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Management of the regional lymph nodes in breast cancer

Authors
Seth P Harlow, MD
Donald L Weaver, MD

Section Editors
Anees B Chagpar, MD, MSc, MPH
Daniel F Hayes, MD
Lori J Pierce, MD

Deputy Editor
Susan E Pories, MD, FACS

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INTRODUCTION — The lymphatic drainage pathways of the breast (axillary, internal mammary [IM], and supraclavicular nodal groups) are the regional areas most likely to be involved with metastatic breast cancer. The indications and outcomes for axillary lymph node dissection (ALND) in women with breast cancer will be reviewed here.

Sentinel lymph node biopsy (SLNB) and the primary surgical management of the breast and radiation therapy (RT) of both the breast and chest wall are discussed separately. (See "Sentinel lymph node biopsy for breast cancer: Indications and outcomes" and "Sentinel lymph node biopsy in breast cancer: Techniques" and "Mastectomy and breast conserving therapy for invasive breast cancer" and "Role of radiation therapy in breast conservation therapy" and "Postmastectomy chest wall irradiation".)

RISK FACTORS FOR LYMPH NODE INVOLVEMENT IN BREAST CANCER

Axillary lymph nodes — The axillary lymph nodes (LNs) receive 85 percent of the lymphatic drainage from all quadrants of the breast; the remainder drains to the IM chain. The likelihood of axillary LN involvement is related to tumor size and location, histologic grade, and the presence of lymphatic invasion [1,2].

Tumor size and margins — The likelihood of axillary LN involvement increases as the size of the primary tumor increases [3-5]. In series of 2282 women with invasive breast cancer or ductal carcinoma in situ (DCIS), the incidence of axillary LN involvement was as follows [5]:

- Tis — 0.8 percent
- T1a — 5 percent
- T1b — 16 percent
- T1c — 28 percent
- T2 — 47 percent
- T3 — 68 percent
- T4 — 86 percent

An analysis of the number of positive nodes based upon tumor size from a contemporary group of 6800 women diagnosed with invasive breast cancer after screening mammography is presented in the following table (table 1) [6].

Thus, ALN metastases are relatively common even with invasive breast cancers ≤1 cm in size [1,2,7-10]. In a report of 919 such women who underwent axillary LN dissection (ALND), axillary LN metastases were detected in 16 and 19 percent of those with T1a (tumor size 0.1 to 0.5 cm in greatest dimension) and T1b tumors (tumor size 0.5 to 1.0 cm), respectively [10]. (See "Tumor node metastasis (TNM) staging classification for breast cancer".)

Axillary LN positivity rates are also higher in women who are found to have residual tumor after reexcision for positive margins following lumpectomy compared to those whose tumors were either excised to a negative margin initially or who had negative reexcisions for an initially positive margin [11]. This is likely attributable to an inaccurate size measurement. Tumor size is generally recorded as the largest dimension on the first excision. If there is even a moderate amount of residual disease at reexcision, the initial excision can significantly underestimate the true size of the lesion. Larger tumors are associated with a higher likelihood of axillary involvement.

Histologic features — Low-grade (grade 1) tumors have a significantly lower rate of axillary LN

metastases compared to grade 2 or 3 tumors [9]. As an example, in data derived from the Surveillance, Epidemiology and End Results (SEER) database, the incidence of axillary LN involvement in patients with grade 1 and grade 3 tumors of similar size was 3.4 and 21 percent, respectively [9].

Tumors that are associated with a less than 5 percent risk of axillary LN metastases include those with a single focus of microinvasion [12,13], <5 mm grade 1 tumors without lymphatic invasion, and mucinous or pure tubular carcinomas <1 cm [14,15]. (See "Pathology of breast cancer: The invasive carcinomas".)

The reported incidence of axillary LN metastases in modern series of women with DCIS ranges from 0 to 4 percent. This is generally accepted to be due to the presence of a small, undetected invasive component rather than the ability of pure DCIS to metastasize to the axilla. Thus, axillary dissection is not routinely performed in women who have pure DCIS. (See "Breast ductal carcinoma in situ and microinvasive carcinoma".)

Tumor location — Axillary LNs are more commonly involved with tumors involving the lateral rather than the medial portion of the breast [3,16,17]. The most likely explanation for this difference is preferential drainage of some medial tumors to the IM nodes [18].

Internal mammary lymph nodes — Like the axillary LNs, the IM nodes receive lymph drainage from all quadrants of the breast [19]. However, medial tumors have a significantly higher rate of IM nodal metastases [20]. Although the IM nodal chain extends from the fifth intercostal space to the retroclavicular region, nodes in the upper three interspaces are most likely to contain metastases [21-23].

Isolated IM nodal metastases are infrequent; more often axillary nodes are involved as well [18,20,24]. In a report that included 7070 cases in which the IM and axillary LNs were examined, IM metastases were detected in 22 percent, but were the only site of metastases in 4.9 percent [18]. Isolated IM involvement was more frequent for medial than lateral tumors (7.6 versus 2.9 percent).

PET scans and integrated PET/CT may reveal IM nodal disease that is unrecognized by conventional staging methods, but neither of these modalities can provide pathologic confirmation [25]. As with axillary nodes, it is possible to have reactive IM nodes after breast biopsy that can confound imaging results. The use of PET-CT in staging breast cancer patients is discussed elsewhere. (See "Initial work-up and staging after a new diagnosis of breast cancer".)

IM metastases had been thought to be associated with a grave prognosis. However, their significance appears to be no different from axillary LN involvement [23,26,27]. The prognosis is worse when both nodal groups are involved [28]. This is reflected in a change in the staging of positive intramammary nodes in the 6th edition of the AJCC Cancer Staging Manual. Positive internal mammary nodes are not the sole consideration for a designation of pN3, the presence and number of positive axillary nodes, supraclavicular and infraclavicular nodes are also taken into account [29].

The management of IM nodes is controversial. Following four early randomized trials showing no survival benefit from extended mastectomy (which included IM nodal dissection) as compared to radical or modified radical mastectomy (even in the absence of chemotherapy), routine dissection of IM nodes was abandoned [30-33]. Furthermore, the widespread use of adjuvant systemic therapy for women with both node-positive and node-negative breast cancer has diminished the importance of the IM nodes in clinical care. (See "Adjuvant chemotherapy for early stage HER2-negative breast cancer" and "Adjuvant endocrine therapy for postmenopausal women with early stage breast cancer" and "Adjuvant endocrine therapy for premenopausal women with early stage breast cancer" and "Clinical decisions in systemic adjuvant therapy for early breast cancer".)

On the other hand, interest has been rekindled in treating the IM nodes because of two developments:

- The increasing use of sentinel lymph node (SLN) mapping, which often identifies nonaxillary nodes, although the ability to identify these nodes does not imply a clinical benefit. (See "Sentinel lymph node biopsy for breast cancer: Indications and outcomes" and "Sentinel lymph node biopsy in breast cancer: Techniques".)
- Results from randomized trials testing the value of postmastectomy radiation therapy as well as a meta-analysis by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) that provide high level evidence that local-regional tumor control is associated with long-term survival benefits [34].

These benefits have been limited to trials that used systemic therapy, which may explain why earlier randomized trials (in which adjuvant systemic therapy was not routinely administered) failed to show a survival benefit from resection of the IM nodes. Further study in this area would be helpful in discerning the clinical risk-benefit ratio of internal mammary node evaluation.(See "Postmastectomy chest wall irradiation".)

Supraclavicular lymph nodes — Supraclavicular metastases are usually associated with extensive axillary LN involvement and are rare in its absence. As an example, in a series of 274 women undergoing routine supraclavicular dissection, supraclavicular metastases were found in 18 and 0.7 percent of those with and without axillary LN metastases, respectively [35].

Supraclavicular metastases are considered a late stage of regional metastatic involvement; however, some patients are cured with aggressive combined modality therapy [36]. As a result, supraclavicular involvement was reclassified in the 2002 TNM staging classification as N3 rather than M1 disease [29]. (See "Clinical features and management of locally advanced breast cancer" and "Tumor node metastasis (TNM) staging classification for breast cancer".)

SENTINEL LYMPH NODE BIOPSY — Sentinel lymph node (SLN) biopsy is increasingly being used as a method to determine whether full ALND is necessary. (See "Sentinel lymph node biopsy for breast cancer: Indications and outcomes" and "Sentinel lymph node biopsy in breast cancer: Techniques".)

Management of sentinel node metastases — For patients who undergo SLN biopsy rather than initial ALND, completion ALND continues to be the standard treatment recommendation if the SLNs are positive [37]. The management of SLN metastases is discussed in detail elsewhere. (See "Sentinel lymph node biopsy for breast cancer: Indications and outcomes" and "Sentinel lymph node biopsy in breast cancer: Techniques".)

AXILLARY DISSECTION — Axillary lymph node dissection (ALND) has traditionally been a routine component of the management of early breast cancer. The benefits of ALND include its impact on disease control (ie, axillary recurrence and survival), its prognostic value, and its role in treatment selection. Histologic examination of removed LNs at the time of ALND is thought to be the most accurate method for assessing spread of disease to these nodes.

However, the anatomic disruption caused by ALND may result in lymphedema, nerve injury, and shoulder dysfunction, which compromise functionality and quality of life. More recently, the role of ALND in breast cancer management has been questioned, particularly in older women who are receiving tamoxifen. This is because of the efficacy of axillary RT in preventing locoregional recurrence, persisting questions as to the survival benefit of ALND, the fact that more women with node-negative breast cancer are receiving adjuvant systemic therapy, and the increasing use of less invasive strategies, especially SLN mapping.

The use of full ALND for staging purposes in clinically node-negative patients is declining with the adoption of the SLN technique by many centers. Moreover, others are using ultrasound of the axilla with fine needle aspiration biopsy for suspicious nodes and to select patients for either SLN or ALND. (See "Sentinel lymph node biopsy for breast cancer: Indications and outcomes" and "Sentinel lymph node biopsy in breast cancer: Techniques".)

Despite these observations, ALND is still performed in many women treated for early stage breast cancer. In a National Cancer Data Base study of data on over 500,000 women with stage I and II breast cancer treated in United States (US) hospitals between 1985 and 1995, only 11 percent of women undergoing breast conserving therapy (BCT) between 1993 and 1995 did not have an ALND. ALND was more likely to be omitted in women with stage I versus stage II disease (15 versus 6 percent), low-grade as compared to high-grade lesions (15 versus 7 to 10 percent), and in women over age 70 [38]. This was before the widespread adoption of SLN biopsy for patients with a clinically node negative axilla.

Indications — Traditionally, an axillary lymph node dissection was recommended in every patient with invasive breast cancer. However, with improved screening techniques and the introduction of sentinel lymph node biopsy techniques, the indications for axillary dissection are limited.

In general the indications include:

- ALND remains the standard approach for women who have clinically palpable axillary nodes.
- Completion ALND is indicated in patients who are SLN-positive. (See "Sentinel lymph node biopsy in breast cancer: Techniques" and "Sentinel lymph node biopsy for breast cancer: Indications and outcomes".)
- All patients with inflammatory breast cancer should have an ALND since the false-negative rate for SLNB will be high because of the presence of partially obstructed, functionally abnormal subdermal lymphatics.

In contrast, ALND is not indicated in patients with ductal carcinoma in situ unless the disease is extensive enough to require a mastectomy.

Level of dissection — ALND extent can be defined by either the number of axillary LNs resected or their anatomic location. Axillary LNs are divided into three levels based upon their relationship to the pectoralis minor muscle:

- Level I: Inferior and lateral to the pectoralis minor muscle
- Level II: Posterior to the pectoralis minor and below the axillary vein
- Level III (infraclavicular): Medial to the pectoralis minor and against the chest wall; their involvement alters nodal staging classification due to their poor prognostic significance. Level III lymph node involvement automatically confers a pN3 status [29]. (See "Tumor node metastasis (TNM) staging classification for breast cancer".)

An accurate determination of the nodal level of a resected specimen can only be made if the specimen is marked by the surgeon or separated into levels before it is evaluated by the pathologist.

The level of dissection is a tradeoff between the greater morbidity of a more extensive ALND and the possibility of leaving residual untreated axillary disease. In studies of skip metastases (ie, involvement of LNs in the upper axilla with uninvolved level I nodes), the incidence of isolated level II nodal metastases ranges from 1.5 to 29 percent [39-44]. Some of this variability is attributable to differences in the definition of level I versus II nodes. Lymphatic mapping studies have demonstrated that skip metastases are most likely explained by individual variations in lymphatic drainage.

The reported incidence of skip metastases in the level III nodes with uninvolved level I nodes is as low as 0.2 to 3.1 percent [39-43,45]. However, in these reports, the level III specimens contained an average of only 2.2 LNs, which may account for the low rates. In other series, between 1.3 and 3.1 percent of level III nodes are involved when both level I and II nodes are negative [40-43]. These numbers correlate well with locoregional recurrence rates following a level I and II ALND in women undergoing BCT (3 percent or less) [46-50].

Level III lymph node dissection significantly increases the morbidity of the ALND. This level is not generally formally dissected, rather clinically suspicious level III nodes are separately resected and labeled as such for the pathologists. (See "Mastectomy and breast conserving therapy for invasive breast cancer".)

In general, a level I and II anatomic ALND is the preferred procedure for axillary assessment [51]. Routine removal of level III nodes is unnecessary for staging but should be carried out to maximize local control if grossly positive axillary LNs are identified intraoperatively. The typical level I/II dissection should yield ≥10 axillary LNs, although the range is highly variable.

The number of positive axillary LNs affects the determination of disease stage and also influences locoregional recurrence rates; the impact on survival is less certain.

- Axillary sampling - The influence of the number of removed axillary LNs on staging has been studied predominantly in reports that compared axillary sampling to full ALND. Axillary sampling (removal of four to six nodes) is an imprecisely defined procedure in which variable amounts of the axillary contents are removed, often without reference to anatomic structures. It has been performed, mainly for staging purposes, in an attempt to reduce the morbidity of ALND [52,53].

One study found that 24 percent of women undergoing axillary sampling were erroneously staged as determined by subsequent complete ALND [54]. This is significantly higher than the false negative rate with sentinel node biopsy (approximately 5 to 10 percent). Axillary sampling does not represent

the standard of care, at least in the United States. (See "Sentinel lymph node biopsy for breast cancer: Indications and outcomes" and "Sentinel lymph node biopsy in breast cancer: Techniques".)

- Axillary recurrence and survival - The risk of axillary recurrence is inversely related to the number of removed ALNs in a formal axillary lymph node dissection. In different studies, axillary failure rates were 5 to 21 percent when fewer than five LNs were removed as compared to 3 to 5 percent when more than five LNs were removed [50,55,56]. Sentinel node biopsy represents a strategy for directed sampling that increases the probability of identifying positive nodes over undirected sampling techniques, thus allowing fewer nodes to be removed without increasing the axillary failure rate. (See "Sentinel lymph node biopsy for breast cancer: Indications and outcomes" and "Sentinel lymph node biopsy in breast cancer: Techniques".)

In contrast to these data addressing the incidence of axillary recurrence, the impact of number of resected ALNs on survival is controversial. Many retrospective reports suggest inferior survival with fewer (often <10) resected axillary LNs [57-63] while others suggest no prognostic impact [53,64,65]. At least some data suggest that a survival detriment is not seen in women undergoing contemporary BCT, as standard breast radiation tangent fields routinely overlap with at least the low axilla [57]. (See 'Axillary radiation therapy' below.)

Impact of ALND on survival — The contribution of enhanced local control to survival from breast cancer has been a point of controversy for many years. However, an increasing body of evidence suggests that improved local control results in better survival. Women who recur locally have a higher rate of distant metastases, and most of these women will die of their cancer [66-69]. Furthermore, at least three randomized trials suggest a decrease in overall mortality by about 10 percent when local control is improved through the use of postmastectomy chest wall irradiation. (See "Postmastectomy chest wall irradiation", section on 'Modern clinical trials'.) Finally, the analysis from the Early Breast Cancer Trialists' Collaborative Group analysis demonstrates that avoidance of a local recurrence does impact 15-year breast cancer mortality, since differences in local treatment that substantially increase local recurrence rates were associated with lower 15-year survival rates [34,70].

The available data regarding the presence of a survival advantage for lymphadenectomy over observation alone are conflicting. The following studies raise the possibility that failure to remove tumor-bearing axillary LNs could be detrimental in patients with breast cancer:

- In one study performed at the Institut Curie, 658 women with a clinically negative axilla were randomly assigned to lumpectomy alone or lumpectomy plus ALND [71]. RT was given to both groups, and women undergoing ALND who had histologically positive LNs received chemotherapy. ALND was associated with significantly better five-year survival (97 versus 93 percent), and a reduced frequency of visceral and supraclavicular metastases, and lymph node recurrences. There was a lower incidence of axillary and supraclavicular failures in patients who underwent ALND, although the only patients to receive chemotherapy were in the ALND group, making this a confounding variable.

However, with longer follow up, survival rates were similar (about 75 percent) in both groups at 10 and 15 years [72].

- A survival benefit for ALND was also suggested in a retrospective population-based cohort of 8038 patients treated for T1-2 breast cancer in British Columbia between 1989 and 1998 [73]. ALND had been omitted from the treatment of 4, 8, and 22 percent of women 50 to 64, 65 to 74, and >74 years old, respectively. Despite the fact that all of the clinical factors associated with the omission of ALND were favorable (ie, smaller tumor size, lower histologic grade, absence of lymphovascular invasion), overall and cancer-specific five-year survival rates were significantly worse in those who had not undergone ALND (68 versus 85 percent, and 86 versus 91 percent, respectively). Systemic therapy use and regional relapse rates were comparable between the women who underwent axillary dissection and those who did not in each age-specific cohort. However, locoregional recurrence rates were not significantly higher if ALND was not performed. These data suggest that positive axillary nodes represent an indicator of the propensity for metastatic behavior rather than a nidus for later disease dissemination, which, if removed, would improve outcomes.

- A similar relationship between ALND and survival was reported in a retrospective review of 257,157 women diagnosed with breast cancer in the SEER database between 1988 and 2000 [63]. Survival was significantly better among women who underwent lymphadenectomy (table 2), even

when controlling for race, use of RT, type of surgery, hormone receptor status, age, and stage. Perhaps more importantly, there was a consistent trend toward decreased survival as the ratio of positive to total number of nodes removed increased. The results were similar if SLN cases (which accounted for only 5.6 percent of the population) were included or excluded from the analysis.

- A meta-analysis of six trials that included over 3000 women who were randomly assigned to ALND or no ALND demonstrated a consistent improvement in absolute survival with ALND, ranging from 4 to 16 percent, across all trials (average 4.5 percent at 10 years) [74]. However, this analysis was limited by several deficiencies: the trials were conducted over a span of four decades (1951 to 1987), few patients had T1a tumors, none used modern systemic adjuvant chemotherapy, and none enrolled women over the age of 70.

- The most frequently quoted data arguing against the need for routine ALND in early stage breast cancer is National Surgical Adjuvant Breast and Bowel Project trial B-04 (NSABP B-04) [75]. Women with clinically node-negative invasive breast cancer were randomly assigned to radical mastectomy (which by definition includes ALND), simple mastectomy plus local nodal irradiation, or simple mastectomy with ALND delayed until positive LNs developed. The inability to detect significant differences among the three groups with respect to disease-free or overall survival (about 57 percent) at 10 years (and in a later report, with 25 year follow-up [76]) has been used to argue against a therapeutic role for ALND. However, this study lacked the statistical power to demonstrate a small but clinically significant survival difference among the groups. Further, many of the women in the simple mastectomy group actually had axillary LNs removed based upon the pathologist's examination.

- A subsequent meta-analysis of three randomized trials comparing axillary dissection versus no dissection published between 2000 and 2007 as well as a 4th trial comparing axillary radiotherapy versus no axillary therapy found no difference in overall survival, metastases, or ipsilateral breast recurrence associated with axillary treatment [77]. This is likely attributable to the widespread use of adjuvant chemotherapy and radiation therapy during this time frame, especially since breast radiation for breast conservation includes at least the low axillary field.

Surgical complications — Major complications of ALND are infrequent, but include injury or thrombosis of the axillary vein and injury to the motor nerves. Lymphedema is more common and is generally of the most concern to patients anticipating the procedure. Other complications include seroma formation, shoulder dysfunction, loss of sensation in the distribution of the intercostobrachial nerve, and mild edema of the arm and breast [78]. (See "Lymphedema: Etiology, clinical manifestations, and diagnosis" and "Lymphedema: Prevention and treatment".)

Seroma — Seroma formation is the most frequently occurring complication, and postoperative closed-suction drainage is beneficial. In one randomized trial, women undergoing 227 ALNDs were randomly assigned to an axillary drain for 24 hours or expectant management [79]. The use of a drain significantly decreased the time to seroma resolution (12 versus 18 days), the mean number of aspirations required, and the average volume of fluid aspirated.

Arm morbidity — Shoulder stiffness, and numbness and paresthesias in the upper arm are common complaints following ALND; although they do not usually interfere with daily living, they may impact on quality of life (QOL) [78,80-83]. In one series, 42 percent of women had subjective or objective arm impairment (eg, pain, reduced grip strength) one year postoperatively [82]. The likelihood of arm edema is higher in women who undergo more extensive ALND, and combined axillary surgery and RT. Sentinel lymph node biopsy is associated with fewer arm complications than full ALND or combined axillary surgery and radiation therapy [84]. These issues are discussed in more detail elsewhere. (See "Lymphedema: Etiology, clinical manifestations, and diagnosis".)

Despite the risk of long-term arm morbidity in women undergoing treatment of early stage breast cancer, these adverse effects do not appear to alter a woman's decision-making with respect to the potential benefit of ALND. In one series that examined how women weigh the potential benefits of ALND against the risks associated with the procedure, 68 and 29 percent of women with invasive cancer and DCIS, respectively, would accept a 40 percent risk of long-term arm dysfunction to gain prognostic information, even if it would not necessarily change their treatment [85].

ROLE OF AXILLARY SURGERY IN OLDER WOMEN TREATED WITH ADJUVANT ENDOCRINE THERAPY — Some investigators suggest that older women do not require axillary lymph node surgery because the knowledge gained does not influence adjuvant treatment choice or outcome. At least

three randomized trials have addressed this issue, all of which suggest that selected older women who have small (<2 cm) estrogen receptor (ER)-positive tumors who have a clinically uninvolved axilla and who are receiving adjuvant endocrine therapy may be treated without immediate axillary surgery without an adverse effect on outcome [86-88]. (See "General principles of management of early breast cancer in older women", section on 'Omission of axillary assessment'.)

Knowledge of the status of the ALNs may not influence treatment recommendation or outcome in patients over 70 years old when primary tumor characteristics are favorable or co-morbid disease is present. The use of endocrine therapy alters the risk benefit ratio in women over 70 with estrogen receptor positive tumors, making the benefit of ALND much lower in this group [89].

AXILLARY RADIATION THERAPY — Full axillary RT is defined here as the use of a third radiation field (in addition to the two tangential radiation fields to the breast or chest wall) encompassing the supraclavicular and upper axillary LNs. (See "Techniques and complications of breast and chest wall irradiation for early stage breast cancer".)

Axillary RT effectively prevents axillary recurrence in patients with clinically negative axillary LNs [47,48,90-92]. It does not, however, provide any information as to the pathologic status of the axilla. In retrospective series, the axillary recurrence rate is approximately 1 to 3 percent following RT to the axilla, and varies depending upon the presence or absence of clinically detectable axillary LNs [47,48,90-92]. In one series from the Joint Center for Radiation Therapy (JCRT), for example, the axillary failure rate in 390 clinically N0 patients at a median follow-up time of 77 months was less than 1 percent compared to 2.9 percent in women with clinically positive axillary LNs [48].

RT versus ALND — Three randomized trials have directly compared locoregional failure rates and survival in women treated with ALND or axillary RT in women with early stage breast cancer:

- In the previously described NSABP B-04 trial, clinically node-negative patients were randomly assigned to total mastectomy and ALND, total mastectomy with regional nodal irradiation, or total mastectomy only with delayed ALND at the time of recurrence [75]. Although the 10-year survival was similar in the three groups, the axillary failure rate was significantly higher in the women treated without primary ALND (18 percent) compared to those undergoing RT or initial ALND (3.1 and 1.4 percent respectively). The rate of axillary failure was probably higher than 18 percent in those undergoing delayed ALND because inoperable axillary recurrences and operable axillary recurrences that occurred simultaneous with or after distant metastases were excluded. It should be noted, however, that the time period for this study was 1971 to 1974, when the use of mammographic screening was neither widespread nor as sophisticated as it is presently. The mean tumor size in this study was generally larger than we identify today. Since the likelihood of subclinical axillary metastases increases with increasing tumor size, we would anticipate that axillary failure rates without dissection or radiation today would be significantly lower than 18 percent, especially in light of our current adjuvant chemotherapy regimens.

- In the Institut Curie trial noted above, women undergoing BCT were randomly assigned to lumpectomy and RT with or without ALND [71]. Patients with histologically positive axillary LNs also received RT to the supraclavicular and IM nodes plus chemotherapy, while those with medial or central lesions received IM nodal irradiation. At a mean follow-up of 54 months, the RT alone group had a higher rate of axillary failure (2.1 versus 0.9 percent) and a significantly lower rate of survival (93 versus 97 percent). However, in a later report with median 180 month follow-up, both the 10 and 15 year survival rates were similar (73.8 versus 75.5 percent at 15 years, respectively), despite the threefold higher axillary recurrence rate with RT alone (3 versus 1 percent, respectively) [72].

- In an Italian trial, 381 women undergoing BCT for tumors <1 cm in diameter who had a clinically negative axilla were randomly assigned to ALND or axillary RT. In a preliminary report with a median follow-up of 26 months, only one axillary recurrence was noted in each treatment arm [93].

All three trials show low rates of axillary failure after either ALND or axillary RT and similar long-term survival. Thus, whether ALND is therapeutic for a subset of patients is still debatable. Only those women with axillary LN involvement have the potential to benefit from ALND, because removal of normal nodes should not alter survival. For this reason, identification of patients who have involved axillary LNs by a less morbid procedure such as SLN biopsy or axillary ultrasound with fine needle aspirate or core biopsy holds great promise. (See "Sentinel lymph node biopsy for breast cancer: Indications and outcomes" and "Sentinel lymph node biopsy in breast cancer: Techniques".)

Complications of axillary radiation — Although treatment with either surgery or RT reduces the rate of axillary recurrence, the benefit must be balanced against the risk of treatment-related morbidity. In general, the rate of complications is higher in women undergoing surgery and RT compared to RT alone [90,94].

Arm edema — The risk and severity of arm edema and impaired arm mobility correlates with the extent of axillary surgery and the combined use of ALND and axillary RT. These issues are discussed in detail elsewhere. (See "Lymphedema: Etiology, clinical manifestations, and diagnosis".)

Brachial plexopathy — Permanent brachial plexopathy from RT to a supraclavicular and axillary apex field occurs in less than 1 percent of women receiving ≤50 Gy in 2 Gy fractions [95,96]. The incidence of plexopathy is significantly higher with an axillary dose greater than 50 Gy, the concomitant administration of chemotherapy [95], and higher daily fractions >2 Gy [96]. The natural history of radiation induced brachial plexopathy is variable. (See "Complications of peripheral nerve irradiation".)

Radiation pneumonitis — The risk of radiation pneumonitis is greater with more lung volume in the tangential fields, three-field rather than two-field RT (supraclavicular, axillary apex, and IM regions), and the use of concurrent as compared to sequential chemotherapy. In one series from the JCRT, the risk of radiation pneumonitis was 0.6 and 3.3 percent in patients undergoing three-field RT without and with chemotherapy, respectively [97]. Higher rates of pneumonitis are seen when both radiation and chemotherapy are administered [98].

Limited axillary RT — An alternative to ALND or full axillary RT is limited RT to tangential fields alone, which includes the lower echelon axillary nodes (usually most of level I and part of level II). In one report that included 92 selected patients treated at the JCRT, no isolated regional nodal failures were observed at a median follow-up of 50 months [97]. One patient had a microscopically positive axillary LN at salvage mastectomy for ipsilateral recurrence. In other series, axillary failure rates with tangential RT alone ranged from 0 to 5 percent [99-101].

Small patient numbers and short follow-up duration limit the interpretation of the above observations. Thus, the adequacy of tangential RT as a substitute for ALND or full axillary RT remains uncertain. The JCRT has initiated a formal prospective trial of this approach in older women with clinically node-negative, early stage disease.

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See "Patient information: Breast cancer guide to diagnosis and treatment".) We encourage you to print or e-mail this topic review, or to refer patients to our public web site, www.uptodate.com/patients, which includes this and other topics.

SUMMARY AND RECOMMENDATIONS

- The status of the axillary lymph nodes is one of the most important prognostic factors in women with early stage breast cancer. Histologic examination of removed lymph nodes is the most accurate method for assessing spread of disease to these nodes. (See 'Introduction' above.)

- ALND remains the standard approach for women who have clinically palpable axillary nodes. The benefits of axillary lymph node dissection (ALND) include its impact on disease control (ie, axillary recurrence and survival), its prognostic value, and its role in treatment selection. However, the anatomic disruption caused by ALND may result in lymphedema, nerve injury, and shoulder dysfunction, which compromise functionality and quality of life. (See 'Axillary dissection' above.)

- For patients who have clinically negative axillary lymph nodes, sentinel lymph node (SLN) biopsy offers a less morbid method to determine if there are positive nodes, in which case axillary node dissection would be necessary. Patients who are SLN-positive should undergo completion ALND. (See "Sentinel lymph node biopsy in breast cancer: Techniques" and "Sentinel lymph node biopsy for breast cancer: Indications and outcomes".)

- Selected elderly women who have small estrogen receptor (ER)-positive tumors, a clinically uninvolved axilla, and who are receiving adjuvant hormone therapy may be treated without immediate axillary surgery. (See 'Role of axillary surgery in older women treated with adjuvant endocrine therapy' above.)

- Axillary radiation therapy (RT) is a reasonable alternative to ALND for clinically node-negative

patients in whom pathologic nodal status would not alter the therapeutic plan. (See 'Axillary radiation therapy' above.)

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GRAPHICS

Tumor size and lymph node status for women undergoing biopsy after screening mammography: breast cancer surveillance consortium, 1996-2001

Variable	Lymph node status										
	Lymph nodes not examined		Negative		No. of positive LN's						Total no.
					1 to 3		4 to 9		≥10		
	No.	Row percent	No.	Row percent	No.	Row percent	No.	Row percent	No.	Row percent	
Total	639	9.4	4828	71.0	937	13.8	267	3.9	133	2.0	6804
Tumor size											
0-10 mm	315	13.3	1882	79.6	133	5.6	22	0.9	13	0.5	2365 (100 percent)
11-20 mm	169	7.0	1760	72.8	394	16.3	72	3.0	24	1.0	2419 (100 percent)
21-50 mm	51	4.2	675	55.6	305	25.1	123	10.1	61	5.0	1215 (percent)
>50	13	6.3	79	38.2	48	23.2	36	17.4	31	15.0	207
Unknown*	91	15.2	432	72.2	57	9.5	14	2.3	4	0.7	598

LN: Lymph nodes.
* Unknown tumor size includes mammography diagnoses only, Paget disease, and pathologically invasive carcinoma, all with size not stated. Excluded from the table were 339 women who had lymph node examinations, including 10 women with an unknown number of positive lymph nodes and 329 women with unknown status of the lymph nodes examined. *Reproduced from: Weaver, D, Rosenberg, R, Barlow, W, et al. Pathologic findings from the breast cancer surveillance consortium. CANCER 2006; 106:732.* *Copyright ©2006 the American Cancer Society. The material is reproduced with the permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.*

Breast cancer specific survival according to stage at diagnosis and lymph node status; SEER database, 1988-2000

	Cancer specific survival, percent				
	Stage of disease				
	I	IIA	IIB	IIIA	IIIB
Number of lymph nodes examined					
0	92	82	71	58	49
1 to 3	98	93	81	72	65
4 to 6	96	91	80	75	71
7 to 9	96	90	81	75	71
10 to 14	96	90	82	71	72
15 to 19	96	89	80	71	69
20+	95	88	78	68	67
Ratio of positive to total number of lymph nodes					
0.01 to 0.25	-	92	85	81	78
0.26 to 0.5	-	85	78	73	76
0.51 to 0.75	-	77	71	67	63
0.76 to 1.00	-	72	61	55	50

SEER: Surveillance, Epidemiology, and End Results Database of the National Cancer Institute. *Data from: Joslyn, SA, et al. Breast Cancer Res Treat 2005; 91:11.*

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