Axillary Lymph Node Dissection in Breast Cancer

Current Status and Controversies, Alternative Strategies and Future Perspectives

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Axillary lymph node dissection (ALND) has traditionally been considered as a standard procedure in the surgical management of patients with breast cancer. The goals of ALND in breast cancer surgery are: (a) to provide accurate prognostic information, (b) to maintain local control of the disease in the axilla and (c) to provide a rational basis for decisions about adjuvant therapy. Although controversial, ALND may also be associated with a small therapeutic benefit. Recently, the question of whether ALND is needed for every patient with invasive breast cancer has been the subject of ongoing debate in the literature. This is mainly due to the widespread use of adjuvant systemic therapy for patients with node-negative breast cancer and to the increasingly frequent detection of small invasive cancers by mammographic screening; the majority of these patients have negative axillae. Sentinel lymph node (SLN) biopsy is a new, promising, minimally invasive procedure, which accurately predicts nodal status with minimal morbidity, and reserves ALND for patients with positive SLN biopsies. However, this method is still investigational. Partial (levels I and II) ALND remains the gold standard in the surgical management of patients with breast cancer.

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The scientist is not content to stop at the obvious
(Charles H. Mayo, MD)

We think of truth as something that is invariable, but add a new circumstance and we have a new truth
(William J Mayo, MD)

The management of operable breast cancer has undergone significant evolution over the past three decades. In the 1970s, the majority of patients with early-stage breast cancer had palpable disease and were managed by mastectomy, with or without postoperative radiation therapy. Systemic chemotherapy and/or hormonal therapy was investigational and was used in a minority of patients (1). Over the past 25 years, mainly because of the widespread use of mammographic screening, a high percentage of patients presented with non-palpable, mammographically detected tumors (2). An increasing number of patients are offered breast-conserving surgery followed by radiation therapy as a preferable alternative to mastectomy (2). Prospective randomized trials in the 1980s and 1990s demonstrated that the rates of overall and disease-free survival from breast cancer are equivalent for mastectomy compared to breast-conserving surgery with postoperative radiotherapy for women with early breast cancer (3–9). Moreover, a large percentage of patients are treated with adjuvant systemic hormonal therapy or chemotherapy. Even in patients with pathologically negative axillary lymph nodes, adjuvant systemic therapy is currently being used in a high percentage of patients with invasive breast cancer (10, 11). These changes in the presentation and management of breast cancer (i.e., increased detection of very small breast cancers during mammographic screening, use of adjuvant systemic therapy for women with both node-positive and node-negative breast cancer, and a greater recognition of the morbidity of axillary lymph node dissection [ALND]) have prompted a re-evaluation of the need for routine ALND (12–14).

ANATOMY

Although the normal lymphatic drainage of the breast is to the axillary lymph nodes, the internal mammary lymph nodes, and the intrapleural lymph nodes, surgical staging is confined to the axillary lymph nodes, since the most comprehensive lymphatic stream from all portions of the breast flows toward the axilla. The axillary nodes vary from 20 to 40 in number (15) and, anatomically, are divided into the following groups (15, 16):

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– Scapular lymph nodes.
– Central lymph nodes.
– Interpectoral or Rotter's lymph nodes.
– Axillary vein lymph nodes.
– Apical lymph nodes.

Nowadays, for the purposes of determining pathologic anatomy and metastatic progression, a simpler nomenclature is generally adopted, based on the relation of the nodes to the pectoralis minor muscle (15, 17):

– *Level I nodes (low nodes)* lie lateral and below to the lateral border of the pectoralis minor muscle.
– *Level II nodes (middle group)* lie behind the pectoralis minor muscle.
– *Level III nodes (upper nodes)* are located medial to the medial border of the pectoralis minor muscle and below the lower border of the clavicle.

Total ALND removes levels I, II and III; this often requires the transection or removal of the pectoralis minor muscle and sacrifice of the medial pectoral nerve. On average, 20–25 nodes are identified using standard pathology procedures (18). Partial ALND removes levels I and II, without transecting this muscle; an average of 15–20 nodes are retrieved. Low ALND removes level I; an average of 4–6 nodes are retrieved. Axillary sampling removes an axillary node or nodes from the lower axilla without defining precise anatomic boundaries (2).

INCIDENCE AND LOCATION OF AXILLARY LYMPH NODE INVOLVEMENT

Assessment of axillary lymph node status

Traditionally, 'clinical staging' of axillary lymph nodes is performed by physical examination. If lymph nodes are felt, they are further categorized as being enlarged owing either to benign causes or to malignant involvement, depending on the consistency of the node (19). However, clinical evaluation of axillary lymph nodes can be highly inaccurate. Up to 67% of nodes thought to be diseased on a clinical basis have been found to be free of metastases by histology. Conversely, 22–45% of nodes that appeared to be disease free on clinical examination have been found to be involved by histologic analysis (20–24).

Although axillary mammography is the simplest imaging technique for lymph nodes in patients with breast cancer (23, 24), this method is far from satisfactory. Only grossly enlarged, lateral nodes are easily visible. Ultrasonography (23, 25, 26) or color Doppler studies of the axillary node basin (27) may be useful in the identification of involved axillary lymph nodes. Computed tomography (CT) of the axilla is more informative than physical examination or mammography (28). CT scan can detect the level of lymph node involvement, describe the patterns of lymph node involvement, and demonstrate possible extracapsular extension of the tumor metastasis. However, CT scan is not an accurate predictor of axillary lymph node metastases, because of its low negative predictive value (28). Magnetic resonance imaging (MRI) may provide superior clinical information about the presence and extent of axillary lymph node involvement compared to other imaging techniques (29). MRI has the additional advantage of being completely non-invasive without requiring exposure to ionizing radiation. However, experience with MRI remains limited. Various nuclear medicine approaches have been proposed, including imaging with gamma-emitting tumor-seeking agents (axillary lymph node scintiphotography), radioimmunoscintigraphy, and positron emission tomography (PET) (30–32). However, none of these diagnostic methods can provide histologic information or detect micromalignancy. Therefore, non-invasive testing does not provide accurate staging information and removal and histologic examination of the axillary lymph nodes have become the 'gold standard' for determining whether lymph node metastases have occurred (2, 33).

Determination of the level of axillary lymph node involvement

The most commonly involved axillary lymph nodes are those in level I (low nodes). These nodes are involved in more than 90% of all patients with any number of positive axillary lymph nodes (34–36). Involvement of only level I lymph nodes occurs in approximately 60% of these patients (34). Involvement of level II lymph nodes without involvement of the level I lymph nodes is much more uncommon ($<3\%$) (34, 35, 37). Involvement of level III lymph nodes with negative levels I and II lymph nodes is rare, occurring in less than 3% of all patients with positive axillary lymph nodes (34, 36–39). It is generally accepted that the risk of having a 'false-negative' partial (levels I and II) ALND is only 1–2% (40). We think it noteworthy that the risk of involvement of the higher lymph-node levels increases substantially with increasing numbers of involved nodes or when lower levels are involved. For example, Gaglia et al. (37) reported that 9% of patients with 1–3 positive lymph nodes and 47% of those with ≥ 4 positive lymph nodes had involvement of level III lymph nodes. In the study by Boova et al. (36) where level I lymph nodes were found to be positive, the level II lymph nodes were involved in 41% of patients and level III lymph nodes in 21%. When level II lymph nodes were involved, 31% of patients also had metastases to level III. Similar results have been reported from others (41). Moreover, a higher incidence of level III involvement has been noted when lymph nodes in lower levels were grossly involved by tumor (41%) compared with when they were only involved microscopically (15%) (39).

Based on the existing data, a partial (levels I and II) ALND is currently considered as the standard of care in the management of patients with invasive breast cancer (2, 33, 42). With this approach, a small number of patients would still be understaged because of a $< 3\%$ risk of isolated level III skip metastases. A total (levels I, II and III) ALND identifies all node-positive patients (39), but it is controversial whether the added morbidity (see below) is warranted for this slight increase in accuracy.

FACTORS INFLUENCING THE RISK OF AXILLARY LYMPH NODE INVOLVEMENT

Tumor size

The incidence of axillary lymph node metastases is related to tumor size (37, 42–46). Much of the current discussion regarding the value of routine ALND relates to patients with lesions ≤ 1 cm in maximum linear dimension (43, 45–50). However, nodal metastases are present in 15–25% of patients with tumors measuring 1 cm or less (44, 49, 51, 52). Even with tumors of 0.5 cm or smaller, axillary lymph node metastases are reported in 3–28% of women. Based on these data, routine ALND has been recommended in the management of even the small breast cancers (2, 33, 49, 52). Of note, it has recently been shown that the benefits of ALND are greatest for younger women with larger palpable tumors (53).

Mode of presentation

Patients with palpable lesions have a higher risk of axillary lymph node involvement than patients in more recent series, in which tumors are more likely to be found by mammography rather than clinical examination (43, 54). Haffty et al. (12) reported that of conservatively treated patients who underwent ALND between 1992 and 1995, only 18% had histologically involved lymph nodes compared with their cohort before 1989, in which nearly 30% had positive nodes. This is probably due to the use of mammography, which has resulted in a high percentage of patients with small, mammographically detected tumors. Tumor palpability—combined with T category—has been proposed as a more accurate predictor of nodal positivity than T category alone (55). However, other investigators found no difference in the incidence of nodal metastases by method of tumor detection (56, 57).

Histologic features of the primary tumor

Three groups of breast cancer patients with an extremely low risk of axillary lymph node metastases have been identified: patients with ductal carcinoma in situ (DCIS), patients with microinvasive carcinoma, and patients with pure tubular carcinoma. In an overview of 9 studies involving a total of 754 patients with DCIS, the incidence of axillary lymph node metastasis was 1.7% (58). For mammographically detected, non-palpable DCIS, the rate was 0% (59). Similar data are available for microinvasive carcinoma; in most reports, nodal metastases are seen in fewer than 5% of patients (60, 61). However, other authors reported nodal metastases in 10–20% of patients (62, 63). Probably, the lack of a standard definition of microinvasion is responsible for this variation. Finally, in patients with pure tubular carcinomas of less than 1 cm, the risk of axillary lymph node involvement is extremely low (64–66).

Many reports have found that lymphatic or vascular invasion were independent predictors of axillary lymph node involvement (38, 43, 45, 67, 68). The presence of extensive tumor neovascularization was shown to correlate with the risk of nodal involvement (69). Patients whose tumors displayed vessel counts in the same range as normal breast tissue (≤ 99 vessels/mm^2) had a 4% risk of axillary lymph node involvement, compared with a risk of 43% when the count was 100–140 vessels/mm^2, and 79% when the count was > 140 vessels/mm^2.

Various other features, such as histologic tumor grade, S-phase fraction, ploidy, extensive intraductal component, estrogen and progesterone receptor status, c-erbB-2 overexpression, etc., may affect the incidence of axillary lymph node involvement (45, 56, 70–74). Further studies are needed to determine whether the use of conventional histologic findings (such as grade and vascular or lymphatic invasion) in addition to these histopathologic indicators may allow for more precise determination of risk. At the present time, it seems that biologic tumors markers are not reliable predictors of lymph node metastases (71, 75).

GOALS OF AXILLARY LYMPH NODE DISSECTION

Axillary lymph node dissection has four goals:

1. *To provide accurate prognostic information*: Histologic examination of the axillary nodes is still the most accurate and sensitive method for detecting metastases (see above). Nodal status remains a major predictor of outcome. For all patients with node-negative cancer, at least a 70% 10-year survival rate may be anticipated (76). This drops to 40% for patients with 1–3 positive nodes, and less than 20% for patients with 4–10 positive nodes.
2. *To maintain local control of disease in the axilla*: Patients who have partial (levels I and II) ALND have recurrence rates of less than 3%, which suggests that ALND is a reliable method of maintaining local tumor control in both node-negative and node-positive patients (77, 78). In patients with palpable adenopathy, ALND is mandatory to prevent the local complication of uncontrolled tumor growth. In these patients ALND would seem to be of possible therapeutic benefit (see below). Radiation therapy is an alternative for achieving local control in the clinically negative patients, especially in patients unfit for general anesthesia and those whose treatment decisions would not be influenced by the information gained from ALND (78–80) (see below, alternative strategies).

3. *To provide a rational basis for decisions about adjuvant therapy*: After completion of surgical treatment, an important decision must be made regarding the use of adjuvant systemic therapy. Traditionally, this decision was based on information obtained from the histopathologic examination of the tumor specimen and the axillary lymph nodes, including assays for tumor markers and hormone receptors (81). Tumor size and axillary nodal status are the primary factors used to define risk groups for metastatic disease (51). Low-risk patients—those with tumors ≤ 1 cm in diameter and negative nodes—should not be considered for adjuvant chemotherapy, except within investigational protocols. High-risk patients—those with tumors ≥ 3 cm in diameter or with nodal metastases—should have adjuvant chemotherapy as standard treatment (82–84). The National Institutes of Health Consensus Conference (1991) (84) concluded that 'adjuvant therapy has become the standard of care for the majority of cases of breast cancer with axillary lymph node involvement'. Intermediate-risk patients—those with tumors up to 1–3 cm in diameter, or with negative nodes but other poor prognostic features (Table 1)—might also be considered for systemic adjuvant therapy (11, 82–84). Early results from clinical trials suggest that patients in this subgroup benefit from adjuvant systemic therapy in terms of improved disease-free survival (11, 82–85). However, an increased overall survival rate has been demonstrated only for patients with node-negative tumors larger than 3 cm in diameter (85). On the other hand, patients with diploid tumors that are smaller than 1 cm in diameter, that have a low nuclear grade and that have a low S-phase fraction as determined by flow cytometry can expect a disease-free survival rate approaching 90% even without additional therapy, and adjuvant cytotoxic therapy is currently not recommended for this select low-risk group (11).
4. *To improve survival (potentially)*: The existence of a survival benefit from ALND for breast cancer patients with clinically negative axillae is controversial. Because of the general acceptance of the NSABP B-04 study (1) (which is the most influential trial to address this question), prophylactic ALND for women with clinically negative axillae is considered diagnostic, but not therapeutic by many oncologists. It should be noted that about 35% of patients of the third arm of this trial (mastectomy alone) had a limited ALND; interestingly, if more than 6 nodes were retrieved. no axillary recurrence was observed. Nevertheless, despite the general acceptance of the B-04 conclusions, several authors have noted that B-04 did not include enough patients to exclude a small survival advantage (86, 87). Recently, Orr published a meta-analysis of the available literature (88). Six randomized controlled trials with nearly 3000 patients were included. All six trials showed that prophylactic ALND improved survival (survival benefit ranging from 4% to 16%). By combining the six trials, an average survival benefit of 5.4% was shown. Orr concluded that ALND improves survival in women with operable breast cancer and that ALND should be performed in most women with palpable tumors for diagnostic, as well as therapeutic, purposes (88). Other authors have shown that a better locoregional tumor control (usually achieved by postoperative irradiation and adjuvant chemotherapy) prolongs survival (89, 90).

Table 1

Potential prognostic factors in primary b reast cancer

	Lower Risk	Higher Risk
Axillary lymph node status	Negative	Positive
Histologic tumor type	Tubular, papillary medullary, colloid	All others
Estrogen receptors	Positive	Negative
Primary tumor size	≤ 2 cm	≥ 2 cm
Nuclear grade	Good	Poor
Histologic grade	Well differentiated	Poorly differentiated
Growth fraction (S-phase, TLI, mitotic index)	Low	High
DNA content	Diploid	Aneuploid
EGF receptor	Negative	Positive
HER-*2/neu* oncogene	Absent	Present
Cathepsin D	Low	High
Age	≥ 35 years	<35 years

MORBIDITY OF ALND

In the era when mastectomy was the only option in the surgical management of breast cancer, the loss of the breast was the main 'morbidity' of the procedure and little attention was paid to the sequelae of axillary dissection. On the contrary, in patients undergoing breast-conservation therapy, ALND is the main cause of both early and late morbidity. Partial mastectomy (and especially lumpectomy) can be performed under local anesthesia (for superficial lesions), even as an outpatient procedure. On the other hand, ALND requires general anesthesia, the use of a drain for a variable period of time postoperatively, and is sometimes an indication for hospital admission after surgery. Return to normal activities is usually delayed because of the pain and decreased range of motion of the arm seen in the early postoperative period (14). Early complications such as skin erythema, wound infection, seroma, and early lymphedema tend to be self-limiting and reversible (91). However, what is of greater concern than the early morbidity of ALND is the long-term and often permanent sequelae of the procedure (Table 2). Major

Table 2

Morbidity of ALND

Early complications	
	Skin erythema
	Wound infection
	Seroma
	Early lymphedema
Late complications	
	Chronic lymphedema
	Shoulder stiffness/dysfunction
	Weakness
	Numbness
	Pain

complications of ALND are rare and include injury or thrombosis of the axillary vein and injury to the motor nerves of the axilla. Minor complications are more common and include edema of the arm and breast, loss of sensation in the distribution of the intercostobrachial nerve, and shoulder dysfunction. The precise incidence of these complications is difficult to ascertain since they are not life threatening and do not require hospitalization, circumstances that often lead to underreporting. However, these complications, and especially postoperative lymphedema, can produce a demonstrable diminution in quality of life (92). Warmuth et al. (91) evaluated 432 patients who were free of recurrence 2–5 years after surgery and reported that numbness was the most frequent complication (35%), followed by pain (30%), arm swelling (15%), limitation of arm movement (8%), and episodes of infection or inflammation (8%). Ivens et al. (93) evaluated 106 patients at least 6 months after ALND and reported numbness (70%), pain (30%), weakness (25%). Of note is that 15% of patients felt that their symptoms were severe enough to interfere with daily living. Linn et al. (94) reported similar findings in 122 patients, evaluated at least one year after surgery (numbness 78%, numbness and pain 22%, restriction of shoulder motion 9%). Hladiuk et al. (95) reported that 42% of patients had subjective or objective impairment of arm function one year after surgery.

Lymphedema of the arm is the most commonly recognized long-term sequelae of axillary dissection that may have a profound impact on quality of life (92). The reported incidence of lymphedema varies widely (10–20% in modern surgical series), depending on the definition of lymphedema used, the extent of the axillary surgery, and the length of the follow-up (93–95). Lymphedema can occur any time during the patient's life, triggered by even a minor trauma, with subsequent inflammation of the affected arm, thereby impairing the ability of the patient to perform job-related functions or enjoy vigorous activities. Specific measures to prevent trauma to the affected arm are needed (91, 92).

ALTERNATIVE STRATEGIES FOR THE MANAGEMENT OF AXILLARY LYMPH NODES

Radiation therapy

Axillary radiotherapy is an alternative form of axillary treatment. The NSABP Protocol B-04 (1) studied the role of axillary management by randomizing clinically node-negative patients to one of three groups: ALND (radical mastectomy), axillary irradiation (simple mastectomy with axillary irradiation) or no axillary treatment (simple mastectomy alone). The axillary failure rates were similar between the first two arms. There was no significant survival advantage for any group (Table 3) and 18% of the patients who did not receive treatment to the axilla subsequently developed axillary node involvement, and underwent a delayed ALND. Similar results concerning survival were reported by Hayward et al. (96). In the study by Cabanes et al. (80), in which 658 clinically node-negative patients treated with lumpectomy and breast radiotherapy were randomized to receive either ALND or complete regional nodal radiotherapy, the incidence of axillary recurrence was similar in the surgical and non-surgical groups. However, with a mean follow-up of 54 months (range, 2–97 months), a significant difference in 5-year distant disease-free survival rate and overall survival rates in favor of surgery was found (97% vs. 93% and 89% vs. 87%, respectively). The existing data therefore indicate that axillary irradiation and ALND are equivalent in terms of local control of the disease for clinically node-negative patients (97), and—according to the B-04 trial and the Guy's Hospital trial—in terms of survival (1, 96). However, because radiation therapy for bulky nodes is frequently ineffective, surgical resection for clinically evident axillary lymph nodes has become the most generally accepted therapy (97). The dose of radiation therapy required to control such nodes is considerably higher than that required to control subclinical involvement and is associated with a much greater risk of complications (98).

Combined therapy (ALND and nodal irradiation)

In most patients, the risk of axillary recurrence after a standard partial (levels I and II) ALND is low ($\leq 3\%$) and nodal irradiation is not usually indicated (78, 98, 99). Even in patients with one to three positive nodes, the risk of nodal recurrence is low after appropriate axillary dissection and nodal irradiation is not usually advised (78, 99). Less settled is the need for axillary-supraclavicular irradia-

Table 3

Survival in clinically negative patients (B-04 Trial) (Ref 1)

Axillary treatment	5 years (%)	10 years (%)
Axillary dissection	75	58
Axillary irradiation	75	59
No treatment	74	54

tion in patients with four or more positive nodes. The use of a third field of radiation reduces the risk of nodal recurrence but is also associated with a small but significant risk of complications. The results of the randomized trials comparing mastectomy with breast-conservation therapy were achieved without nodal irradiation, thus establishing this approach as a reasonable option. Whether some subgroups (e.g., patients with more than 50% of nodes involved or with extensive extracapsular spread) derive more benefit from such treatment has not been established, but nodal irradiation is commonly used in these patients to reduce the risk of local recurrence (98). However, the role of axillary irradiation after ALND remains controversial; recently, Mehta & Haffty (100) concluded that even for patients with four or more positive lymph nodes, omission of axillary irradiation after breast-conserving surgery followed by radiation therapy to the intact breast with appropriate adjuvant systemic therapy results in a reasonable long-term survival with a high rate of locoregional control (10-year actuarial nodal recurrence-free rate of 96%). Probably, considering axillary irradiation after technically inadequate surgery (i.e. ALND when <5 lymph nodes are recovered) seems to be a more reasonable option, since in these cases the risk of axillary failure is increased (6%) when only breast tangential fields were used, compared with 1% among patients treated with full axillary radiotherapy (78).

Induction chemotherapy or hormonal therapy and the axillary lymph nodes

Induction chemotherapy followed by breast-conservation therapy is an alternative to mastectomy in patients in whom the size of the primary tumor relative to the size of the breast makes conservative surgery an inappropriate choice (101–103). Induction chemotherapy can reduce bulky nodal disease, perhaps making it amenable to sterilization with radiation therapy, and in some cases may completely eliminate histologic evidence of nodal metastases (104). In a recent study, Kuerer et al. (105) concluded that patients with negative axillae after tumor downstaging with induction chemotherapy (on both physical and ultrasound examinations) may be potential candidates for omission of ALND if the axillae have to be irradiated because minimal axillary disease remains in these cases. Patients with positive findings on preoperative physical or ultrasound examination should receive ALND to ensure local control. A prospective randomized trial of ALND versus axillary radiotherapy in patients with clinically negative axillae following induction chemotherapy is currently underway. There is less experience regarding the response of nodal metastatic disease to hormonal therapy, but some patients with hormone receptor-positive tumors will have regression of the nodes under treatment with hormonal therapy (97). However, if the medical treatment leads to the nodes becoming clinically negative, the patient may become a good candidate for axillary radiation therapy, or even observation; additional regional treatment will be required only in the case of an axillary recurrence (see below, axillary failure)

Axillary observation without any therapy as an alternative to surgery, radiation therapy and medical therapy in the clinically node-negative patient

In the B-04 protocol of the NSABP, axillary observation (with treatment only when there was clinical evidence of disease progression) was not associated with decreased survival (Table 3) (1). Randomized clinical trials have shown that even in the premammographic era, when approximately 40% of patients with clinically negative axillary lymph nodes had histological evidence of nodal metastases, adequate therapy at the time of first evidence of disease progression led to regional control rates that were little different from those obtained with prophylactic resection (106). As previously reported, a meta-analysis of these randomized trials indicated that if observation led to a survival disadvantage, it was probably in the range of 4% (88).

ALND in the elderly patient: is it indicated?

Unless comorbid conditions adversely affect one's life expectancy or tolerance to therapy, older women should be treated with standard surgical procedures (including ALND and breast-conserving therapy, if so desired) for breast cancer, as outcome is comparable to that in younger patients (107–109). Therefore, chronologic age alone should not prevent healthy elderly women from receiving appropriate surgery. Physiologic age and the presence of comorbid conditions should be the primary determinants of local therapy. In medically unfit elderly patients, general anesthesia may have mortality rates of 1% to 2% (110); in these cases lumpectomy under local anesthesia combined with tamoxifen seems to be a more reasonable alternative (97). For elderly patients with hormone receptor-positive tumors who have either limited life expectancy or extreme aversion to even limited surgical excision, tamoxifen may be a reasonable alternative as the sole therapy (111).

AXILLARY FAILURE

Axillary failure in the absence of axillary treatment

The NSABP B-04 trial (1) showed no significant differences among the three groups of patients in terms of disease-free or overall survival rates (Table 3). Forty percent of patients with clinically negative nodes had histologic involvement and yet only 18% of those treated by simple mastectomy alone required subsequent ALND for the development of clinically positive nodes. These findings suggest that untreated nodes do not serve as a reservoir for further tumor dissemination and that not all histologically positive nodes will become biologically active. Similar results were found in the CRC Kings/Cambridge trial (112), which demonstrated an increased local relapse rate without axillary dissection, but again no effect on overall patient survival. Baxter et al. studied 112 patients treated with breast-conserving surgery without ALND or radiation to the axillae (113); they reported a 10-year actuarial nodal control rate of 72%. Patients with nodal failure proceeded to ALND with minimal morbidity. The same authors demonstrated a significant effect of tumor size on axillary failure. Sun et al. (114) reported that subsequent ALND was required in 13% of 126 patients who had not had ALND at the time of initial surgery, for various reasons (such as advanced age, medical contraindications, or patient's choice). The same group reported a 5-year actuarial cause-specific survival of 92%, therefore concluding that adopting an approach of delayed ALND does not seem to compromise the patient's outcome. In contrast, White et al. (115) reported that omission of ALND correlated with reductions in overall, disease-free, and breast cancer-specific survival. These investigators found that a significant number of patients with small invasive tumors of the breast will have axillary lymph node metastases at the time of diagnosis (9.8% for T1a, and 19.4% for T1b) and concluded that ALND should remain the standard approach for the surgical therapy of all patients with invasive cancer of the breast, regardless of tumor size. Baum & Coyle (116) reported a personal series of 73 patients with early breast cancer treated by simple mastectomy alone with no treatment to the axillae; progression of axillary nodal disease (which was noted in 48% of the patients) was associated with the appearance of distant metastases within 8 months. Salvage therapy after axillary failure can be achieved using surgery and/or radiotherapy. From a technical point of view, surgery may be complicated in the presence of extensive, large, fixed axillary lymphadenopathy; in this setting, radiotherapy may be a wiser option. The role of adjuvant systemic therapy in this setting is not known. In a small but significant percentage of patients (3 –11%), uncontrollable axillary recurrence occurred despite salvage treatment (117). Based on these data, many surgeons believe that the policy of not treating the axilla, adopting a watch policy, and treating the nodes on recurrence produces a risk that locoregional recurrence will be uncontrollable and may cause significant patient morbidity, with a potential increase in mortality (115, 118). For these reasons, the watch policy is generally considered as inappropriate for the majority of patients with invasive breast cancer.

Axillary failure following axillary dissection

ALND in patients with operable breast cancer provides excellent tumor control with an axillary recurrence rate of 0–3 %, whether lymph nodes are pathologically involved or not (1, 119–121). However, the incidence of axillary failure is greatly increased after inadequate surgery (i.e. axillary sampling or low-level I ALND) (78, 120, 122–124); in those cases, postoperative axillary irradiation should be considered (see: alternative strategies). The Danish Breast Cancer Cooperative Group (DBCCG) found that the probability of early ipsilateral axillary relapse of cancer decreased with the number of nodes removed (125). After 2 years, the recurrence rate was 12% for patients with no lymph nodes removed, 7% with one or two nodes removed, and 2% with three or more nodes removed. In a more recent report (126) the DBCCG concluded again that the extent of surgery seems important for locoregional tumor control and accurate axillary lymph-node staging and that—in combination—these might lead to superior recurrence-free and overall survival. Nowadays, partial (levels I and II) ALND should be considered as the standard of care in the surgical management of breast cancer (33). However, certain exceptions to this approach may be considered; for invasive tumors that are ≤ 1 cm and tumors of a favorable histologic type (i.e., tubular, mucinous, papillary), removal of level I nodes may be sufficient (see below). On the contrary, removal of level III nodes (total ALND) is advised when encompassing obvious disease (33).

Axillary failure following combined therapy (axillary lymph node dissection and nodal irradiation)

As previously reported, axillary irradiation should be considered, particularly after a technically inadequate surgery (see: alternative strategies, combined therapy). In the JCTR series, when five or fewer lymph nodes were recovered, the risk of axillary failure among 'node-negative' patients was 6% when only breast tangential fields were used, compared with 1% among patients treated with full axillary radiotherapy (78). In the study by Benson & Thorogood, the incidence of axillary failure in patients who had 'negative' axillary samplings was 8% when surgery alone was used, compared with 0% when postoperative radiotherapy was also given; for node-positive patients, the respective failure rates were 12% and 4% (120). However, if a partial (levels I and II) ALND had been performed, the incidence of axillary failure in lymph node-negative patients was 3% with surgery alone, compared with 0% when radiotherapy was added; among node-positive patients, the respective failure rates were 3% and 2%.

Axillary failure following irradiation

In a study by Haffty et al. (127), 327 patients were treated with lumpectomy alone without ALND, followed by radiation therapy to the breast and regional lymph nodes. The overall 10-year survival rate was 71% and the 5-year actuarial nodal control rate was 97%. This treatment policy was associated with minimal morbidity. The authors concluded that for selected patients undergoing breast-conservation therapy, especially those in whom the results of the ALND will not influence decisions regarding systemic therapy, lumpectomy alone followed by radiation therapy to the intact breast and regional lymph nodes results in a high rate of locoregional control (79, 127). In a study by Wazer et al. (128), 73 clinically node-negative women, aged >65 years, were treated by local tumor excision, breast and regional lymph node irradiation, and tamoxifen (in 66 patients). At a median follow-up of 54 months, Wazer et al. found an 8-year rate of regional lymph node control of 100% and minimal morbidity associated with either regional irradiation or tamoxifen. The authors concluded that a less aggressive local therapy—using lymph node irradiation instead of ALND for node-negative patients—results in a satisfactory disease outcome with few complications. In the Institut Curie trial (80), axillary failures were observed in 7 of 332 patients treated with lumpectomy alone, followed by irradiation to the axillary and internal mammary lymph nodes (group A); in the same study, axillary failures were observed in 3 out of 326 patients who had undergone lumpectomy and axillary dissection followed by internal mammary lymph node irradiation (group B). The authors concluded that treatment (group A vs. Group B) affected axillary lymph-node recurrences, although this difference was of marginal statistical significance ($p = 0.05$).

FUTURE PERSPECTIVES

Selective ALND

The role of selective ALND is currently under investigation. Selective ALND in breast cancer patients focuses on (14):

- Identification of patients with a low risk for nodal involvement.
- Identification of patients whose treatment will not be affected by axillary status.
- Sentinel lymph node biopsy.

As previously described, the risk of axillary lymph node metastases is extremely low in patients with ductal carcinoma in situ (DCIS) (58, 59), microinvasive carcinoma (60, 61), and pure tubular carcinoma of less than 1 cm (64–66). These patients probably would not benefit from an ALND. The role of ALND in patients with invasive cancer smaller than 1 cm remains controversial (see above, tumor size). Although some authors propose selective ALND for this group of patients, the majority support routine partial (levels I and II) ALND as the standard of care in the management of these patients (33, 115, 129).

An alternative approach is to select patients in whom the axillary nodal status will not alter the treatment plan (127). Linn et al. found that for 54% of patients who had clinically negative nodes and unfavorable biopsies, ALND played no role in the decision about whether standard adjuvant therapy was indicated (94). Those patients received adjuvant therapy on the basis of unfavorable characteristics of the primary biopsy, which included 1) biochemical estrogen and progesterone receptor status negative, 2) tumor size ≥ 2 cm, 3) aneuploid DNA content with percentage S-phase ≥ 5.8 or diploid DNA content with percentage S-phase ≥ 3.4. The presence of any one of these conditions in a primary tumor was considered as an indication for systemic adjuvant therapy. In this study, only 5% and 3% of patients received radiation therapy and/or high-dose adjuvant chemotherapy, respectively, because of ALND. The authors concluded that further controlled studies will be needed to determine whether ALND is necessary for all breast cancer patients. Similar results were reported by Naslund et al. (130), who found that in only 36% of patients undergoing ALND did information gained from this procedure influence the postoperative treatment.

Despite these efforts for a selective ALND on the basis of identification of patients in low-risk groups or whose treatment plan would not be affected by knowledge of the axillary nodal status, a large percentage of patients with breast cancer do not fall into those categories. Moreover, these methods for selecting patients to undergo ALND are not infallible and may result in undertreatment of some patients, who will not receive potentially life-saving adjuvant therapy. On the other hand, omitting ALND and giving adjuvant therapy to all patients with breast cancer will result in the overtreatment of a significant percentage of these patients. A highly accurate, minimally invasive procedure to recognize the axillary nodal status in these patients is therefore required. Sentinel lymph node (SLN) biopsy is a new technique that identifies patients with axillary lymph node involvement with minimal, if any, morbidity and that reserves ALND for patients with positive SLN biopsies (2, 131). The SLN concept is based on the orderly progression of tumor cells within the lymphatic system. Metastasis to lymph nodes is not a random event and can be determined by identifying the lymph flow from the tumor site to the primary draining lymph node. Since the SLN is defined as the first lymph node in a regional lymphatic basin, which receives lymph flow from a primary tumor, it will be the first to contain metastasis, and its biopsy will accurately predict regional nodal status. Thus, if the SLN does not contain metastatic cancer, the remainder of the nodal basin will also be negative for metastatic disease (131). If the SLN biopsy is positive, then a partial (levels I and II) ALND should be performed. However, Chu et al. (132) recently questioned the need for ALND in patients with sentinel node micrometastases from T1/T2 lesions, or in patients with sentinel node metastases from T1a lesions. They found that the rate of non-sentinel node involvement was 7% when the sentinel lymph node had a micrometastases (≤ 2 mm), compared with 55% when the sentinel lymph node had a macrometastasis (>2 mm). In addition, the rate of non-sentinel node tumor involvement increased with the size of the primary tumor. The SLN can be identified by searching the nodal basin for lymph nodes that concentrate colloidal material after injection of the material into the tissue surrounding the primary cancer (131). The most widely used colloid materials are the dye isosulfan blue and radiolabeled technetium sulfur colloid. SLN biopsy can be performed using either of these two colloids alone or in combination (131). Used properly, SLN biopsy is a simple, low-cost procedure that has minimal morbidity and is highly predictive of nodal status. At present, SLN is considered as an investigational procedure (33, 131, 133).

Endoscopic ALND

Endoscopic ALND has been proposed in order to achieve optimal cosmetic results in breast cancer surgery (134–137). Endoscopic ALND—a minimally invasive technique—is a potential alternative to standard 'open' ALND. The advantages of minimally invasive surgery (i.e., smaller incision, less pain, and earlier recovery) have been proposed as the rationale for performing axillary exploration and/or dissection and even sentinel lymphadenectomy through an endoscopic approach (134–137). However, experience is limited, and the role of endoscopy remains to be defined in the future.

CONCLUSIONS AND PRACTICAL RECOMMENDATIONS

Currently, most investigators recommend ALND for all patients undergoing either breast-conserving surgery or mastectomy for T1 or T2 lesions. To provide adequate prognostic information, at least 10 lymph nodes should be examined (126). A partial (levels I and II) dissection seems to be the most appropriate procedure for both staging and local control because it removes the bulk of the axillary nodal tissue (33); this procedure has been adopted by most surgeons and was recommended by the NIH Consensus Conference in 1991 (84). The role of selective ALND and sentinel lymph node biopsy remains to be defined in the future. Meanwhile, these approaches should be considered as investigational.

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