



Original Article

Positive axillary sentinel lymph node: Is axillary dissection always necessary?

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SUMMARY

There is considerable interest in foregoing axillary dissection (AD) when the sentinel node (SN) is positive in early breast cancer, particularly when axillary involvement is minimal (micrometastases or isolated tumor cells). In fact, clinical practice has run ahead of the evidence, since recent population-based data indicate that AD is 'underused' in breast cancer patients when the SN is positive. Several trials are addressing the problem (IBCSG 23–01, ASCOG Z0011, EORTC AMAROS). Only Z0011 has published interim results, finding, after a median follow-up of 6.3 years, no differences in locoregional recurrence or regional recurrence between patients, with a positive SN, who received AD vs. no further axillary treatment. Our own retrospective study evaluated patients with micrometastases or isolated tumor cells in the SN who received no further axillary treatment. We found high five-year survival and low cumulative incidence of axillary recurrence, supporting the findings of Z0011 and justifying the increasingly common practice of foregoing AD in women with minimal SN involvement. It is important to sound a note of caution however: If axillary dissection is not always necessary in women with a positive axilla, it seems important to be able to reliably identify the patients at high risk of developing overt axillary disease who should receive elective AD. Ancillary analyses of the IBCSG 23–01 and AMAROS trials, still in follow-up, may be able to do this.

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Introduction

It took many decades for conservative surgery to be accepted as an oncologically valid treatment for early breast cancer, and there are still surgeons in western countries who prefer mastectomy. The situation with sentinel node biopsy (SNB) was very different. SNB was widely adopted within a few short years of its introduction and now is almost universally applied. Such a rapid change in surgical practice is rare. Studies show that SNB can safely replace the routine application of axillary dissection (AD), allowing patients with an uninvolved sentinel node (SN) (close to two-thirds of those who receive SNB^{1–5}) to be spared unnecessary AD. However, the management strategy for the remaining third of patients with a positive SN – who may have residual axillary node disease – is still under debate. This article examines this issue and the available evidence, and attempts to draw conclusions regarding the safety of foregoing AD when the SN is positive.

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For and against AD when the SN is positive

Since AD is often associated with considerable morbidity, both surgeons and their patients are motivated to avoid it whenever possible. Both whole-breast irradiation (that includes part of the axilla), and systemic adjuvant treatment, can eliminate low-volume lymph node metastases,^{6–8} so patients who receive these treatments are expected to be at low risk developing axillary disease. Furthermore, studies on patients with a positive SN who received AD, show that a considerable fraction had no further axillary involvement, and this fraction therefore receives AD unnecessarily. When the SN is macrometastatic, the frequency of non-SN metastases varies from 46% to 80%;⁹ when the SN is micrometastatic, the frequency varies from 0% to 80%;^{9,10} and when the SN contains isolated tumor cells only, the frequency of non-SN 15–19%.^{9,10} The other side of the coin, of course, is that a considerable fraction of patients do have non-SN metastases, and it is generally considered that such metastases should be removed, because knowledge of the total number of involved nodes provides important prognostic information and guides adjuvant axillary radiotherapy and chemotherapy decisions.^{11–14} Axillary clearance may also have a small therapeutic effect through improved regional

control, even though a considerable fraction of patients with occult axillary metastases never develop overt axillary involvement¹⁵ and at least one trial has shown that survival for mastectomy without AD, and radical mastectomy are equivalent, indicating that AD is only a staging procedure providing no survival benefit.

Another reason for not automatically performing AD when the SN is positive is that nomograms can be used to identify patients with the greatest risk of additional axillary nodes, and only these should be offered AD.^{11,16}

The situation on the ground

What treatments are women with a positive SN actually receiving? The 2009 study on the US National Cancer Data Base¹⁷ examined women with a positive SN treated from 1998 to 2005 and a median follow-up of 63 months. Of nearly a hundred thousand patients with a positive SN, 87,000 had macroscopic SN disease, and 10,000 had microscopic SN disease. The large majority with macroscopic disease received AD, and about two-thirds of those with microscopic disease received AD. This study acknowledged several biases but found that AD did not improve outcomes in patients with microscopic SN involvement. The study did find, however, a non-significant trend to better outcomes in patients with a macroscopically involved SN who received AD, compared to those who received SNB alone.

The study also examined factors influencing whether a patient had SNB alone or also received AD. It was found that, in women diagnosed in 2004–2005, SNB alone was more likely in older patients, those with smaller tumors, and those treated at centers not designated by the National Cancer Institute.

The study by Yi et al.¹⁸ examined data on nearly 27,000 US breast cancer patients with a positive SN, archived in the SEER database. This study also found no difference in overall survival between those who did and those who did not receive AD. The most interesting aspect of this study was that it revealed marked changes over time in the use of AD in women with a positive SN. Increasing numbers with microscopic SN involvement did not to receive AD – up to nearly 40% in 2004. There was also a strongly significant, though less marked trend, for more patients with a macroscopically positive SN not to receive AD.

Retrospective studies

The retrospective MIRROR study¹⁹ identified all Dutch breast cancer patients with favorable tumor characteristics who had SNB before 2006, and only micrometastases or isolated tumor cells in the axilla (not simply the SN). The study examined outcomes in relation whether or not the axilla received further treatment, and also the effect of use and non-use of adjuvant treatments. Since there were no guidelines regarding use of adjuvant treatments when the SN is positive, and various other factors influenced their use, these were adjusted for in the multivariate analyses.

The multivariate analyses found that, in patients with micrometastases or isolated tumor cells in the axilla who did not receive systemic therapy, disease-free survival was significantly worse than in those who did receive systemic therapy, even after adjusting for potential confounders. Interestingly, whether or not AD was performed had no influence on outcomes. The study also compared outcomes to those in matched series of patients with a negative axilla: disease-free survival was significantly worse in the positive axilla group. It appears therefore that even a minimally involved axilla is associated with worse disease free-survival than a clear axilla; nevertheless systemic treatment is able to cancel this poor prognostic effect, irrespective of whether the micrometastases/isolated tumor cells are in the SN or other axillary nodes.

The European Institute of Oncology addressed the issue of foregoing AD when the SN is minimally involved in early breast cancer in a single-centre retrospective study.²⁰ The study analyzed outcomes in 377 consecutive patients treated between 1999 and 2007 who had a single micrometastatic sentinel node and for various reasons (including refusal and participation in a trial) did not receive AD. Classical and competing risks survival analyses were used to estimate prognostic factors for axillary recurrence, first events, and overall survival. Median patient age was 53 years (range 26–80); median follow-up was 5 years (range 1–9). Most (91.8%) patients received conservative surgery. Five-year overall survival in the cohort was 97.3%. There were 10 local events, 2 Simultaneous axillary and local recurrences, 6 axillary recurrences, and 12 distant events. The cumulative incidence of axillary recurrence was 1.6% (95% CI 0.7–3.3). By multivariable analysis, tumor size and grade were significantly associated with axillary recurrence. It was concluded that the high five-year survival and low cumulative incidence of axillary recurrence in this cohort provided justification for the increasingly common practice of foregoing AD in women with minimal SN involvement, and suggested that AD can safely be avoided in women with small, low-grade tumors. Nevertheless a subset of patients might be at high risk of developing overt axillary disease and efforts should be made to identify such patients by ancillary analyses of the results of ongoing or recently published clinical trials.

Randomized trials

Several randomized trials are addressing what to do in cases where the SN is positive. In the AMAROS EORTC trial, which has now closed and is in follow-up, patients with a positive SN were randomized to AD or axillary radiotherapy (RT). This was an equivalence study, hypothesizing that both treatment modalities will result in the same degree of regional control and survival. The interesting premise of AMAROS is that RT to the axilla may be an acceptable and less invasive alternative to AD. One publication on AMAROS patients has emerged.²¹ It reported a multivariate analysis to assess variables influencing the administration of adjuvant chemotherapy. Adjuvant chemotherapy was given to similar numbers of patients in both arms (58% in the AD arm; 61% in the axillary RT arm) Adjuvant hormonal therapy was given to similar numbers of patients in both arms (78% vs. 76%). Among the patients treated with AD, 5% received adjuvant axillary radiation therapy because >3 lymph nodes were positive. The study found that knowledge of further nodal involvement did not influence decisions on whether to give adjuvant systemic therapy, in fact systemic adjuvant therapy was mainly administered based on tumor and patient characteristics. Only in the 5% of patients with >3 involved lymph nodes did knowledge of further nodal involvement did have an impact: based on this finding they were given adjuvant axillary RT. This study seems to show, therefore, that axillary status has little influence on adjuvant treatment in current practice, while in the past knowledge of axillary status was considered essential for deciding whether or not adjuvant treatment should be given.

The IBCSG multicentric trial closed for low accrual in February 2010. It recruited 890 patients and aimed to determine the prognostic significance of micrometastasis (including isolated tumor cells) in one SN only. Patients meeting this criterion were randomized to AD or no further axillary treatment.²²

The American College of Surgeons Oncology Group Z0011 trial closed in April 2010 after randomizing 889 patients.²³ The trial closed early for low accrual and low number of events. Patients with hematoxylin and eosin-detected metastasis in the SN were randomized to either AD or no further axillary treatment. Adjuvant systemic therapy was at the discretion of treating physicians. The original endpoint was overall survival.²³ An analysis of locoregional

recurrences in less than 50% of the originally projected number of patients (338 in the AD arm 245 in the no further axillary treatment arm) was published recently²³ after a median follow-up of 6.3 years. The analysis found no significant difference between the arms in terms of regional recurrence or local recurrence.

Overall survival, as well as disease-free survival, were presented in an updated analysis of Z0011 results at the ASCO General Meeting of 2010.²⁴ In the abstract, median follow-up was 6.2 years. This analysis reported that five-year “in-breast” recurrence after AD was 3.7% compared to 2.1% in patients who received SNB only; five-year nodal recurrence was 0.6% after AD compared to 1.3% ($p=0.44$) for no further axillary treatment. The corresponding figures for five-year overall survival were 91.9% vs. 92.5% ($p=0.24$), and for disease-free survival were 82.2% vs. 83.8% ($p=0.13$).

The abstract concluded that “despite the widely-held belief that AD improves survival” no significant survival differences were found between the AD and no AD groups in SN node-positive women; there was “no trend to clinical benefit for AD in patients with limited nodal disease.”

However it must be emphasized that the trial closed with under half of the projected number of patients recruited, and it is unclear whether the analysis had the power to detect a small difference in five-year overall survival and disease-free survival between the two arms.

The Z0011 and IBCSG 23–01 trials are lost opportunities: as Monica Morrow has noted²⁵ both trials were ahead of their time, as many surgeons were unwilling to randomize patients considering it unethical not to perform AD. The result was that both trials closed early without accruing sufficient patients, and may be underpowered to show whether axillary dissection is always necessary if the SN is positive (micro-metastatic or otherwise). A meta-analysis of the results of the Z0011 and 23–01 trials both would also be difficult because the recruitment criteria and methods of assessing the SN differed.

As discussed above, the attitude that not performing AD is unethical has now completely reversed and rapidly increasing numbers of patients with a positive SN no longer receive AD^{17,18} even though guidelines are that AD should be performed.²⁶

Conclusions

Notwithstanding the disappointing early closures of Z0011 and 23–01 trials, evidence from other sources appears sufficiently robust to justify not performing AD if the SN is micrometastatic in women with small cancers having favorable prognostic factors. However this option should be discussed with the patient. On the other hand, if the SN is macrometastatic a cautious attitude should prevail, and foregoing AD should not be routine. Perhaps nomograms may be a sufficiently accurate for deciding whether further axillary treatment is necessary in patients with a macrometastatic SN.^{16,27} Alternatively axillary ultrasound in a clinically clear axilla may be able to identify patients in whom elective AD is advisable. Finally, in the near future gene expression profiles may prove the most reliable means of deciding whether further axillary treatment is warranted when the SN is positive.

Conflict of interest statement

The authors have no conflict of interest to declare.

References

- Veronesi U, Galimberti V, Paganelli G, et al. Axillary metastases in breast cancer patients with negative sentinel nodes: a follow-up of 3548 cases. *Eur J Cancer* 2009;**45**(8):1381–8.

- Veronesi U, Viale G, Paganelli G, et al. Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. *Ann Surg* 2010;**251**(4):595–600.
- Mansel RE, Goyal A. European studies on breast lymphatic mapping. *Semin Oncol* 2004;**31**(3):304–10.
- Dabbs DJ, Fung M, Landsittel D, McManus K, Johnson R. Sentinel lymph node micrometastasis as a predictor of axillary tumor burden. *Breast J* 2004;**10**(2):101–5.
- Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003;**349**:546–53.
- Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997;**15**:2483–93.
- Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;**347**:1233–41.
- Gadd M, Harris J, Taghian A, et al. Prospective study of axillary radiation without axillary dissection for breast cancer patients with a positive sentinel node. Presented at *San Antonio Breast Cancer Symposium*, December 8–11, 2005, San Antonio, TX.
- Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: A meta-analysis. *Cancer* 2006;**106**:4–16.
- Noguchi M. Avoidance of axillary lymph node dissection in selected patients with node-positive breast cancer. *Eur J Surg Oncol* 2008;**34**(2):129–34.
- Katz A, Smith BL, Golshan M, et al. Nomogram for the prediction of having four or more involved nodes for sentinel lymph node-positive breast cancer. *J Clin Oncol* 2008;**26**:2093–8.
- Peintinger F, Reitsamer R, Stranzl H, et al. Comparison of quality of life and arm complaints after axillary lymph node dissection vs sentinel lymph node biopsy in breast cancer patients. *Br J Cancer* 2003;**89**:648–52.
- Purushotham AD, Upponi S, Klevesath MB, et al. Morbidity after sentinel lymph node biopsy in primary breast cancer: Results from a randomized controlled trial. *J Clin Oncol* 2005;**23**:4312–21.
- Truong PT, Vinh-Hung V, Cserni G, et al. The number of positive nodes and the ratio of positive to excised nodes are significant predictors of survival in women with micrometastatic node-positive breast cancer. *Eur J Cancer* 2008;**44**:1670–7.
- Standards of the Commission on Cancer, volume II. Registry Operations and Data Standards*. Chicago, IL: Commission on Cancer; 1998.
- Van Zee KJ, Manasseh DM, Bevilacqua JL, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol* 2003;**10**:1140–51.
- Bilimoria KY, Bentrem DJ, Hansen NM, et al. Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. *J Clin Oncol* 2009;**27**:2946–53.
- Yi M, Giordano SH, Meric-Bernstam F, et al. Trends in and outcomes from sentinel lymph node biopsy (SLNB) alone vs. SLNB with axillary lymph node dissection for node-positive breast cancer patients: experience from the SEER database. *Ann Surg Oncol* 2010;**17**(Suppl 3):343–51.
- de Boer M, van Deurzen CH, van Dijk JA, et al. Micrometastases or isolated tumor cells and the outcome of breast cancer. *N Engl J Med* 2009;**361**(7):653–63.
- Galimberti V, Botteri E, Chifu C, et al. Can we avoid axillary dissection in the micrometastatic sentinel node in breast cancer? *Breast Cancer Res Treat* 2011, in press. doi: 10.1007/s10549-011-1486-2.
- Straver ME, Meijnen P, van Tienhoven G, et al. Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. *J Clin Oncol* 2010;**28**(5):731–7.
- Galimberti V. International Breast Cancer Study Group Trial of Sentinel Node Biopsy. *J Clin Oncol* 2006;**24**(1):210–1.
- Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 2010;**252**(3):426–32.
- Giuliano AE. ACOSOG Z0011: A randomized trial of axillary node dissection in women with clinical T1–2N0M0 breast cancer who have a positive sentinel node. *ASCO Annual Meeting* 2010, abstract.
- Morrow M. Patterns of care with a positive sentinel node: echoes of an opportunity missed. *Ann Surg Oncol* 2009;**16**(9):2429–30.
- National Comprehensive Cancer Network (NCCN). *Clinical Practice Guidelines in Oncology Breast*, version 2. 2008.
- van den Hoven I, Kuijt GP, Voogd AC, van Beek MW, Roumen RM. Value of Memorial Sloan-Kettering Cancer Center nomogram in clinical decision making for sentinel lymph node-positive breast cancer. *Br J Surg* 2010;**97**(11):1653–8.