Review

Axillary Node Interventions in Breast Cancer
A Systematic Review

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IMPORTANCE Recent data from clinical trials have challenged traditional thinking about axillary surgery in patients with breast cancer.

OBJECTIVES To summarize evidence regarding the role of axillary interventions (surgical and nonsurgical) in breast cancer treatment and to review the association of these axillary interventions with recurrence of axillary node metastases, mortality, and morbidity outcomes in patients with breast cancer.

EVIDENCE REVIEW Ovid MEDLINE (1946–July 2013), Cochrane Database of Systematic Reviews (2005–July 2013), Cochrane Database of Abstracts of Reviews of Effects (1994–July 2013), and Cochrane Central Register of Controlled Trials (1989–July 2013) were searched for publications on axillary interventions in breast cancer. Clinical trials, observational studies, and meta-analyses with at least 2-year follow-up were included. A total of 1070 publications were reviewed, 17 of which met final inclusion criteria.

FINDINGS Partial mastectomy followed by whole breast radiation is breast-conserving therapy. For women with no suspicious, palpable axillary nodes who undergo breast-conserving therapy, there is little evidence of benefit from surgical complete axillary node dissection compared with sentinel node biopsy alone. Complete axillary node dissection in patients with no palpable lymph nodes, compared with sentinel node biopsy, provides no survival benefit and is associated with a 1% to 3% reduction in recurrence of axillary lymph node metastases, but is associated with a 14% risk of lymphedema. Surgical axillary staging via sentinel node biopsy in patients with benign axillary nodes on radiological and clinical examination helps to inform decisions regarding adjuvant systemic and radiation therapy. Patients and physicians should tailor axillary lymph node interventions to maximize regional disease control and minimize morbidity. Complete axillary lymph node dissection is indicated in patients who present with palpable or needle biopsy–proven axillary metastases, patients with positive sentinel nodes undergoing mastectomy (who do not, as a standard, receive adjuvant radiation), patients with more than 3 positive sentinel nodes undergoing breast-conserving therapy, and patients not meeting eligibility criteria for recent trials establishing the safety of sentinel node biopsy alone in patients with breast cancer and metastases in their sentinel nodes.

CONCLUSION AND RELEVANCE Available evidence suggests that axillary node dissection is associated with more harm than benefit in women undergoing breast-conserving therapy who do not have palpable, suspicious lymph nodes, who have tumors 3.0 cm or smaller, and who have 3 or fewer positive nodes on sentinel node biopsy.

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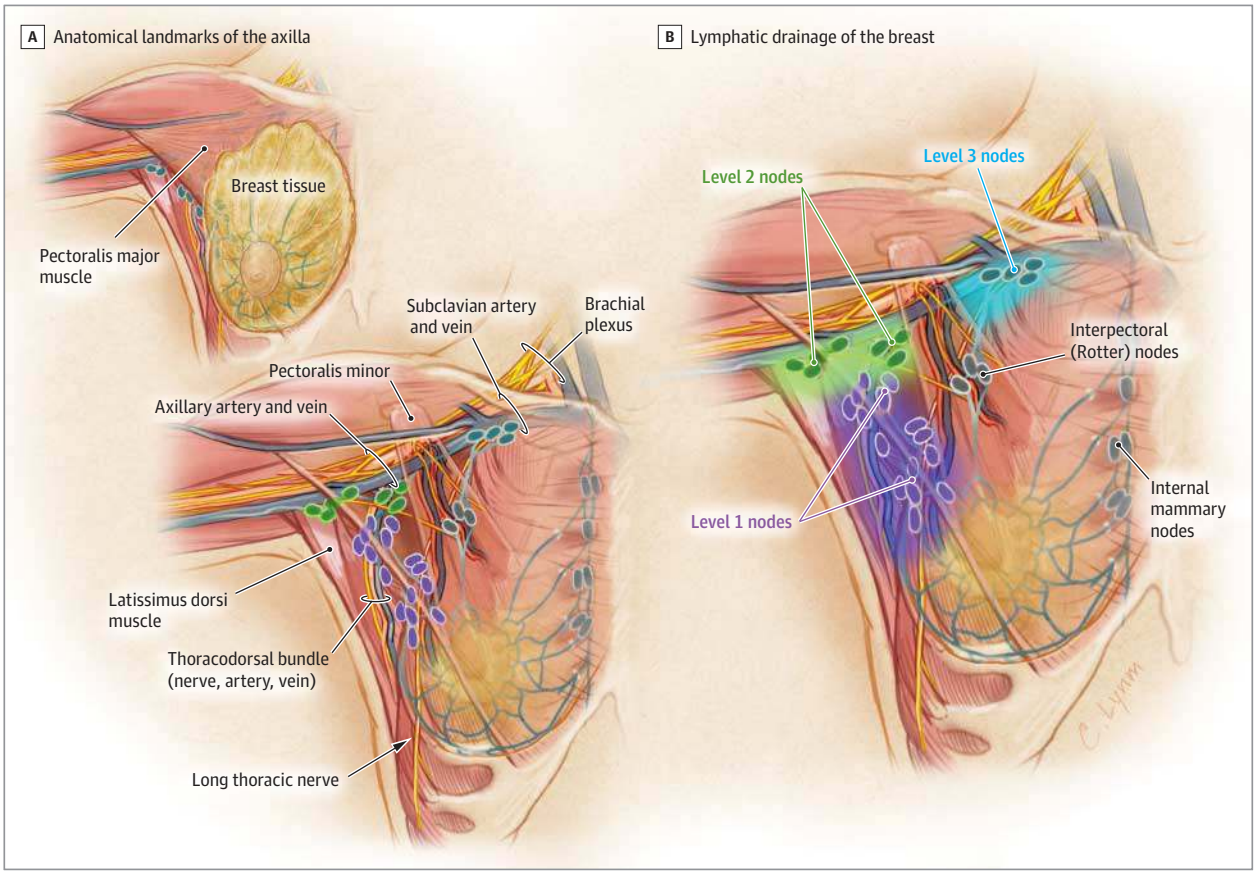
Figure 1. Anatomical Landmarks of the Axilla and Lymphatic Drainage of the Breast



Sentinel nodes are identified within levels 1 and 2. Anatomical landmarks of the thoracodorsal bundle, long thoracic nerve, and axillary vein are used to delineate tissue removed during a level 1 and 2 complete axillary lymph node dissection.

In the United States, nearly 230 000 breast cancers are diagnosed annually.[1] Over the past 20 years, the average tumor size at initial presentation has decreased by 10% every 5 years[2] and is currently 1.8 cm.[3] The majority of patients now have the option of choosing breast-conserving therapy (BCT), which requires partial mastectomy (removal of the tumor with a margin of surrounding normal tissue) followed by radiation therapy, or total mastectomy (removal of the entire breast) alone. Breast-conserving therapy is supported by randomized prospective trials[4,5] and provides equivalent survival compared with total mastectomy. Because of effective systemic therapies and population screening, 5-year breast cancer survival in the United States has now reached 90%.[1]

The second major component of a breast cancer operation is axillary lymph node surgery. A complete axillary node dissection for patients with breast cancer was introduced in the 1800s, both for staging and to achieve regional disease control.[6,7] If breast cancer has spread to the lymph nodes, patients require more aggressive systemic therapies (such as chemotherapy) and, in some cases, axillary/chest wall radiation to improve survival and decrease recurrence.[8] Complete axillary node dissection involves removal of all tissue between the anatomical landmarks (**Figure 1**) of the axillary vein (superiorly), the thoracadorsal bundle (laterally), and the long thoracic nerve (medially); 10 to 40 nodes are removed, and this is referred to as a level 1 and 2 node dissection. Level 1 and 2 lymph node dissection surgery is associated with an increased risk of adverse outcomes, including lymphedema (14%), limited shoulder/arm motion (28%), and neuropathic pain (31%).[9] A desire to minimize morbidity led to the development of the sentinel lymph node (SLN) biopsy technique.

With improvements in breast cancer screening,[10] more patients now present without palpable or sonographically evident nodal metastases.[11] First described in 1994,[12] breast SLN biopsy takes advantage of the orderly pattern of lymphatic drainage. Radioactive technetium Tc 99m and/or blue dye (isosulfan or methylene blue), are injected directly into the breast or into the skin of the breast. The first 1 to 4 nodes that take up Tc 99m and/or blue dye are subsequently removed and evaluated for metastases because these nodes are presumed to be those to which metastatic disease would first spread. If there is no evidence of metastases in the sentinel nodes, there is less than a 10% chance that the axilla harbors any nodal metastases,[13,14] obviating the need for further surgery. With the introduction and validation of SLN biopsy, complete axillary node dissection as the initial axillary intervention is no longer an acceptable option for patients in the United States who have no palpable or ultrasound evidence of axillary metastases.[13,15-17]

Prior to 2011, however, clinical practice guidelines[18] advised *completion* axillary node dissection (complete axillary node dissection after SLN biopsy reveals metastases) for patients undergoing

BCT to achieve regional disease control and obtain staging information. In 1999, the American College of Surgeons Oncology Group (ACOSOG) initiated the Z11 trial to determine whether completion axillary node dissection improves outcomes in patients with sentinel node metastases undergoing BCT.[19,20] The results of this randomized trial have substantially changed surgical practice.[21]

Therefore, herein we review the risks and benefits of SLN biopsy compared with complete axillary node dissection and compared with nonsurgical axillary interventions (ie, axillary radiation) in women with breast cancer who do not have palpable lymph nodes or ultrasound evidence of axillary lymph node metastases. The rate of recurrence of axillary node metastases, mortality, and morbidity associated with each intervention are reviewed.

Methods

We searched the following online databases: Ovid MEDLINE (1946–July 2013), Cochrane Database of Systematic Reviews (2005–July 2013), Cochrane Database of Abstracts of Reviews of Effects (1994–July 2013), and Cochrane Central Register of Controlled Trials (1989–July 2013). Medical Subject Headings used were *axilla*, *explode breast neoplasms*, *lymph node excision*, *neoplasms staging*, and *sentinel lymph node biopsy* and key-word searches were performed for *axillary node clearance/dissection/excision*, *lymph node biopsy*, and *breast cancer*. Non–English-language studies and case reports were excluded. Retrieval for this review was limited to meta-analyses, randomized clinical trials, and cohort, longitudinal, or prospective studies that reported on oncologic outcomes after axillary surgery or radiation in patients with breast cancer. The resulting 1070 publications were reviewed. Randomized trials were included if they met the eligibility criteria of at least 2 years of follow-up. Nonrandomized studies were included if the patients enrolled in the studies had a diagnosis of breast cancer and underwent surgery and the studies had at least 2 years of postoperative follow-up in at least 50% of patients undergoing treatment for breast cancer that included surgery or radiation of the axillary nodes (eFigure in the Supplement). End points reviewed were isolated recurrence of axillary lymph node metastases, complication rates, and survival with the different surgical techniques and interventions. All abstracts were reviewed by 2 authors (R.R. and D.E.). The 17 studies meeting final inclusion criteria were fully reviewed and summarized by 3 authors (R.R., D.E., and C.B.). Most studies were excluded because of their retrospective review design. The American College of Cardiology/American Heart Association[22] level of evidence classification system was used to rate the evidence.

Results

Recurrence of Axillary Lymph Node Metastases

In cancer operations, the risk of recurrence must be weighed against the benefits of new, less invasive surgical strategies.

Axillary Lymph Node Dissection vs No Directed Treatment

Complete axillary lymph node dissection involves removal of level 1 and 2 nodes. The risk of local regional recurrence with and without axillary node dissection is primarily dependent on the absolute number of lymph nodes with metastases and the size of the metastatic disease in the node (axillary tumor burden),[23,24] with lymphatic spread in invasive cancers being associated with larger tumor size,[25,26] higher tumor grade,[26,27] younger age at diagnosis,[25] and lymphovascular invasion.[27] The initial National Surgical Adjuvant Bowel and Breast Project (NSABP) B-04[28] trial was started in 1971 (**Table 1**). Patients without evidence of suspicious, palpable axillary metastases were randomized to receive radical mastectomy (removal of the entire breast, level 1 and 2 axillary nodes, and pectoralis major and minor muscles; n = 362), total mastectomy (removal of all breast tissue with preservation of pectoralis muscles and axillary nodes) with axillary radiation (n = 352), or total mastectomy alone (n = 365). In the 2 groups without axillary node dissection, the risk of developing axillary node metastases was 18.6%. If palpable axillary node metastases developed, patients underwent subsequent complete axillary node dissection. Overall survival at 25 years was not significantly different (P = .68) between groups. The NSABP B-04 trial supported the adoption of combining surgery with radiation as a multimodal approach to breast cancer. The trial suggested that patients with breast cancer may benefit from less radical surgical interventions, but it may have been underpowered to detect small differences in survival.[33]

Greco et al[29] omitted axillary surgery altogether in 401 patients who primarily underwent partial mastectomy followed by whole breast radiation therapy (Table 1). All tumors were 3.0 cm or smaller and patients were primarily (81%) postmenopausal and had no evidence of suspicious, palpable axillary metastases. Axillary lymph node metastatic recurrence was 1.7% to 10% among subsets of T1 tumors and 18% in T2 tumors. Martelli et al[34] reported a 1.8% recurrence rate of axillary lymph node metastases for 110 women aged 65 years or older with T1 tumors treated with BCT and postoperative adjuvant tamoxifen but no axillary surgery (Table 1). There were no axillary lymph node metastatic recurrences among the 109 controls who underwent BCT with complete axillary lymph node dissection.

A second subset in the NSABP B-04 trial examined outcomes for patients with palpable, suspicious nodes who were randomized to receive radical mastectomy (n = 292) or total mastectomy with radiation therapy and no lymph node dissection (n = 294) (Table 1). The risk of recurrence of axillary node metastases was slightly higher in the group receiving radiation to the axilla alone (8%) vs the radical mastectomy group (1%; P = .40). As a result, patients presenting with palpable, suspicious axillary nodes are offered complete axillary lymph node dissection after pathologic confirmation of nodal metastases. Pathologic confirmation of palpable nodes can be obtained via percutaneous fine needle aspiration or core needle biopsy.[35,36] In general, complete axillary lymph node dissection provides excellent regional control, with reported recurrence of axillary lymph node metastases of 0% to 3.5%[14,32,34,37-44] in patients with and without suspicious, palpable axillary nodes.

Complete Axillary Lymph Node Dissection vs Radiation Therapy

Prior to establishing the efficacy of SLN biopsy, there was an interest in axillary radiation as an alternative to complete axillary lymph node dissection for patients with breast cancer. Axillary radiation trials focused on patients without palpable, suspicious nodes and T1 to T2 breast cancers (**Table 2**). In a large clinical trial, Louis-Sylvestre et al[38] randomized 658 patients younger than 70 years to either partial mastectomy with complete axillary node dissection or partial mastec-

Table 1. Trials of Axillary Lymph Node Dissection vs No Directed Axillary Therapy (Level A Evidence)

Source	Study Period	Participant Age	Axillary Status	Tumor Size	Follow-up	Study Interventions	Sample Size	Recurrence, No. (%)	Survival, % (SE)[a]
Fisher et al,[4] 2002	1971-1974	Any age (70% >50 y)	Palpable, suspicious nodes on examination	Mean, 3.7 (SD, 2) cm	Mean, 20 y	Radical mastectomy	292	22 (8)[b]	11 (2)
						Total mastectomy + radiation	294	33 (11)[b]	10 (2)
Fisher et al,[4] 2002	1971-1974	Any age (70% ≥50 y)	No palpable, suspicious nodes on examination	Mean, 3.7 (SD, 2) cm	Mean, 20 y	Radical mastectomy	362	15 (4)	19 (2)
						Total mastectomy + radiation	352	15 (4)	13 (2)
						Total mastectomy	365	23 (6)[c]	19 (2)
Greco et al,[29] 2000	1986-1994	Any age (85% >50 y)	No palpable, suspicious nodes on examination	All tumors <3.0 cm on examination	Median, 5.1 y	Partial mastectomy or mastectomy with no axillary lymph node dissection + radiation if age <70 y	401	19 (5)	Not evaluated
Martelli et al,[30] 2010	1996-2000	Median, 76 y	No palpable, suspicious nodes on examination	Any tumor size (93% T1/T2)	Median, 15 y	BCT + axillary lymph node dissection	109	0	96
						BCT alone	110	2 (1.8)	94
Hughes et al,[31] 2004[d]	1994-1999	>70 y	No palpable, suspicious nodes on examination	All tumors <2.0 cm on examination	Median, 5 y	BCT + tamoxifen	200	0	87
						Partial mastectomy + tamoxifen	204	2 (1)	86
Rudenstam et al,[32] 2006	1993-2002	Median, 74 y	No palpable, suspicious nodes on examination	Any tumor size (56% <2 cm)	Median, 6.6 y	Mastectomy or BCT + axillary lymph node dissection	234	2 (1)	75
						Mastectomy or BCT with no axillary surgery	239	6 (3)	73

Abbreviation: BCT, breast-conserving therapy (partial mastectomy followed by whole breast radiation).

[a] No statistically significant difference in survival among groups.

[b] Includes recurrence in axilla, supraclavicular/subclavicular nodal area, or internal mammary nodes.

[c] Excludes 68 women who were found to have axillary metastases after total mastectomy and underwent axillary lymph node dissection.

[d] Complete axillary dissection was allowed but discouraged; data presented are for patients who did not undergo axillary lymph node dissection.

Table 2. Trials of Axillary Lymph Node Dissection vs Axillary Radiation (Level A Evidence)

Source	Study Period	Participant Age	Axillary Status	Tumor Size	Follow-up	Study Interventions	Sample Size	Recurrence, No. (%)	Survival, %[a]
Johansen et al,[45,46] 1990	1951-1957	Any age (70% ≥50 y)	Palpable, suspicious nodes ≤2.5 cm or no palpable, suspicious nodes on examination	Any tumor size	Mean, 50 y	Total mastectomy + radiation	219	Not reported	1% (65% breast cancer–specific deaths)
						Extended radical mastectomy[b]	206	Not reported	2% (64% breast cancer–specific deaths)
Louis-Sylvestre et al,[38] 2004	1982-1987	Mean, 50 y	No palpable, suspicious nodes on examination	All tumors <3.0 cm on examination	Median, 5 y	BCT + axillary node dissection[c]	326	2 (0.6)[d]	75
		Mean, 52 y				BCT + radiation to axilla	332	6 (1.8)[d]	74
Hoebers et al,[37] 2000	1983-1997	Mean, 64 y	No palpable, suspicious nodes on examination	Median size on examination, 2.0 cm	Median, 3.4 y	BCT + radiation to axilla and supraclavicular nodes	105	2 (2)	83
Veronesi et al,[47] 2005	1995-1998	Median, 57 y	No palpable, suspicious nodes on examination	All tumors <1.5 cm on intraoperative examination	Median, 5.2 y	BCT alone (no axillary intervention)	214	3 (1.5)	95
						BCT + axillary radiation	221	1 (0.5)	97

Abbreviation: BCT, breast-conserving therapy (partial mastectomy followed by whole breast radiation).

[a] No statistically significant difference in survival among groups.

[b] Extended radical mastectomy: radical mastectomy with supraclavicular and internal mammary node dissection.

[c] Radiation to supraclavicular nodes if node metastases identified on pathology.

[d] $P = .04$ for comparison between the 2 groups.

tomy with axillary radiation. All received whole breast radiation. At 15-year follow-up, there was no survival difference between groups, with 75% overall survival for those who underwent axillary lymph node dissection and 74% in those who received axillary radiation (Table 2). Recurrence of axillary node metastases was 1% after axillary lymph node dissection and 3% after axillary radiation ($P = .04$). Pathological examination of axillary node dissection specimens demonstrated that 21% of patients had axillary metastases. Despite the high rate of axillary metastasis that must have been present in both groups, there was a low rate of palpable recurrence of axillary node metastases in the radiation group. In a similar trial by Veronesi et al,[47] an equally low recurrence rate of axillary lymph node metastases (0.5%) was observed (Table 2). Recurrence of axillary lymph node metastases can be reduced by targeted axillary radiation when no surgery is performed at the axillary site. In a study of 105 patients by Hoebers et al,[37] there were no isolated recurrences of axillary lymph node metastases after partial mastectomy with adjuvant whole breast radiation that included extended axillary and supraclavicular fields

Table 3. Trials of Axillary Lymph Node Dissection vs SLN Biopsy (Level A Evidence)

Source	Study Period	Participant Age	Axillary Status	Tumor Size	Follow-up	Study Interventions	Sample Size	Recurrence, No. (%)	Survival, %[a]
Veronesi et al,[14,48] 2010	1998-1999	Median, 56 y for complete axillary node dissection Median, 55 y for sentinel node only	No palpable, suspicious nodes on examination	All tumors ≤2.0 cm on final pathology	Mean, 7.9 y	BCT + negative SLN biopsy result	167	2 (1.2)	89
						BCT + SLN biopsy and completion axillary lymph node dissection[b]	92	0	89
						BCT + SLN biopsy and complete axillary lymph node dissection[c]	257	0	89
Canavese et al,[49] 2009	1998-2001	Mean, 58 y	No palpable, suspicious nodes on examination	All tumors <5.0 cm on final pathology	Median, 5.5 y	BCT or mastectomy + negative SLN biopsy result	79	0	94
						BCT or mastectomy + completion axillary lymph node dissection[b]	31	0	90
						BCT or mastectomy + complete axillary lymph node dissection	115	1 (0.9)	90
Mansel et al,[43] 2006[d]	1999-2003	Mean, 57 y	No palpable, suspicious nodes on examination	Any tumor size (74% <2.0 cm)	Mean, 1 y	BCT or mastectomy + negative SLN biopsy result	368	1 (0.8)	98
						BCT or total mastectomy + complete axillary node dissection	496	3 (0.6)	98
						BCT or total mastectomy + SLN biopsy + completion axillary lymph node dissection	83	0	98
						BCT or total mastectomy + SLN biopsy + axillary radiation if positive SLN biopsy result	33	0	98
Zavagno et al,[44] 2008	1999-2004	Mean, 57 y	No palpable, suspicious nodes on examination	All tumors ≤3.0 cm on examination	Median, 4.6 y	BCT or mastectomy + negative SLN biopsy result	218	1 (0.4)	87
						BCT or mastectomy + SLN biopsy+ completion axillary node dissection	94	0	89
						BCT or mastectomy + SLN biopsy + complete axillary node dissection	352	0	89
Krag et al,[13] 2010	1999-2004	Any age (75% ≥50 y)	No palpable, suspicious nodes on examination	Any tumor size (98% ≤4.0 cm)	Mean, 7.9 y	BCT or mastectomy + negative SLN biopsy result	1978	8 (0.4)	83
						BCT or mastectomy + negative SLN biopsy result and complete axillary node dissection	2011	14 (0.7)	84

Abbreviations: BCT, breast-conserving therapy (partial mastectomy followed by whole breast radiation); SLN, sentinel lymph node.

[a] No statistically significant difference in survival among groups.

[b] Completion axillary lymph node dissection = complete axillary node dissection after SLN biopsy reveals metastatic disease.

[c] Complete axillary lymph node dissection = performed regardless of result of SLN biopsy.

[d] Study closed early because of benefits of SLN biopsy alone group; results are for intention to treat analysis. Also included are 123 patients who underwent "4 node axillary sampling"; 1 recurrence was in this group.

(Table 2). Fifty-year follow-up from the Copenhagen Breast Cancer Study[45] revealed similar results (Table 2). Primary axillary radiation (targeted radiation to the axilla without any axillary surgery) provides adequate regional control without compromising survival in patients without palpable, suspicious axillary nodes. Primary axillary radiation, however, cannot provide the staging information afforded by SLN biopsy. Patients without sentinel node metastases do not require axillary radiation[18]; however, without this pathologic information, all patients with breast cancer would have to receive axillary radiation, resulting in overtreatment. Consequently, primary axillary radiation is not commonly used in patients without evidence of axillary metastases on examination and ultrasound.[37,38,46,47]

Axillary Lymph Node Dissection vs SLN Biopsy

Sentinel node biopsy allows selective removal of the first few nodes that drain the breast. These nodes are analyzed with serial sectioning to obtain staging information.[13,14,48] Early investigations validated SLN biopsy and confirmed its sensitivity for identifying axillary metastases and accurately reflecting the pathologic status of the entire axilla (**Table 3**).[14,15,42,43,48,50] The largest of these studies was the NSABP B-32 trial,[13] conducted at 80 centers in the United States and Canada. The NSABP B-32 trial included patients with a diagnosis of invasive ductal or lobular breast cancer without palpable, suspicious lymph node metastases (Table 3). A total of 2807 women were randomized to receive SLN biopsy followed by complete axillary node dissection and 2804 women were randomized to receive SLN biopsy followed by observation if the SLN biopsy result was negative (n = 2011) or completion axillary node dissection if the SLN biopsy found metastases (n = 793). The mean time in the study for patients with a negative SLN biopsy result was 95.6 months. Recurrence of axillary node metastases was seen in 8 patients (0.4%) who underwent SLN biopsy followed by complete axillary node dissection and in 14 (0.7%) of patients who underwent SLN biopsy and completion axillary node dissection only for nodal metastases

Table 4. Axillary Lymph Node Dissection or Not for Positive SLN Biopsy Result (Level B Evidence)

Source	Study Period	Participant Age	Axillary Status	Tumor Size	Follow-up	Study Interventions	Sample Size	Recurrence, No. (%)	Survival, %[a]
Giuliano et al,[19,33] 2011	1999-2004	Median, 56 y	No palpable, suspicious nodes on examination	Tumors ≤3.0 cm on examination	Median, 6.3 y	BCT + positive SLN biopsy result + completion axillary node dissection	388	2 (0.5)	88.8
		Median, 54 y				BCT + positive SLN biopsy result	425	4 (0.9)	89.9
Straver et al,[41] 2010	2001-2005	Median, 57 y	No palpable, suspicious nodes on examination	Tumors ≤3.0 cm on examination	NA[b]	BCT or mastectomy + negative SLN biopsy result	NA[b]	NA[b]	NA[b]
						BCT or mastectomy + SLN biopsy + completion axillary lymph node dissection	NA[b]	NA[b]	NA[b]
						BCT or mastectomy + positive SLN biopsy result + axillary radiation	NA[b]	NA[b]	NA[b]
Galimberti et al,[52] 2013	2001-2010	Median, 54 y	No palpable, suspicious nodes on examination	Tumors ≤5.0 cm on intraoperative gross measurement	Median, 5 y	BCT or mastectomy + positive SLN biopsy result + completion axillary node dissection	464	1 (0.2)	87.8
						BCT or mastectomy + positive SLN biopsy result alone	467	4 (0.8)	84.4

Abbreviations: BCT, breast-conserving therapy (partial mastectomy followed by whole breast radiation); NA, data not available; SLN, sentinel lymph node.

[a] No statistically significant difference in survival among groups.

[b] Planned accrual of 4767 patients; results pending.

(P = .22). There was no significant difference in survival between groups. Similarly designed international studies as well as a meta-analysis have yielded the same results (Table 3).[13,40,44,48,49] The meta-analysis[40] revealed no difference in overall survival, disease-free survival, or regional lymph node recurrence for SLN biopsy vs complete axillary node dissection in patients without palpable, suspicious lymph nodes and negative SLN biopsy result. Available evidence suggests that compared with complete axillary lymph node dissection, SLN biopsy identifies axillary node metastasis 90% to 99% of the time that nodal metastases are present.[13,14,41-44,48-50] The techniques sensitivity improves with greater surgeon experience with the procedure.[51] A false-negative rate of 1% to 10% raises the concern for recurrence due to residual metastases, but, in practice, this has not been observed, with rates of axillary node metastatic recurrences of only 0%[14,49] to 3%[13,43,48] following SLN biopsy. For breast cancer patients without evidence of axillary metastases on examination or ultrasound, the weight of the evidence from multiple trials supports SLN biopsy as the appropriate axillary intervention.

SLN Biopsy Alone

The above cited trials showed the benefits of multimodal approaches to breast cancer treatment with less need for surgery. Studies also showed that nonsurgical treatments such as radiation or systemic chemotherapy effectively treated nodal metastases. These observations called into question the need for completion axillary node dissection even when metastases were demonstrated by SLN biopsy. To examine this question, the ACOSOG Z11 trial was initiated (**Table 4**). Patients had clinical T1 to T2 (0.1-5 cm) NOMO cancers and were undergoing partial mastectomy with SLN biopsy. Key exclusion criteria were receipt of partial breast radiation, T3/T4 (>5 cm or chest wall/skin invasion) tumors, presentation with palpable/matted lymph nodes, and 3 or more metastatic lymph nodes on SLN biopsy. Patients found to have SLN metastases were randomized to either observation or receipt of completion axillary node dissection. All patients received adjuvant whole breast radiation, and, although not specified in the protocol, 97% received adjuvant systemic therapy per local institutional treatment paradigms. Study end points were survival and recurrence. The trial was terminated before complete accrual because of an unexpected low event rate in both groups. Eight hundred ninety-one patients were randomized, with a median follow-up of 6.3 years. Analysis was performed on the treatment received; 32 patients in the axillary node dissection group did not receive axillary lymph node dissection and 11 patients in the SLN biopsy alone group underwent axillary lymph node dissection. Two of 420 patients with axillary node dissection (0.5%) had a recurrence of axillary lymph node metastases vs 4 (0.9%) of 436 in the SLN biopsy alone group (P = .45).[20] Results supporting ACOSOG Z11 were recently published from the International Breast Cancer Study Group Trial 23-01[52] (Table 4). The results of the similarly designed After Mapping the Axilla: Radiotherapy or Surgery (AMAROS) trial are pending (Table 4). For patients with tumors 5 cm or smaller and no suspicious axillary lymph nodes on clinical examination who are undergoing BCT and systemic therapy, omitting completion axillary node dissection in the setting of 3 or fewer metastatic lymph nodes on SLN biopsy does not increase the risk of recurrence of axillary lymph node metastases.

Survival

As described above, the NSABP B-04 trial randomized 1079 patients with breast cancer who had no palpable, suspicious axillary nodes to receive radical mastectomy, total mastectomy with axillary radiation, or total mastectomy alone (Table 1).[28] With a mean follow-up of 20 years, there were no differences in disease-free, distant disease-free, or overall survival. Rudenstam et al[32] randomized 473 women aged 60 years or older with breast cancer and no palpable, suspicious axillary nodes to receive complete axillary node

dissection or no axillary treatment[32] (Table 1). With a median follow-up of 6.6 years, disease-free and overall survival were nearly identical. Similarly, Martelli et al[34] randomized 219 women with breast cancer and no palpable, suspicious axillary nodes to complete axillary dissection or no axillary treatment (Table 1).[34] After 5 years of follow-up, there was no difference in disease-free or overall survival. Several randomized trials have compared axillary dissection with SLN biopsy in patients with no suspicious, palpable axillary nodes (Table 3). None reported a difference in disease-free or overall survival.[13,40,43,44,48] All studies demonstrated that in patients without suspicious, palpable nodes, complete axillary node dissection does not affect survival compared with SLN biopsy. No trials exist assessing survival in women with suspicious palpable nodes randomized to a no-axillary-intervention group.

Adverse Outcomes With Axillary Surgery

Both axillary surgery and axillary radiation therapy can cause shoulder and arm symptoms including lymphedema, pain or numbness, and reduced range of motion (**Table 5**). The incidence of complications is dependent on the approach used to ascertain symptoms and on the period between axillary treatment and assessment. Patient factors such as obesity[55] and higher tumor stage[56] can increase morbidity. Shoulder and arm morbidity was carefully ascertained at multiple time points following axillary surgery in the ALMANAC trial.[43] Axillary node dissection was associated with significant reductions in shoulder flexion and abduction at 1 month but range of motion had returned to near baseline by 12 months. Similarly, 62% of women reported arm pain or numbness at 1 month and 31% still reported these symptoms at 12 months. Clinicians rated these symptoms as severe in only 1% at 12 months. Women may develop measurable arm swelling after axillary surgery without symptoms; consequently, lymphedema rates are generally higher for studies that measure arm volumes or circumferences than for studies that rely on patient-reported symptoms. Unlike other shoulder and arm symptoms, the prevalence of lymphedema generally increases over time.[42] Subjective lymphedema is reported by 14% of patients following axillary dissection,[43] 4% of patients following axillary radiation,[37] and 5% to 7% of patients following SLN biopsy.[9,43] Randomized prospective clinical trials consistently report reduced rates of shoulder and arm morbidity for SLN biopsy compared with axillary dissection.[9,19,42-44,53]

Table 5. Long-term Rates of Adverse Outcomes Associated With Axillary Operations

Outcome	Axillary Lymph Node Dissection, %	Sentinel Node Biopsy Alone, %
Lymphedema	10-20[9,43,53,54]	5-7[9,43,53,54]
Quality-of-life reduction	35[9]	23[9]
Arm pain/numbness	31[9,42]	11[43,50]

Discussion

Due to earlier stages of presentation and the data available to guide treatment, survival after a diagnosis of breast cancer in the United States is excellent.[11] One common dilemma, however, is whether to perform a completion axillary node dissection (**Figure 2**). Factors that need to be considered when making this decision include the risk of additional metastatic disease, the chances of developing symptomatic axillary metastases if completion axillary lymph node dissection is not performed, and the risk of underutilization of adjuvant therapies because of a lack of the complete staging information gained from axillary node dissection.

Risk of Additional Axillary Metastases

One factor to consider when determining whether completion axillary node dissection is required is the risk of additional nodal metastases beyond the sentinel nodes removed. Various nomograms have been developed for this.[57-59] One of the most widely validated[57,60-62] is the Memorial Sloan-Kettering nomogram.[57] This nomogram was developed using retrospective data on 702 patients and then validated in a 373-patient prospective cohort.[57] The nomogram[63] is available online[63] and uses tumor and nodal metastatic characteristics to predict the risk of additional nodal metastases. While helpful, the nomogram is a guide, and each patient must weigh the risk of finding additional nodal metastases vs the risk of clinically significant lymphedema.

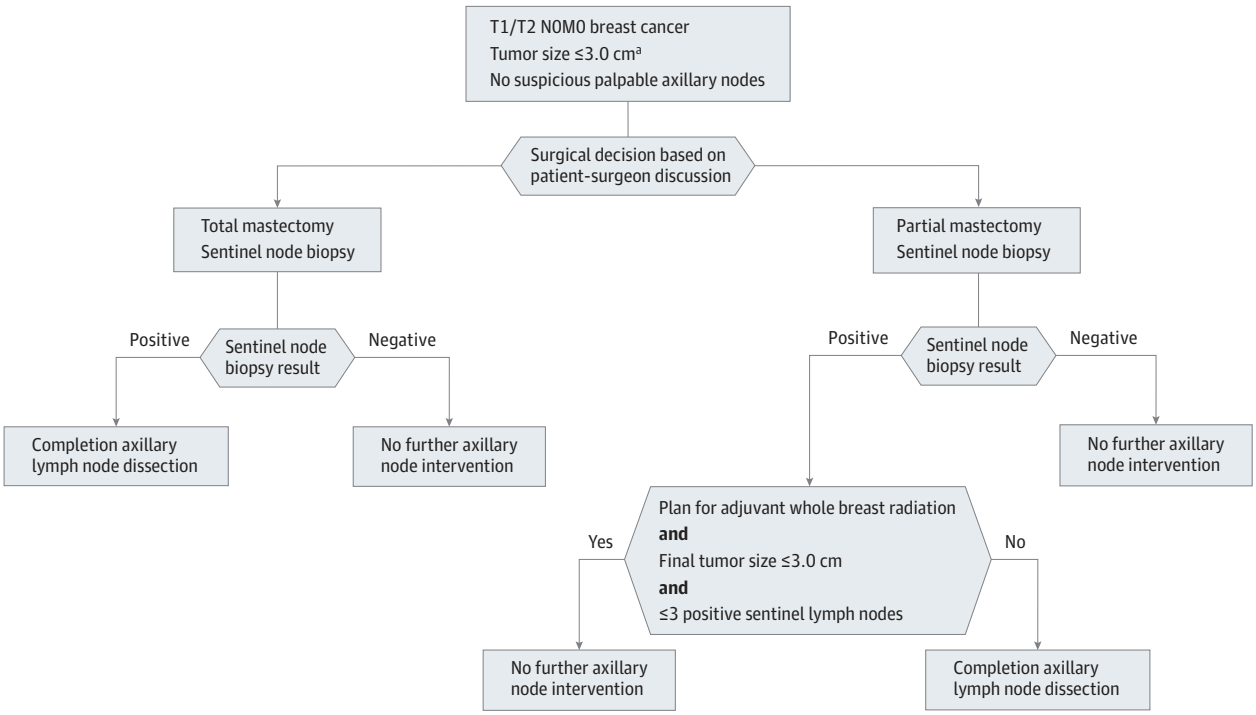
Risk of Developing Symptomatic Axillary Recurrence

Although the majority of studies reveal a low rate of recurrence,[4,24,28-30,64] even in the setting of presumed residual nodal metastases, recurrence of axillary lymph node metastases can negatively affect quality of life. In particular, axillary metastatic disease that involves the chest wall, brachial plexus, or pectoralis musculature may not be amenable to surgery and has the potential to result in significant pain and disability.[65] An increased risk of recurrence of axillary lymph node metastases is seen in patients who have diagnoses at a younger age,[66-68] have higher-grade tumors,[23] have estrogen/progesterone receptor–negative tumors,[67] and have not had radiation.[66] For patients with high-risk disease who would not meet ACOSOG Z11 inclusion criteria, completion axillary node dissection is indicated to prevent potential development of symptomatic recurrence of axillary lymph node metastases. Scenarios in which complete axillary node dissection is still supported by data include patients (1) with palpable, suspicious axillary nodes (even if there is a good response to neoadjuvant chemotherapy); (2) undergoing mastectomy with a positive SLN biopsy result; (3) with a positive SLN biopsy result who cannot get radiation therapy; 4) with a positive SLN biopsy result who will not get adjuvant systemic therapy; and (5) who would not meet inclusion criteria for the ACOSOG Z11 trial.

Adjuvant Therapy Decisions

In the past, axillary nodal status was a critical factor considered in adjuvant systemic therapy decisions. With the validation of SLN biopsy, the same staging information is obtained with less morbidity. Now, in the era of personalized therapy, decisions regarding adjuvant treatments are often guided by molecular tumor profiling, making it necessary to continue assessing the value of surgical axillary staging. These commercially available genomic assays,[69-73] along with traditional pathologic tumor markers, often drive decisions regarding adjuvant chemotherapy, sometimes irrespective of nodal status.[74] One of the genomic assays is able to provide information regarding recurrence risk in estrogen receptor–positive tumors based on 16 cancer genes.[69-71] It was developed specifically to determine what benefit may be obtained from adding chemotherapy to a treatment regimen. There remain, however, clinical scenarios in which additional

Figure 2. Proposed Treatment Algorithm for Patients With Breast Cancer Who Present With No Palpable, Suspicious Axillary Nodes Based on the Results of the Systematic Review[a]



[a]If initial tumor size is >3.0 cm or patient is to undergo neoadjuvant chemotherapy, algorithm does not apply.

nodal metastases may influence decisions on systemic therapy; for these patients, a tailored approach with completion axillary node dissection is appropriate.

Conclusion

Among patients with breast cancer but no palpable lymph nodes, complete axillary node dissection provides no survival benefit compared with SLN biopsy but reduces the risk of recurrence of axillary node metastases by 1% to 3%.[15,40,44,48,49] However, complete axillary node dissection is associated with a 14%[43] risk of lymphedema compared with only 5% to 7% in patients undergoing SLN biopsy.[9,47] In the future, multimodal treatment will be dependent on primary tumor features, including molecular markers, potentially rendering the staging information obtained via axillary lymph node dissection inconsequential.

ARTICLE INFORMATION

Author Contributions: Dr Rao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Rao, Euhus, Balch.
Acquisition of data: Rao, Mayo.
Analysis and interpretation of data: Rao, Euhus.
Drafting of the manuscript: Rao, Euhus, Mayo, Balch.
Critical revision of the manuscript for important intellectual content: Rao, Euhus, Mayo, Balch.
Statistical analysis: Mayo.
Administrative, technical, or material support: Rao, Mayo.
Study supervision: Rao, Euhus, Balch.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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