancer. It started with the introduction of the radical mastectomy by Halsted at the end of the nineteenth century [2]. Subsequently, in the 1930s, D.H Patey of the UK popularized the modified radical mastectomy (MRM), which focused on sparing the pectoral muscle while removing the breast tissue and axillary content (I–III). This operation eventually replaced the radical mastectomy when long-term follow-up not only failed to demonstrate breast cancer recurrence when preserving the pectoral muscles, but also showed no difference in survival outcomes compared with radical mastectomy [3].

These findings led clinicians to question the impact of local or regional control on overall survival. The National Surgical and Adjuvant Breast Project (NSABP) addressed these questions, and Dr. Bernard Fischer postulated that breast cancer was a systemic disease at presentation. One of the initial trials conducted by the NSABP—the NSABP B-04 [4]—was a randomized clinical trial that aimed to address the controversy over the ideal management of ALND. Conducted between 1971 and 1974, the study included 1079 patients with operable invasive breast cancer and clinically negative lymph nodes. These patients were randomized to one of three arms: (1) radical mastectomy, (2) total mastectomy without axillary dissection but with postoperative radiation, and (3) total mastectomy with a delayed axillary dissection only if patients developed clinically positive axillary nodes. An additional 586 patients with clinically positive lymph nodes were randomized to either radical mastectomy or total mastectomy without axillary surgery, but with postoperative radiation.

Based on 20 year of follow-up data, the B-04 trial demonstrated no survival advantage among both the node-negative treatment group and the node-positive treatment group; however, the trial was neither designed nor powered to address the question of axillary recurrence and survival. This trial also demonstrated the necessity of surgical lymph node dissection in identifying regional disease and the superiority of surgical lymph node dissection when compared with axillary radiation for local disease control among clinically node-positive patients. Yet, the results failed to show a significant survival advantage from removing occult positive nodes at the time of initial surgery or from the addition of radiation therapy [4, 5].

Despite these findings, surgical management did not change and ALND remained the standard of care. The lack of power to detect small survival benefit for those who had ALND was the critical factor behind this decision [4]. Critics of the study highlighted that, in the mastectomy-only group, many surgeons still included a large number of axillary nodes with the specimen [6–8].

Subsequently, the surgical treatment of the breast and the axilla moved toward a less radical intervention and the ALND was challenged by the introduction of SLNB. The concept for SLNB in breast cancer continued to develop. In 1993, Dr. David Krag and colleagues reported results of lymphatic mapping using

technetium-99 to identify the first draining lymph node and lymphoscintigraphy was used as a confirmatory method. The authors concluded that the technique reliably localized the sentinel lymph node (SLN) of primary melanoma [9]. In 1994, Dr. Armando Giuliano and colleagues first described the use of SLNB in breast cancer patients using isosulfan blue dye [10]. Giuliano described it as an accurate method to obtain information about the axilla in clinically node-negative breast cancer patients.

Utilization of the combined blue dye and isotope mapping technique was first reported by Albertini et al. [11]. This theory was then replicated by Veronesi et al. [12] who performed SLNB in 163 consecutive patients using dual tracer (technetium-99 and lymphoscintigraphy) followed by complete axillary dissection. SLNB was able to accurately predict axillary disease in 97.5% of patients and in all patients with tumors less than 1.5 cm in diameter. Finally, in 2003 Veronesi et al. designed a randomized trial to compare SLNB and axillary dissection. They assigned patients with primary breast cancer and tumors less than 2 cm to either SLNB and axillary dissection or SLNB followed by axillary dissection only if metastases were found. This was the first trial to validate the accuracy of the SLNB as a predictor of the axillary status [1].

4.3 Technical Considerations of SLNB

A SLNB procedure consists of locating the sentinel lymph node through the use of an intradermal or subareolar injection at the tumor site with either a radiolabeled colloid (technetium-99m), blue dye (isosulfan blue, patent blue, or methylene blue), or a combination of both [13, 14].

Using the radiolabeled colloid technique, patients are injected with 0.5 ml or 0.5 mCi of filtered technetium-99m sulfur colloid (radiocolloid) into the skin, subdermally or in the peritumoral area of the breast, before surgery. Surgeons may perform a lymphoscintigram to document the drainage pattern of the breast lymphatics to the regional lymph nodes. During surgery, a gamma probe emits a signal that guides the surgeon to identify the sentinel node. The node with the greatest absolute counts can be defined as a radioactive node. It is generally accepted that all sentinel nodes with counts greater than 10% of the node with the highest absolute count should be removed. This guideline has been validated at Memorial Sloan Kettering Cancer Center and has shown that the rule of 10% correctly identifies 98.3% of positive nodes in patients with multiple sentinel nodes [15].

Surgeons utilizing the blue dye technique inject the blue dye intraoperatively into the breast and perform a gentle massage to help transfer the dye to the sentinel node. Sentinel nodes are identified by direct visualization of a blue lymphatic tract or blue-stained node. Different types of blue dye are used for SLNB: isosulfan blue dye, patent blue dye, or methylene blue dye. None of them is considered to be gold standard. Isosulfan blue dye, one of the first dyes approved by the US Food and Drug Administration (FDA) for use in SLNB, is a vital blue dye that is taken up by

the lymphatic channels and trapped within the primary draining nodal basin. Isosulfan has a documented risk of allergic and anaphylactic reactions and can cause rash, hives, urticaria, pruritus, and hypotension. Allergic reactions, such as anaphylaxis, have been reported with the use of isosulfan, and series have shown incidence rates up to 2% [16]. The largest single institution review conducted by Memorial Sloan Kettering Cancer Center (2392 patients) described a 0.5% incidence of hypotension and a 1.6% incidence of allergic reactions to isosulfan blue dye [17]. To date, there are no recorded deaths related to isosulfan blue dye use. Alternatively, while methylene blue is equally effective, less costly, and has a lower risk of systemic reactions, it has been reported to have adverse reactions such as skin eruptions, rashes, subcutaneous tissue necrosis, and abscess formation [18–20].

The injection technique for SLNB has been examined in several studies, and multiple approaches have been described for injection of the blue dye, such as subdermal, intradermal, retroareolar, or peritumoral. Many studies suggest the superiority of intradermal injection compared with subdermal or deeper peritumoral breast injections [21, 22]. It is important to recognize that intradermal or subareolar injections of blue dye may cause tattooing of the nipple or skin, which may persist for months in patients undergoing breast conservation. In a patient undergoing a mastectomy, either an intradermal or subareolar injection of the blue dye is recommended. For a patient undergoing lumpectomy a retroareolar injection of the blue dye provides adequate localization without leaving the breast tattooed for an extended period of time.

Identification and removal of any suspicious nodes that are neither blue nor radioactive should be performed at the same procedure, as cancer-filled nodes may not take up dye or colloid. If the sentinel node is not identified, in general, an axillary node dissection should be performed, (level I and II ALND).

4.4 The SLN Era

4.4.1 Clinically Node-Negative Proof of Concept

To date, SLNB is routinely recommended in patients without clinical involvement of the axilla and spares patients from a complete axillary dissection if the sentinel node is negative. This concept is supported by several randomized controlled trials with long-term follow-up comparing axillary recurrence rates for SLNB and ALND.

Veronesi et al. [23] conducted a study comparing outcomes in 516 patients at a single institution randomized to SLNB alone versus SLNB plus routine completion ALND if the sentinel node was negative. At 10-years of follow-up, they reported no difference between the two groups with respect to disease-free survival (DFS); the overall survival (OS) was slightly higher in the SLNB alone group; however, this was not statistically significant.

The NSABP B-32 randomized controlled trial was subsequently designed to assess OS, DFS, rates of local recurrence, and associated morbidity in SLN-negative patients that underwent SLNB only versus ALND [24]. This study reported no significant difference in OS, DFS, and local recurrence between the two groups. Additionally, the study confirmed the low rate of regional recurrence after SLNB, which was previously reported in non-randomized studies. This proves that when the SLN is negative, SLNB alone is an appropriate, safe, and effective therapy for breast cancer patients with clinically negative lymph nodes.

4.4.2 Clinically Node Negative with Positive SLNB

The concept of the SLNB became adopted for the clinically node-negative patients with high sensitivity and specificity. The next question became whether having metastatic disease in the SLNB necessitates an ALND as the majority of patients with a positive SLN do not have additional nodes involved with disease. Three trials challenged this concept: Z0011, IBCSG 23-01, and AMAROS [25–27].

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial [25] was designed to compare the sentinel node biopsy for the clinically node-negative patient undergoing planned breast-conserving therapy with planned whole breast radiotherapy where women with one or two positive nodes were randomized to ALND versus no further axillary surgery. The Z0011 trial demonstrated no benefit in clearing axillary nodes when there was involvement of up to two sentinel nodes, and there was a very low axillary recurrence rate in patients not receiving completion ALND (0.9% after 6.3 years of follow-up). Therefore, the authors concluded that there is no difference in survival, local recurrence, or regional recurrence in patients with <2 positive sentinel nodes whether they receive ALND or not.

The IBCSG 23-01 [26] was a trial designed to determine whether axillary dissection could be omitted in patients with early breast cancer and one or more micrometastasis on SLNB. Patients were randomly assigned (in a 1:1 ratio) to either undergo axillary dissection or not to undergo axillary dissection. The primary outcome was DFS, and additional interests included axillary recurrence rates and complications. This trial reported no difference in DFS between axillary dissection versus no axillary dissection in patients with micrometastasis at a median follow-up of 5 years. Furthermore, they reported a low rate of disease recurrence in the patients with no axillary dissection (<1%) [23].

Furthermore, since the ACOSOG Z0011 and IBCSG 23-01 trials showed that patients with limited disease in the SLN treated with BCS, whole breast radiation, and adjuvant systemic therapy can be spared ALND without compromising locoregional control or survival, researchers now raised the question as to whether axillary radiotherapy provides comparable regional control with fewer side effects than axillary dissection.

Subsequently, studies such as the AMAROS trial [27], a multicenter randomized controlled trial designed to compare outcomes in patients with clinical T1–2 N0

primary breast cancer, found to have one or two positive nodes in SLNB who were randomly assigned to axillary radiotherapy or axillary lymph node dissection. The primary endpoint of the study was DFS; secondary endpoints included axillary recurrence rates and axillary surgical complications in the two groups of patients. The study confirmed that axillary lymph node dissection and axillary radiotherapy after a positive sentinel node biopsy provide excellent and comparable axillary control for patients with T1–2 primary breast cancer and a much lower rate of lymphedema in the axillary radiaiton arm.

4.5 Challenging Scenarios and Unanswered Questions

4.5.1 Prophylactic Mastectomy

In the modern era, prophylactic mastectomy has become an accepted procedure for patients with increased risk for developing breast cancer—such as BRCA-1 and BRCA-2 mutation carriers—as well as patients who are non-mutation carriers desiring symmetry, wishing to obviate the need for additional breast imaging, or experiencing anxiety about developing contralateral breast cancer. In a recent meta-analysis, the risk for nodal metastasis in this population was reported as 1.2%. SLNB is not a completely benign procedure with a small risk for developing lymphedema. Additionally, the risk of finding occult cancer is low: 3.2% for ductal carcinoma in situ (DCIS) and around 1.8% for invasive cancer, specifically 0.5% for invasive ductal carcinoma and 1.4% for invasive lobular carcinoma [28–30]. The majority of these cancers are at extremely low risk of harboring significant nodal disease, thus SLNB is not recommended routinely in patients undergoing prophylactic mastectomy.

4.5.2 Ductal Carcinoma in Situ

Patients with palpable DCIS or large areas of diffuse suspicious microcalcifications on core biopsy are at higher risk of having concomitant invasive disease. For the women undergoing breast-conserving surgery, SLNB is not currently recommended; however, it can be considered for patients considered high risk for having underlying associated invasive disease. The National Comprehensive Cancer Network (NCCN) updated the guidelines to recommend considering SLNB selectively for patients undergoing mastectomy. For patients considering mastectomy, these cases should be managed on an individual basis and merit a discussion with the multidisciplinary team as to whether information gleaned from a SLNB will impact further treatment decisions.

4.5.3 Multicentric Lesions

Based on the theory that multiple foci of cancer have different drainage patterns and have a false negative rate, it was initially thought that multicentric tumors were a contraindication for SLNB. Evidence suggests that breast fluid drains through the same afferent lymphatic channels to the same axillary sentinel node [31]. Additionally, the literature has reported success in identifying SLN with comparable false negative rates in patients with unifocal or multifocal lesions [32, 33]. Similar results have been reported in a five-year follow-up of a large series evaluating patients with multicentric breast cancer from a single institution. Patients underwent SLNB, and axillary dissection was performed only in cases of positive SLNB. From 138 patients with negative SLNB who did not receive axillary dissection, three patients (2.2%) developed axillary recurrence. Since axillary recurrence was infrequent in the group of negative SLNB, the recommendation states SLNB is an acceptable procedure for nodal staging in patients with multicentric breast disease and clinically negative axilla [6].

4.5.4 Elderly and Axillary Staging

Data suggest that there is an association between increasing age at diagnosis and the presence of more favorable cancer characteristics [34–36]. Therefore, researchers began investigating whether older patients with clinically negative nodes may benefit from a less aggressive axillary surgical approach.

The IBCGS trial 10-93 was one of the first randomized trials comparing axillary surgery versus no axillary surgery in patients older than 60 years old with clinically node-negative disease and adjuvant hormonal therapy. The results of this trial showed that avoiding axillary surgery altogether in this patient population transiently improved quality of life [36]. In certain elderly patients with clinically node-negative disease, SLNB can be omitted if the nodal status would not affect adjuvant treatment decisions [37]. In the CALGB 9343 trial, Hughes et al. [38] proved this concept with a 10-year follow-up study of women over 70 years old with clinically early stage node negative, estrogen receptor-positive breast cancer. Patients underwent lumpectomy and were randomized to receive either tamoxifen plus radiation or tamoxifen alone. The study results showed low rates of locoregional recurrence in both groups and no significant differences in time to distant metastasis, breast cancer-specific survival, or OS between the two groups. Six axillary recurrences were identified in the tamoxifen group and no axillary recurrence among the tamoxifen plus radiation group; however, just 244 received axillary staging, which represented one-third of the population.

The lack of consensus about management in elderly patients with breast cancer has led to practice variation with both over- and undertreatment of many patients. A study using the American College of Surgeons National Cancer Database, which represents approximately 80% of all newly diagnosed breast cancer, demonstrated significant variation in the performance of axillary staging in patients $\geq$over

70 years old with early breast cancer across the USA [39]. Pesce et al. [39] showed that patients treated at academic institutions were 18.5% less likely to undergo axillary staging compared to practices in the community setting (OR 0.81, 95% CI 0.76–0.87).

Additionally, recent randomized clinical trials comparing axillary versus no axillary dissection in older patients (aged 65–80 years) with early breast cancer demonstrated a lack of benefit from axillary dissection after postoperative radiotherapy and adjuvant tamoxifen [40, 41]. While the omission of axillary staging in elderly patients with clinically negative axilla results in increased regional recurrence, it does not appear to impact survival [42].

Therefore, the NCCN recommends that axillary staging may be considered optional for older patients when the decision about a patient's need for adjuvant therapy is not affected by the results of the axillary dissection [43].

4.5.5 Prior Breast or Axillary Surgery

The majority of the large clinical trials excluded patients with prior breast or axillary surgery [12, 44]. Even though prior axillary surgery is often considered a contraindication for subsequent SLNB, there are limited data to support this concept. Retrospective single institution data suggest that SLNs may be identified even after prior surgeries in the breast or in the axilla [45, 46]. In addition, high success of SLNB after a surgical biopsy has been reported, regardless of the biopsy method or the excision volume removed before SLNB [47]. A study from Port et al. [48] demonstrated that a previous axillary operation (either an axillary dissection or previous successful or failed sentinel lymph node biopsy) did not prevent success of SLNB even when fewer than 10 nodes were removed during the previous procedure. The identification of the second SLNB was performed combining isotope mapping and dye techniques.

In a systematic review and meta-analysis of the literature including all studies on repeat SLNB in locally recurrent breast cancer, Maaskant-Braat et al. [50] reported the success rates of SLN identification by repeat axillary mapping based on previous axillary procedure and breast treatment. Overall, lymphatic mapping was successful in 405 of 572 patients (70.8%) (95% CI: 66.9–74.5). In patients with previous SLNB, lymphatic mapping was reported in 179 and was visualized in 148 of them (82.7%) (95% CI: 76.2–87.8). Among patients with previous ALND, lymphatic mapping was reported in 197 and visualized in 139 of them (70.6%) (95% CI: 63.6–76.7), which is significantly lower than after a previous SLNB ($P < 0.01$). The study also classified the lymphatic mapping data according to previous breast treatment. Among patients with previous breast-conserving therapy or lumpectomy, lymphatic mapping was recorded in 425 patients and was successful in 309 of them (72.7%) (95% CI: 68.2–76.8). Among patients with a previous mastectomy, lymphatic mapping was reported in 41 patients and successful in 31 of them (75.6%) (95% CI: 59.4–87.1) (P = NS). The authors concluded that the longer the interval between the first and second lymphatic

mapping in addition to the less invasive nature of the prior intervention lead to better results on reoperation after previous axillary or breast surgery. Therefore, unnecessary lymph node dissections may be avoided in selected groups of patients. These findings reinforced the updated clinical practice guideline to support the use of SLNB in patients who have undergone prior breast surgery [51].

4.5.6 Pregnancy

Breast cancer in pregnancy constitutes a challenging situation. Mammary gland changes associated with lactation as well as difficulty imaging pregnant patients can delay the diagnosis and treatment of breast cancer in this population. The role of SLNB in pregnant patients with early-stage breast cancer has been controversial. Initially, the recommendations from two consensus panels in 2001 and 2005 were against performing SLNB in pregnancy [51]. Subsequently, in 2006, an international panel accepted SLNB as an appropriate consideration in this population after informed discussion between surgeon and patient [52, 53]. The American Society of Clinical Oncology reported that there are insufficient data to change the 2005 recommendations specifying that pregnant patients should not undergo SLNB [54, 55]; however, other studies have reported that this procedure can be safely performed in pregnant patients [56, 57].

The potential concerns about using SLNB in pregnant patients include fetal harm from radiation exposure (radiocolloid use), fetal harm from possible teratogenicity of blue dyes, and fetal harm from maternal anaphylaxis to isosulfan blue dye, among others [51, 58, 59]. In terms of radiation exposure, the doses of injected radioactivity are relatively low with rapid clearance and uptake at the injection site and are surgically removed shortly after injection. This topic has been widely studied, and some authors have concluded that concern of radiation exposure should not preclude the use of SLNB during pregnancy [59–61]. Additionally, SLN procedures have been shown to lead to a negligible dose to the fetus of 0.014 mGy or less, which is much less than the National Council on Radiation Protection and Measurements' limit to a pregnant woman [62].

Dana-Farber/Harvard Cancer Center reported one of the largest studies of SLNB during pregnancy. The study included 81 women diagnosed with breast cancer during pregnancy between 1996 and 2013, and 47 were clinically node-negative patients who had surgery while pregnant: Twenty-five (53.2%) patients underwent SNB, 20 (42.6%) patients underwent upfront ALND, and two (4.3%) underwent no lymph node surgery. 99-Tc alone was used in 16 patients, methylene blue dye alone in seven patients, and two patients had unknown mapping methods. Mapping was successful in all patients. There were no SNB-associated complications. Among patients who underwent SNB, there were 25 live-born infants, of whom 24 were healthy, and one had cleft palate (in the setting of other maternal risk factors). The conclusion is that SLNB appears to be safe and accurate using either methylene blue or 99-Tc; however, numbers remain limited and further research is warranted [61].

4.6 Conclusion

The development, validation, practice, and evolution of SLNB have positively affected the treatment of early breast cancer. It provides accurate diagnosis and prognostic information in clinically node-negative early breast cancer patients and constitutes a paramount tool to advise patients and guide surgical and adjuvant treatments. In many cases, SLNB has replaced ALND and patients are spared the additional morbidity attributed to this procedure. The management for breast cancer will continue to evolve, and tailored treatment remains the goal. Axillary lymph node status will continue to have a critical role in both staging and in achieving locoregional control in selected breast cancer patients.

References

1. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V et al (2003) A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 349(6):546–553
2. Halsted WSI (1894) The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. Ann Surg 20(5):497–555
3. Adair F, Berg J, Joubert L, Robbins GF (1974) Long-term followup of breast cancer patients: the 30-year report. Cancer 33(4):1145–1150
4. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N (2002) Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 347(8):567–575
5. Wickerham DL, Costantino JP, Mamounas EP, Julian TB (2006) The landmark surgical trials of the national surgical adjuvant breast and bowel project. World J Surg 30(7):1138–1146
6. Port ER, Tan LK, Borgen PI, Van Zee KJ (1998) Incidence of axillary lymph node metastases in T1a and T1b breast carcinoma. Ann Surg Oncol 5(1):23–27
7. Harris JR, Osteen RT (1985) Patients with early breast cancer benefit from effective axillary treatment. Breast Cancer Res Treat 5(1):17–21
8. Moore MP, Kinne DW (1996) Is axillary lymph node dissection necessary in the routine management of breast cancer? Yes. Important Adv Oncol 245–250
9. Alex JC, Weaver DL, Fairbank JT, Rankin BS, Krag DN (1993) Gamma-probe-guided lymph node localization in malignant melanoma. Surg Oncol 2(5):303–308
10. Giuliano AE, Kirgan DM, Guenther JM, Morton DL (1994) Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 220(3):391–398. discussion 8–401
11. Albertini JJ, Lyman GH, Cox C, Yeatman T, Balducci L, Ku N et al (1996) Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. JAMA 276(22): 1818–1822
12. Veronesi U, Galimberti V, Zurrida S, Pigatto F, Veronesi P, Robertson C et al (2001) Sentinel lymph node biopsy as an indicator for axillary dissection in early breast cancer. Eur J Cancer 37(4):454–458
13. Zakaria S, Hoskin TL, Degnim AC (2008) Safety and technical success of methylene blue dye for lymphatic mapping in breast cancer. Am J Surg 196(2):228–233
14. Blessing WD, Stolier AJ, Teng SC, Bolton JS, Fuhrman GM (2002) A comparison of methylene blue and lymphazurin in breast cancer sentinel node mapping. Am J Surg 184 (4):341–345

15. Chung A, Yu J, Stempel M, Patil S, Cody H, Montgomery L (2008) Is the "10% rule" equally valid for all subsets of sentinel-node-positive breast cancer patients? Ann Surg Oncol 15 (10):2728–2733
16. Newman LA (2004) Lymphatic mapping and sentinel lymph node biopsy in breast cancer patients: a comprehensive review of variations in performance and technique. J Am Coll Surg 199(5):804–816
17. Montgomery LL, Thorne AC, Van Zee KJ, Fey J, Heerdt AS, Gemignani M et al (2002) Isosulfan blue dye reactions during sentinel lymph node mapping for breast cancer. Anesth Analg 95(2):385–388 (table of contents)
18. Borgstein PJ, Meijer S, Pijpers R (1997) Intradermal blue dye to identify sentinel lymph-node in breast cancer. Lancet 349(9066):1668–1669
19. Stradling B, Aranha G, Gabram S (2002) Adverse skin lesions after methylene blue injections for sentinel lymph node localization. Am J Surg 184(4):350–352
20. Brady EW (2002) Sentinel lymph node mapping following neoadjuvant chemotherapy for breast cancer. Breast J. 8(2):97–100
21. Kern KA (1999) Sentinel lymph node mapping in breast cancer using subareolar injection of blue dye. J Am Coll Surg 189(6):539–545
22. Klimberg VS, Rubio IT, Henry R, Cowan C, Colvert M, Korourian S (1999) Subareolar versus peritumoral injection for location of the sentinel lymph node. Ann Surg 229(6): 860–864 (discussion 4–5)
23. Veronesi U, Viale G, Paganelli G, Zurrida S, Luini A, Galimberti V et al (2010) Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg 251(4):595–600
24. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP et al (2010) Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 11(10):927–933
25. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW et al (2011) Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 305(6):569–575
26. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P et al (2013) Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 14(4):297–305
27. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE et al (2014) 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. 15(12):1303–1310
28. Nagaraja V, Edirimanne S, Eslick GD (2016) Is sentinel lymph node biopsy necessary in patients undergoing prophylactic mastectomy? A systematic review and meta-analysis. Breast J. 22(2):158–165
29. Boughey JC, Khakpour N, Meric-Bernstam F, Ross MI, Kuerer HM, Singletary SE et al (2006) Selective use of sentinel lymph node surgery during prophylactic mastectomy. Cancer 107(7):1440–1447
30. Boughey JC, Attai DJ, Chen SL, Cody HS, Dietz JR, Feldman SM et al (2016) Contralateral prophylactic mastectomy (CPM) consensus statement from the American Society of Breast Surgeons: data on CPM outcomes and risks. Ann Surg Oncol 23(10):3100–3105
31. Jin Kim H, Heerdt AS, Cody HS, Van Zee KJ (2002) Sentinel lymph node drainage in multicentric breast cancers. Breast J. 8(6):356–361
32. Kumar R, Jana S, Heiba SI, Dakhel M, Axelrod D, Siegel B et al (2003) Retrospective analysis of sentinel node localization in multifocal, multicentric, palpable, or nonpalpable breast cancer. J Nucl Med 44(1):7–10

33. Tousimis E, Van Zee KJ, Fey JV, Hoque LW, Tan LK, Cody HS 3rd et al (2003) The accuracy of sentinel lymph node biopsy in multicentric and multifocal invasive breast cancers. J Am Coll Surg 197(4):529–535
34. Pierga JY, Girre V, Laurence V, Asselain B, Dieras V, Jouve M et al (2004) Characteristics and outcome of 1755 operable breast cancers in women over 70 years of age. Breast 13(5): 369–375
35. Diab SG, Elledge RM, Clark GM (2000) Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 92(7):550–556
36. International Breast Cancer Study G, Rudenstam CM, Zahrieh D, Forbes JF, Crivellari D, Holmberg SB et al (2006) Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10–93. J Clin Oncol 24(3):337–344
37. Mc CD, Gemignani ML (2016) Current management of the Axilla. Clin Obstet Gynecol 59(4):743–755
38. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B et al (2013) Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 31(19):2382–2387
39. Pesce C, Czechura T, Winchester DJ, Huo D, Winchester DP, Yao K (2013) Axillary surgery among estrogen receptor positive women 70 years of age or older with clinical stage I breast cancer, 2004–2010: a report from the National Cancer Data Base. Ann Surg Oncol 20 (10):3259–3265
40. Martelli G, Boracchi P, Ardoino I, Lozza L, Bohm S, Vetrella G et al (2012) Axillary dissection versus no axillary dissection in older patients with T1N0 breast cancer: 15-year results of a randomized controlled trial. Ann Surg 256(6):920–924
41. Martelli G, Boracchi P, Orenti A, Lozza L, Maugeri I, Vetrella G et al (2014) Axillary dissection versus no axillary dissection in older T1N0 breast cancer patients: 15-year results of trial and out-trial patients. Eur J Surg Oncol 40(7):805–812
42. Liang S, Hallet J, Simpson JS, Tricco AC, Scheer AS (2016) Omission of axillary staging in elderly patients with early stage breast cancer impacts regional control but not survival: a systematic review and meta-analysis. J Geriatr Oncol 140–147
43. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al (2017) Breast cancer, Version 2.2017: National Comprehensive Cancer Network; 6 Apr 2017. Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp
44. Viale G, Zurrida S, Maiorano E, Mazzarol G, Pruneri G, Paganelli G et al (2005) Predicting the status of axillary sentinel lymph nodes in 4351 patients with invasive breast carcinoma treated in a single institution. Cancer 103(3):492–500
45. Heuts EM, van der Ent FW, Kengen RA, van der Pol HA, Hulsewe KW, Hoofwijk AG (2006) Results of sentinel node biopsy not affected by previous excisional biopsy. Eur J Surg Oncol 32(3):278–281
46. Renaudeau C, Lefebvre-Lacoeuille C, Campion L, Dravet F, Descamps P, Ferron G et al (2016) Evaluation of sentinel lymph node biopsy after previous breast surgery for breast cancer: GATA study. Breast 28:54–59
47. Haigh PI, Hansen NM, Qi K, Giuliano AE (2000) Biopsy method and excision volume do not affect success rate of subsequent sentinel lymph node dissection in breast cancer. Ann Surg Oncol 7(1):21–27
48. Port ER, Fey J, Gemignani ML, Heerdt AS, Montgomery LL, Petrek JA et al (2002) Reoperative sentinel lymph node biopsy: a new option for patients with primary or locally recurrent breast carcinoma. J Am Coll Surg 195(2):167–172
49. Intra M, Trifiro G, Viale G, Rotmensz N, Gentilini OD, Soteldo J et al (2005) Second biopsy of axillary sentinel lymph node for reappearing breast cancer after previous sentinel lymph node biopsy. Ann Surg Oncol 12(11):895–899

50. Maaskant-Braat AJ, Voogd AC, Roumen RM, Nieuwenhuijzen GA (2013) Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. Breast Cancer Res Treat 138(1):13–20
51. Lyman GH, Giuliano AE, Somerfield MR, Benson AB 3rd, Bodurka DC, Burstein HJ et al (2005) American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 23(30):7703–7720
52. Loibl S, von Minckwitz G, Gwyn K, Ellis P, Blohmer JU, Schlegelberger B et al (2006) Breast carcinoma during pregnancy. International recommendations from an expert meeting. Cancer 106(2):237–246
53. Schwartz GF, Giuliano AE, Veronesi U, Consensus Conference C (2002) Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast April 19 to 22, 2001, Philadelphia, Pennsylvania. Hum Pathol 33(6):579–589
54. Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE (2016) Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol JCO2016710947 (Epub ahead of print)
55. Lyman GH, Temin S, Edge SB, Newman LA, Turner RR, Weaver DL et al (2014) Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 32(13):1365–1383
56. Gentilini O, Cremonesi M, Trifiro G, Ferrari M, Baio SM, Caracciolo M et al (2004) Safety of sentinel node biopsy in pregnant patients with breast cancer. Ann Oncol 15(9):1348–1351
57. Gentilini O, Cremonesi M, Toesca A, Colombo N, Peccatori F, Sironi R et al (2010) Sentinel lymph node biopsy in pregnant patients with breast cancer. Eur J Nucl Med Mol Imaging 37(1):78–83
58. Toesca A, Luini A, Veronesi P, Intra M, Gentilini O (2011) Sentinel lymph node biopsy in early breast cancer: the experience of the European Institute of Oncology in Special Clinical Scenarios. Breast Care (Basel). 6(3):208–214
59. Spanheimer PM, Graham MM, Sugg SL, Scott-Conner CE, Weigel RJ (2009) Measurement of uterine radiation exposure from lymphoscintigraphy indicates safety of sentinel lymph node biopsy during pregnancy. Ann Surg Oncol 16(5):1143–1147
60. Morita ET, Chang J, Leong SP (2000) Principles and controversies in lymphoscintigraphy with emphasis on breast cancer. Surg Clin North Am 80(6):1721–1739
61. Gropper AB, Calvillo KZ, Dominici L, Troyan S, Rhei E, Economy KE et al (2014) Sentinel lymph node biopsy in pregnant women with breast cancer. Ann Surg Oncol 21(8):2506–2511
62. Pandit-Taskar N, Dauer LT, Montgomery L, St Germain J, Zanzonico PB, Divgi CR (2006) Organ and fetal absorbed dose estimates from 99mTc-sulfur colloid lymphoscintigraphy and sentinel node localization in breast cancer patients. J Nucl Med 47(7):1202–1208