Reassessing the role of axillary lymph-node dissection in patients with early-stage breast cancer

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Introduction: There is considerable controversy regarding the value of axillary lymph-node dissection in the adjuvant systemic therapy of patients with early-stage breast cancer. Our objective was to assess the impact of nodal status in assigning adjuvant chemotherapy to these patients. **Methods:** We carried out a review of all patients with stage I or II breast cancer treated at 3 university-affiliated hospitals in Saskatoon between Jan. 1, 1998, and Dec. 31, 2000. Data collected included: patient age, sex, tumour size, hormone receptor status, nuclear grade and presence of lymphovascular invasion. Patients were categorized as being at low, high or intermediate risk for recurrence based on Canadian consensus guidelines and at low or high risk according to criteria established by the United States National Institutes of Health (NIH). The influence of nodal status on subsequent treatment was determined assuming that all patients younger than 70 years at high risk of recurrence would receive chemotherapy. **Results:** We identified 327 women with stage I or II breast cancer in whom all prognostic factors were available for analysis. Applying the Canadian criteria to determine the need for adjuvant chemotherapy, 68% of women would receive chemotherapy regardless of lymph-node status. Applying the NIH criteria, 82.5% of women younger than 70 years would receive adjuvant chemotherapy regardless of nodal status. **Conclusions:** Nodal status has little influence on subsequent management. Adoption of a selective approach to axillary lymph-node dissection could avoid the potential morbidities of this procedure in many patients with early-stage breast cancer.

Introduction : La valeur de l'exérèse des ganglions lymphatiques axillaires dans la thérapie systémique adjuvante chez les patientes atteintes d'un cancer du sein au stade précoce soulève beaucoup de controverse. Nous voulions évaluer l'influence de l'état des ganglions sur la décision de soumettre ces patientes à une chimiothérapie adjuvante. **Méthodes :** Nous avons étudié le dossier de toutes les patientes atteintes d'un cancer du sein au stade I ou II qui ont été traitées à trois hôpitaux affiliés à une université de Saskatoon, entre le 1er janvier 1998 et le 31 décembre 2000. Les données recueillies portaient sur les aspects suivants : âge de la patiente, sexe, taille de la tumeur, statut des récepteurs hormonaux, catégorie nucléaire et présence d'un envahissement lymphovasculaire. On a classé les patientes selon les catégories de risque faible, élevé ou intermédiaire de récidive établies par le document de concertation canadien et selon les catégories de risque faible ou élevé établies par les National Institutes of Health (NIH) des États-Unis. On a déterminé l'influence de l'état des ganglions sur les traitements subséquents en supposant que toutes les patientes de moins de 70 ans qui étaient à risque élevé de récidive recevraient une chimiothérapie. **Résultats :** Nous avons trouvé 327 femmes atteintes d'un cancer du sein au stade I ou II pour lesquelles tous les facteurs de pronostic étaient disponibles aux fins d'analyse. Si l'on applique les critères canadiens pour déterminer le besoin d'une chimiothérapie adjuvante, 68 % des femmes recevraient une chimiothérapie sans égard à l'état de leurs ganglions lymphatiques. Si l'on applique les critères des NIH, 82,5 % des femmes de moins de 70 ans recevraient une chimiothérapie adjuvante sans égard à l'état de leurs ganglions. **Conclusions :** L'état des ganglions a peu d'influence sur la prise en charge subséquente. L'adoption d'une façon sélective d'aborder l'exérèse des ganglions lymphatiques axillaires pourrait éviter les morbidités que cette intervention peut entraîner chez beaucoup de patientes atteintes d'un cancer du sein au stade précoce.

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The management of patients with early-stage breast cancer has evolved rapidly over the past few decades, as has the approach to the axilla. In particular, the role of axillary lymph-node dissection (ALND) has become increasingly controversial; many surgeons have questioned its necessity especially in view of the recent introduction of sentinel lymph-node (SLN) biopsy. Although SLN biopsy offers a potentially less morbid means of assessing the status of the axilla, availability, cost and accuracy of the procedure are limiting its widespread application. As such, ALND remains the standard for assessing the axilla in patients with early-stage breast cancer.[1–3] Initially practised in an attempt to improve cure rates, ALND has been shown to contribute little to overall survival.[4–6] Although proponents of ALND stress its importance for prognosis and to guide systemic adjuvant therapy, the liberalization of indications for chemotherapy has led others to question the need for routine ALND.[7–11] Furthermore, ALND is associated with potential morbidity and frequently requires the patient to undergo a separate operation.[12–14]

The aim of this study was to assess the frequency of well-established prognostic factors in patients with breast cancer and thereby estimate the value of information provided by ALND to guide adjuvant systemic therapy.

Methods

All breast cancer patients with stage I or II disease, treated at the Saskatoon Cancer Centre between Jan. 1, 1998, and Dec. 31, 2000, were identified. Data collected from the Saskatoon Cancer Centre database and from pathology reports included the following: age; sex; operative procedure; tumour location, size and grade; estrogen receptor (ER) status; presence or absence of lymphovascular invasion (LVI); and lymph-node status. Patients with incomplete data sets were excluded. Only women were included in the analysis.

The women were then stratified into low, high or intermediate risk for recurrence according criteria defined by Canadian consensus guidelines (Table 1).[1] Tumours of modified Bloom–Richardson grade II or III were considered high grade. According to the Canadian guidelines, the management of women at intermediate risk is to be individualized. To facilitate analysis, women with tumour size 1 cm or less and ER-negative status were also considered candidates for chemotherapy.

Women were also stratified using the United States National Institutes of Health (NIH) breast cancer consensus guidelines into high and low risk for recurrence.[15] According to these guidelines, all women with tumours greater than 1 cm in diameter are considered high risk for recurrence and should be offered systemic adjuvant therapy.

To determine the frequency with which axillary dissection would be necessary in order to assign adjuvant chemotherapy, women were assigned to high-, low- or intermediate-risk groups according to the Canadian consensus guidelines, and low or high risk according to the NIH guidelines, regardless of nodal status. The frequency with which axillary dissection was required to assign chemotherapy (assuming all high-risk women would receive chemotherapy) was then determined.

Women younger than 70 years and women 70 years of age or older were analyzed separately, since both the NIH consensus and the Canadian consensus state that the management of women older than 70 should be individualized.

Results

Over the 3-year period reviewed, 394 patients with stage I or II breast cancer were identified. Sixty-seven of these were excluded (2 were men and 65 had incomplete data). The remaining 327 women consisted of 211 who were less than 70 years of age and 116 women 70 years or older (who underwent lumpectomy alone, lumpectomy with ALND, simple mastectomy or modified radical mastectomy) (Table 2).

Among the 211 women less than 70 years of age, according to the Canadian consensus guidelines, only 24 met criteria for low risk of recurrence (Table 3). One of these 24 women (4.2%) had positive axillary lymph nodes. One hundred and forty-three women were stratified to

Table 1

Stratification for Risk of Recurrence According to the Canadian Consensus Guidelines[1]

Patient's risk for recurrence	Definition
High risk	1. Tumour diameter > 3 cm irrespective of any other factors
	2. Tumour diameter > 1 cm with any other unfavourable prognostic factor (high grade, ER negative, or presence of LVI)
Low risk	1. Tumour diameter ≤1 cm with all prognostic factors favourable (low grade, ER positive, absence of LVI)
Intermediate risk	1. Tumour diameter ≤ 1 cm and ER positive with 1 or 2 other unfavourable factors
	2. Tumour diameter > 1 cm with all prognostic factors favourable (low grade, ER positive, absence of LVI)
High risk due to ER status*	1. Tumour diameter ≤ 1 cm and ER negative with 0, 1 or 2 other unfavourable factors

*Patients who would normally be classified as intermediate risk but due to negative ER status are upgraded to high risk regardless of grade or LVI because they are usually treated as such.
ER = estrogen receptor, LVI = lymphovascular invasion.

the high-risk category, of whom 57 (40%) had involved axillary lymph nodes. Forty-four women were found to be at intermediate risk of recurrence, and 14 of these women (32%) had involved axillary nodes.

If high risk is considered sufficient to recommend chemotherapy, only intermediate- and low-risk women (a total of 68 [32.2%]), would require ALND to guide the use of adjuvant systemic therapy (Table 4). Fifty-seven of the 143 (39.9%) women who would not have received ALND had positive lymph nodes. In contrast, under the NIH consensus guidelines, only women with tumours 1 cm or less in diameter would require ALND to guide management. In this case, only 37 (17.5%) of the 211 women younger than 70 years would require ALND. Sixty-five of the 174 (37.4%) women who would not have received ALND had positive lymph nodes.

Among women age 70 years of age or older, a higher proportion fell into the low- and intermediate-risk categories (Table 5). Of the 22 low-risk women (19.0%), 2 women (9.1%) had positive axillary lymph nodes. Forty-nine women (42.2%) were assigned to the high-risk category, of whom 16 (32.7%) had positive axillary lymph nodes. Forty-five women (38.8%) were stratified to the intermediate category, of whom 5 (11.1%) had positive lymph nodes.

The difference in the number of women requiring ALND between the Canadian and NIH criteria is even larger in women older than 70 years than in the younger cohort. Under the Canadian criteria, 67 (57.8%) of 116 women older than 70 years would require ALND to guide the use of adjuvant systemic therapy (Table 6). Sixteen of the 49 (32.7%) women who would not have received ALND had positive lymph nodes. In contrast, according to the NIH consensus, 35 (30.2%) of the 116 would require ALND. In this group of women, 19 of the 81 (23.4%) women who would not have

Table 2

Summary of Patient Groups by Age and Treatment

| | Patient age, yr | | | |
| | < 70 (n = 211) | | ≥ 70 (n = 116) | |
Surgical procedure	No. (and %)	Mean age (and range)	No. (and %)	Mean age (and range)
Lumpectomy alone	3 (1.4)	57 (47–69)	4 (3.4)	82.5 (75–89)
Lumpectomy with axillary lymph-node dissection	106 (50.2)	57 (33–69)	45 (38.8)	76.1 (70–90)
Simple mastectomy	0	—	7 (6.0)	85.4 (76–93)
Modified radical mastectomy	102 (48.3)	53 (25–69)	60 (51.7)	77.3 (70–87)

Table 3

Distribution of Patients Younger Than 70 Years at Low, Intermediate and High Risk for Recurrence of Breast Cancer

| | | Lymph-node status, no. (and %) | |
Disease category	Patients, no. (and %)	Negative	Positive
Low risk	24 (11.4)	23 (95.8)	1 (4.2)
High risk	143 (67.8)	86 (60.1)	57 (39.9)
Intermediate risk	44 (20.8)	30 (68.2)	14 (31.8)
≤ 1.0 cm tumour diameter + 1 prognostic factor*		7	6
≤ 1.0 cm tumour diameter + 2 prognostic factors†		0	0
> 1 cm tumour diameter + 0 prognostic factors‡		23	8

*Either high-grade tumour or presence of lymphovascular invasion
†Both high-grade tumour and presence of lymphovascular invasion
‡Low-grade tumour, positive estrogen receptor status and absence of lymphovascular invasion

Table 4

Summary of Interpretation of Data According to Canadian and National Institutes of Health (NIH) Criteria for Patients Younger Than 70 Years

| | Patients, no./total no. (and %) | |
Information for interpretation	Canadian	NIH
Women requiring ALND to guide management	68/211 (32.2)	37/211 (17.5)
Women in whom ALND would not guide management	143/211 (67.8)	174/211 (82.5)
Women who would not have undergone ALND but had positive lymph nodes	57/143 (39.9)	65/174 (37.4)

ALND = axillary lymph-node dissection.

Table 5

Distribution of Patients 70 Years of Age or Older at Low, Intermediate and High Risk for Recurrence of Breast Cancer

| | | Lymph-node status, no. (and %) | |
Disease category	Patients, no. (and %)	Negative	Positive
Low risk	22 (19.0)	20 (90.9)	2 (9.1)
High risk	49 (42.2)	33 (67.3)	16 (32.7)
Intermediate risk	45 (38.8)	40 (88.9)	5 (11.1)
≤ 1.0 cm tumour diameter + 1 prognostic factor*		10	2
≤ 1.0 cm tumour diameter + 2 prognostic factors†		1	0
> 1 cm tumour diameter + 0 prognostic factors‡		29	3

*Either high-grade tumour or presence of lymphovascular invasion
†Both high-grade tumour and presence of lymphovascular invasion
‡Low-grade tumour, positive estrogen receptor status and absence of lymphovascular invasion

received ALND had positive lymph nodes.

Discussion

Over the past several decades the surgical management of breast cancer has become increasingly conservative, whereas systemic therapies have become more widespread in application.[3,4,16,17] Not surprisingly, management of the axilla in early-stage breast cancer has become highly controversial, with many questioning the need for ALND when the risk of metastasis is low or when knowledge of nodal status will have little influence on subsequent therapy.[1,7–10,18]

In recent years, several prognostic factors have been increasingly used to guide the adjuvant therapy of patients with early-stage breast cancer. Among these, tumour size and lymph-node status have been shown to correlate best with the risk of cancer recurrence as well as overall survival.[19] Although ALND presently remains the standard of care by which to assess the axilla, SLN biopsy has been introduced as a technique to identify patients with involved lymph nodes while sparing patients the morbidity associated with levels I and II ALND.[20] However, SLN biopsy also carries potential complications as well as significant costs and as yet has not attained widespread use in the community.

When debating the advantages and disadvantages of ALND there are many issues to consider. First, there is good evidence that chemotherapy improves both the disease-free and overall survival of patients with both node-negative and node-positive breast cancers, suggesting that knowledge of nodal status may be unnecessary to determine whether patients should receive adjuvant systemic therapy. In addition, ALND is associated with several significant complications including a 10%–20% rate of shoulder dysfunction, a 2%–30% chance of arm edema, up to 50% chance of breast edema and an 80% rate of numbness in the distribution of the intercostal brachial nerve.[12,13] On the other hand, proponents of ALND advocate its routine performance based on its importance for staging and prognosis, superiority in achieving local control of the axilla and possibly providing an improvement in overall survival. Conversely, primary axillary radiotherapy has shown similar efficacy in preventing axillary recurrence with potentially fewer adverse effects, and radiotherapy to the axilla can be easily incorporated during treatments routinely administered as part of breast-conserving therapy.[2,4,21] Finally, it is controversial whether routine axillary dissection confers a survival advantage, and if so the effect is likely minimal.[2,4,8,22]

One further issue to consider if both ALND and axillary radiation were to be omitted is the rate and management of patients who would subsequently present with clinically positive axillary lymphadenopathy. The true incidence of the development of clinically involved nodes is difficult to determine, and may be lower than expected if one assumes clinically apparent disease will develop in all patients with microscopic metastases. This is especially true in light of recent studies suggesting that neoadjuvant chemotherapy is able to eradicate nodal disease in many patients, implying that ALND may not be necessary for local control of the axilla.[23,24]

For patients who are 70 years of age or older, both the Canadian consensus guidelines and the NIH consensus state that the decision to recommend adjuvant chemotherapy needs to be individualized, as the benefit of chemotherapy has been shown to diminish with increasing age and elderly patients are less apt to tolerate the potential side effects of aggressive chemotherapeutic regimens.[25] Among our patient population, application of the Canadian and NIH criteria for omitting ALND would reduce its need to 32% and 17.5%, respectively, in patients with early-stage breast cancer.

The major deterrent to adopting a selective approach to ALND remains the lack of universal criteria to stratify patient risk for recurrence. Without clear risk stratification, indications for assigning adjuvant therapy will remain ill-defined. Although the 2001 NIH consensus states that all patients with tumours greater than 1 cm in diameter should receive chemotherapy, the use of other established prognostic factors remains in its infancy. Clinicians recognize the importance of various prognostic factors, but their use in patient management is unpredictable. The Canadian Guidelines for the Care and Treatment of Breast Cancer follow suit, recognizing large tumour size, high grade, ER negativity and LVI as unfavourable prognostic factors but concluding that there are insufficient data on the natural history of tumours with various combinations of these factors to predict outcome.[26] Hence, the assignment of chemotherapy to intermediate-risk patients with poor prognostic factors

Table 6

Summary of Interpretation of Data According to Canadian and National Institutes of Health (NIH) Criteria for Patients 70 Years of Age or Older

	Patients, no./total no. (and %)	
Information for interpretation	Canadian	NIH
Women requiring ALND to guide management	67/116 (57.8)	35/116 (30.2)
Women in whom ALND would not guide management	49/116 (42.2)	81/116 (69.8)
Women who would not have undergone ALND but had positive lymph nodes	16/49 (32.7)	19/81 (23.4)

ALND = axillary lymph-node dissection.

is to be individualized. However, as prognostic factors are better defined, the indications for adjuvant treatment will almost certainly be based solely on primary tumour characteristics with the results of ALND having little influence.

Irrespective of the value of lymph-node dissection in guiding adjuvant treatments, nodal status remains the most reliable predictor of patient outcome. This information can be important both to physicians and to patients. A recent study demonstrated the importance of prognostic information to patients, finding that most women with invasive breast cancer would risk and accept the potential morbidities of ALND, including a 40% risk of arm dysfunction, to gain prognostic information that would not change treatment.[27]

Our findings support the position that ALND is infrequently necessary to determine whether a patient should receive chemotherapy. Using established criteria for the assignment of chemotherapy and age as a consideration for the administration of cytotoxic systemic treatments, up to 82.5% of patients fulfilled criteria to receive chemotherapy based on primary tumour characteristics alone. We conclude that with the increasing tendency to give systemic therapy to node-negative patients, ALND or possibly SLN biopsy could be reserved for patients in whom nodal status is required to guide adjuvant therapy or when the patient wants the prognostic information gained from axillary dissection. Adoption of a selective approach to ALND could avoid significant costs and spare many women the potential morbidities of these procedures.

Competing interests: None declared.

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