

Axillary lymph node management in breast cancer with positive sentinel lymph node biopsy

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Abstract

The surgical treatment of localized breast cancer has become progressively less aggressive over the years. The management of the axillary lymph nodes has been modified by the introduction of sentinel lymph node biopsy. Axillary dissection can be avoided in patients with sentinel lymph node negative biopsies. Based on randomized trials data, it has been proposed that no lymph node dissection should be carried out even

in certain patients with sentinel lymph node positive biopsies. This commentary discusses the basis of such recommendations and cautions against a general omission of lymph node dissection in breast cancer patients with positive sentinel lymph node biopsies. Instead, an individualized approach based on axillary tumor burden and biology of the cancer should be considered.

Key words: Tumor sub-types; Micro-metastatic; Node positive; Breast cancer; Axillary lymph node dissection; Macro-metastatic; Axillary recurrence

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Core tip: Management of the axilla in breast cancer has been modified by the introduction of sentinel lymph node biopsy. Axillary dissection can be avoided in sentinel lymph node negative patients. More recently, it has been proposed that lymph node dissection could be avoided even in patients with sentinel lymph node positive biopsies. The basis of such proposals is discussed here and caution is advised against a universal omission of lymph node dissection in breast cancer patients with positive sentinel lymph node biopsies. Instead, an individualized approach based on axillary tumor burden and biology of the cancer should be considered.

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INTRODUCTION

Over the years the surgical management of the primary tumor in localized breast cancer has become

less extensive and less mutilating. It has progressively been reduced in extent from radical mastectomy to total mastectomy and later to lumpectomy with corresponding decrease in morbidity^[1]. Reduction of surgical extent has become possible because of increasing awareness and screening that have contributed to earlier diagnosis and stage migration and because of the introduction of other effective treatments such as radiation and systemic therapies. Progress in biologic understanding of the disease has allowed the integration of targeted therapies in the adjuvant treatment of breast cancer. Complete resection of the primary tumor with negative margins remains a cornerstone of treatment for localized breast cancer. More recently, the introduction of the sentinel lymph node biopsy has changed the management of the axilla in patients with localized breast cancer allowing avoidance of lymph node dissection in patients with pathologically negative sentinel nodes^[2]. This development has led to a decrease of the percentage of patients with local adverse effects of dissection such as lymphedema and paresthesia which may significantly decrease quality of life and functionality and sometimes cause severe effects such as wound infections, cellulitis and systemic infections^[3,4].

The standard management of the axilla in patients with positive sentinel lymph nodes remains a complete lymph node dissection but recent data have challenged this posit and produced controversy^[5]. The American Society of Clinical Oncology (ASCO) recently published a revised guideline on sentinel lymph node biopsy for patients with early stage breast cancer^[6]. The guideline advises against completion axillary lymph node dissection (ALND) for patients who meet criteria that include T1 or T2 primary lesions, one or two positive axillary sentinel lymph nodes (SLN) without extra-capsular infiltration and a plan to undergo breast conserving surgery followed by conventionally fractionated whole-breast radiotherapy. Patients with larger tumors, more than two positive SLN, inflammatory breast cancer, undergoing mastectomy or planned to receive unconventional radiation treatments are excluded from this recommendation. The recommendation is based on data from one randomized trial, the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial^[7]. Some additional trials provide related, although circumferential evidence, on the issue and will be included in this discussion (Table 1). Another randomized trial, for example, the International Breast Cancer Study Group (IBCSG) 23-01 trial addresses a similar clinical question in a different patient population with only micrometastatic lymph node disease^[8] and thus its relevance for the decision of omission of ALND in patients with macrometastatic disease is questionable. IBCSG 23-01 showed the non-inferiority of avoiding ALND vs performing an ALND regarding disease-free survival

(DFS) and overall survival (OS) in 931 patients with mainly (90%) positive Estrogen Receptor (ER) status and T1 or T2 primary tumors (70% T1 and more than 90% less than 3 cm in major diameter)^[8]. DFS was 84% and 88% ($P = 0.16$) and OS 98% in both arms ($P = 0.73$). Omission of lymph node dissection in patients with isolated tumor cells (less than 0.2 mm in diameter) or micrometastatic (0.2-2 mm in diameter) only disease in the axilla could be advocated with less controversy given the results of IBCSG 23-01 and the predicted lower incidence of additional positive nodes and lower risk of recurrence in patients with micrometastatic only disease in the axilla compared with counterparts with macrometastases^[9]. In addition, in a large retrospective analysis, patients with micrometastatic disease in the axilla, in contrast to patients with macrometastases in whom there was a trend towards inferior outcomes, had equivalent survival if no complete dissection was performed^[10]. Nevertheless, even in these patients, about 20% can be expected to have additional axillary involvement^[9]. It is interesting to note that patients with micrometastatic disease have a lower disease-free survival compared with lymph node negative patients and benefit from adjuvant therapy^[11].

The Z0011 trial randomized 891 patients with T1 or T2 breast cancers and one or two positive axillary SLN (both patients with macrometastases and micrometastases were included) to further ALND or no further surgical treatment^[7]. The initial trial plan was for randomization of 1900 patients but had to be modified due to slow accrual and lower than expected mortality rate. The study was able to demonstrate the non-inferiority of no further surgical treatment for the end-points of OS and DFS. Being the only randomized trial attempting to answer a very important clinical question, Z0011 has been scrutinized and shortcomings previously discussed^[12]. The two groups were well-balanced but ALND group had slightly more patients with T2 disease (32.1% vs 29.4%, and even some T3 tumors, as the upper range of size in this group was 7 cm), lymphovascular invasion (40.6% vs 35.2% in the SLN only group) and grade II/III tumors (78% vs 74.4% in the SLN only group). In addition, the ALND group had less patients with the good prognostic features of ER and PR positivity (66.8% vs 68.9%) and no positive SLN (1.2% vs 7%, these patients should have been excluded but were included for the intention-to-treat analysis). Micrometastatic lymph node disease was present in a statistically significant higher percentage of patients in the SLN group (44.8% vs 37.5%). Despite these inequalities all favoring the SLN group over the ALND group, OS and DFS were similar in the two groups (92.5% vs 91.8% and 83.9% vs 82.2% respectively). The study had a high rate of loss to follow-up (166 of 891 patients, 18.6%), a source of potential bias. Her2/Neu testing was not standard at the time of the study and no data were

Table 1 Trials discussed in this paper informing directly or indirectly on the question of completion of axillary lymph node dissection in patients with sentinel lymph node biopsy-positive breast cancer patients

Trial [Ref.]	Comment
ACOSOG Z0011 ^[7]	The main randomized trial informing the clinical question
IBCSG 23-01 ^[8]	Randomized trial in patients with micrometastatic only axillary disease
Yegiyants <i>et al</i> ^[14]	Small study of patients followed after micrometastases found in SLN biopsy
Martelli <i>et al</i> ^[15]	Randomized trial comparing ALND <i>vs</i> no surgery in older patients
IBCSG Trial 10-93 ^[16]	Similar to reference 15
Avril <i>et al</i> ^[17]	Similar to references 15 and 16 but in a younger patient population
Louis-Sylvestre <i>et al</i> ^[19]	Randomized trial comparing ALND with axillary radiation treatment
Wang <i>et al</i> ^[21]	Retrospective SEER-based study in patients with lobular carcinomas

SLN: Sentinel lymph node; ALND: Axillary lymph node dissection; SEER: Surveillance, Epidemiology and End Results.

reported. ER and PR negative patients represented a minority with only about 16% of patients in each arm. After exclusion of the 166 patients lost to follow-up and 301 patients with only micrometastatic lymph node disease, there remain 424 patients (about two thirds ER and PR positive) who can inform us on the question of macrometastatic disease.

The LN tumor burden in the patient population of the Z0011 study appears to be low with only 21% of patients in the ALND group having additional positive nodes and 13.7% having a total of four or more positive nodes^[7]. One can predict that a similar (or even lower based on somewhat better prognostic characteristics) percentage of patients in the SLN group would have additional disease. The low tumor burden is also depicted in the higher OS rates in the study compared with the rate of 80% anticipated. Available models predict that patients with T2 disease and two positive sentinel nodes (that is still meeting the eligibility criteria of Z0011) may have much higher probabilities of additional positive nodes. For example the Memorial Sloan Kettering Cancer Center (MSKCC) model predicts that a patient with a grade III tumor of 5 cm, and 2 positive SLN may have a probability of over 90% for additional positive nodes^[13]. The question remains if patients with higher axillary LN burdens will have similar outcome without ALND as seen in Z0011. It is important to note that the predicted risk of additional positive lymph nodes may not be the only determinant of risk of recurrence. For example in a small study of 47 patients with positive SLN (33 with micrometastases only) and a low risk of 11.5% of additional LN positivity by the MSKCC model two patients (4.2%) had an axillary recurrence^[14]. On the other hand, as studies performed before the routine introduction of SLN biopsy that compare ALND with no dissection in older patients (mean age over 70 years old) with small primaries (mostly T1a and T1b), ER positive and clinically negative axilla have shown, most patients with a predicted low burden axillary disease will not have a clinically apparent axillary recurrence even if left untreated^[15,16]. These patients are spared the adverse effects of ALND without adverse

oncologic outcome in the short term. Nevertheless even these studies suggest that axillary recurrences are much more frequent (up to three times) if no axillary intervention is undertaken, although low in absolute numbers^[15,16]. In addition another study with the same design that included younger patients (mean age 62 years old) showed a statistically significant worse overall and disease-free survival in patients with no axillary intervention as compared with the group that underwent ALND^[17].

An additional question is the generalizability of results to sub-types of breast cancer not well-represented or not studied in Z0011 (ER negative and Her2 positive). Trying to address this short-coming, the authors of the study performed an exploratory analysis of the positive and negative ER/PR groups that showed no statistically significant differences. Nevertheless, this represents weak evidence for the negative sub-group and optimally clinical decisions based on exploratory analyses should be avoided. Overall the less common sub-types of breast cancer such as triple negative and Her2/Neu positive benefit from very little high quality evidence to support omitting ALND. This is particularly worrisome in triple negative patients for whom there is currently no proven targeted therapy to control residual disease. Moreover, for Her2/Neu positive patients that have efficacious targeted therapies available to them, these therapies can produce only small percentages of complete responses in the metastatic setting and thus their ability to control significant residual disease burden in the axilla remains unproven^[18]. The same is true for radiation therapy which is an efficacious treatment for localized or oligometastatic disease but is not possible for more widespread disease. In addition in a randomized study of ALND *vs* radiation therapy in breast cancer patients with clinically negative axillary nodes the axillary recurrence was almost 4 times higher in the radiation treatment arm (2.2% *vs* 0.6% at 5 years)^[19]. In this study patients were mostly ER positive and had a low incidence of 21% of positive nodes in the ALND and similar axillary disease positivity could be expected to have been present in the radiation arm.

Table 2 Considerations for omission of completion axillary lymph node dissection in patients with positive sentinel lymph node

Axillary lymph node dissection may be omitted
T1 or T2 primary
One or two positive SLN without extra-capsular extension
Lumpectomy and conventional radiation therapy planned
ER and PR positive, Her2/Neu negative (equivalent to Luminal A) biology
Patient older than 65 yr old
Ductal histology
Axillary lymph node dissection should be the standard but omission could be discussed in an individualized basis
Patient younger than 65 yr old
Biology other than Luminal A
Lobular histology
Axillary lymph node dissection should be performed
T3, T4 or inflammatory primary
More than two positive SLN and/or extra-capsular extension
Mastectomy or unconventional radiation therapy planned

SLN: Sentinel lymph node.

Another sub-type of breast cancer not well-represented in the Z0011 study is lobular carcinoma. Only 7.7% of patients had this sub-type which has a different biologic behavior from ductal carcinoma, is more often multifocal and tends to metastasize to unusual locations such as the gastrointestinal tract and peritoneal surfaces^[20]. A retrospective study of the Surveillance, Epidemiology and End Results database suggested that there are no differences in overall or disease-specific survival between patients with lobular carcinoma who fulfilled the Z0011 criteria and did or did not undergo completion ALND^[21]. Most of the patients had T1 tumors (median size of the two groups 1.7 and 1.8 cm), 70% had one positive LN and over 90% had ER positive tumors.

A final issue that should be considered in evaluating the strength of the available data as a basis for clinical decisions is the length of follow-up. As the authors of Z0011 note, it would have taken more than 20 years to observe the pre-specified 500 deaths in their study population and thus the trial was closed prematurely with less than the target accrual number. Although the fact that no differences were observed in OS and local recurrences at 6 years is reassuring, at least for the shorter term, concerns remain regarding longer term applicability. The population studied with mainly ER positive disease (more than 80% of whom would be expected to be Her2 negative) has, often, even in the metastatic setting, a more indolent course (not unusually with bone only disease) and thus OS at 6 years may be too short for definite conclusions when studying localized disease. Moreover, and at closer scrutiny, local recurrence rates display some discernible differences between the two groups in Z0011^[22]. The ALND group had numerically more (3.6% vs 1.9% in the SLN group) in-breast recurrences. These recurrences should not have been influenced by the treatment assigned and probably reflect the aforementioned base-line differences in the two groups. In contrast, axillary

recurrences were more prevalent in the SLN group (0.9% vs 0.5% in the ALND group). Although this difference was not statistically significant and small in absolute numbers (reflecting the low disease burden in the axilla), it is still an 80% difference and may imply that the two treatments are not equal in controlling axillary disease. Increased axillary tumor burden may accentuate such differences in local control and eventually global outcomes.

Fisher's model proposes that breast cancer is a systemic disease from an early point in time and has been used to justify less aggressive surgical interventions^[23]. In fact this model, in conjunction with the current models of the plasticity of tumor initiating cells and their genetic instability, predict that the lower the residual tumor burden is the lower becomes the probability of resistant clones to emerge spontaneously or as a result of treatment pressure^[24,25]. These cannot currently be satisfactorily treated with systemic therapies.

In conclusion, the randomized data available are not sufficient to recommend omitting completion ALND in all patients with T1/T2 disease and up to two positive SLN that will undergo lumpectomy and whole breast irradiation. A more prudent policy would be to consider ALND omission only in older post-menopausal patients with ductal carcinomas, clinically negative axilla, no extra-nodal extension and ER/PR positive disease. In other patients with one or more deviations from the studied population of Z0011 trial the standard should remain a completion ALND (Table 2) and an individualized decision should be reached, optimally with involvement of the patient, awaiting more confirmatory data, especially in sub-types other than luminal A (immunohistochemically determined as ER/PR positive and Her2/Neu negative). Longer follow-up is required to ensure that ALND omission is safe and oncologic outcomes are equivalent at long term in patients with luminal A sub-type breast cancers and extend of disease within the acceptable

for consideration of ALND omission rate but higher expected tumor burdens such as patients with T2 tumors and 2 positive SLN.

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