



Long-term follow-up of 5262 breast cancer patients with negative sentinel node and no axillary dissection confirms low rate of axillary disease

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Abstract

Aim: It is established that axillary dissection (AD) can be safely avoided in breast cancer patients with a negative sentinel node (SN). In the present study we assessed whether the rate of axillary disease was sufficiently low on long term follow-up to consolidate the policy of AD avoidance.

Methods: We retrospectively analysed data on 5262 consecutive primary breast cancer patients with clinically negative axilla and negative SN, treated from 1996 to 2006, who did not receive AD. We used univariate and multivariate analyses to assess the influence of patient and tumour characteristics on first events and survival. The primary endpoint was the development of axillary disease as first event.

Results: After a median follow-up of 7.0 years (interquartile range 5.4–8.9 years) survival for the series was high (91.3%; 95% CI 90.3–92.3 at 10 years) and only 91 (1.7%) patients developed axillary disease as first event. Axillary disease was significantly more frequent in patients with the following characteristics: <35 years at diagnosis, tumour >1 cm, multifocality/multicentricity, G3, ductal histotype, Ki67 \geq 30%, peritumoral vascular invasion, luminal B-like subtype, HER2 positivity, mastectomy, and not receiving radiotherapy.

Conclusion: Long-term follow-up of our large series confirms that axillary metastasis is infrequent when AD is omitted in SN-negative breast cancer patients, and has low impact on overall survival.

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Introduction

The debate on sentinel node biopsy (SNB) in early breast cancer is currently focused on the extent to which the findings of the AZ0011¹ and IBCSG 23.01² trials –

that axillary dissection is not necessary in many patients with a positive sentinel node – can be applied in clinical practice.³ The recent guideline update from the American Society of Clinical Oncology⁴ recommended that most women with one to two metastatic sentinel nodes (SNs) undergoing breast-conserving surgery with whole-breast radiotherapy should not undergo axillary dissection (AD), while women with SN metastases who undergo mastectomy should receive AD.

It has been clear for a long time that when the SN is negative no further axillary treatment is necessary,^{5,6}

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even though estimates of the false negative rate of the SNB technique are around 6–10%. In fact, numerous studies have reported that the actual rate of disease appearance in the axilla after a negative SN is always considerably lower than the estimated false negative rate.⁷ Thus in the single-centre trial of Veronesi et al.⁶ only 2 cases of overt axillary metastasis occurred in the SNB arm after 10 years, at variance with a false negative rate of 8.8%, with 10-year breast cancer-related event-free survival in both arms at around 89%. Similarly, in the NSABP B-32 trial, the regional node recurrence rate was 0.4% in the AD arm and 0.7% in the SNB only arm, while the false negative rate in the AD arm was 9.8%. Disease-free survival was indistinguishable in both groups at around 82% after eight years.⁸

Furthermore, in a previous retrospective analysis of 3548 patients with a negative SN who did not undergo AD, we found that after a median follow-up of 48 months, only 31 patients (0.9%) developed overt axillary metastases, and that 5-year overall survival for the whole series was 98%.⁹ In the present retrospective study we re-evaluated the risk of axillary disease in an expanded series of patients with SN-negative breast cancer with considerably longer follow-up. We also developed a model to predict the risk of axillary disease in these patients.

Patients and methods

Data were extracted from the European Institute of Oncology (IEO) breast cancer database. The database is updated by surgeons, checked by the Data Quality Control Unit and used in weekly interdisciplinary discussions to help decide personalised adjuvant treatments according to protocols in force at our institute.

We retrieved data on 5262 consecutive patients with primary breast cancer, clinically negative axilla and negative SNB, treated at the IEO from 1996 to 2006. Follow-up closed for the purposes of this study on May 1st 2013. Patient and tumour characteristics are summarized in [Table 1](#).

SNB was performed as described elsewhere.¹⁰ Briefly ⁹⁹Tc-labelled radiocolloid in 2 ml of saline was injected subdermally close to the tumour, under imaging control if the cancer was non palpable. Lymphoscintigraphy was performed to verify the presence of an SN. Surgery was performed the same day or the day after, and the SN detected intraoperatively using a gamma probe, which also aided its surgical removal. SNs were usually examined intraoperatively, using an extensive technique that examined the whole lymph node.¹¹ When a negative result was obtained, AD was not performed (all cases in present series).

Patients were scheduled for follow-up at six-month intervals for 5 years at our outpatient clinic, and yearly thereafter. Follow-up examination included palpation and ultrasound exploration.

Statistical methods

The main study endpoint was risk of developing axillary metastasis as first event during follow-up. Cumulative incidence of axillary metastasis was calculated from the date of surgery until the date of breast cancer-related first event or date of last follow-up, whichever occurred first. We also evaluated overall survival (OS), calculated from the date of surgery to date of death (any cause) or date of last contact, and also outcomes in patients who developed axillary metastasis, starting follow-up from the time of diagnosis of axillary disease. OS was represented by the Kaplan–Meier method. Univariate and multivariate Cox proportional hazard regression models were used to assess the influence of clinical and tumour characteristics on the development of axillary metastasis and OS. Factors considered in the analyses included: age, tumour size, multifocality/multicentricity, tumour grade, Ki67, hormone receptor status, perivascular invasion (PVI) and type of surgery (mastectomy vs. breast-conserving surgery).

We developed a risk score for the development of axillary metastasis based on factors that were significantly associated with outcome at multivariate analysis.

In previous studies, approximately 6% of non-sentinel nodes were positive in patients with a negative SN.¹¹ Assuming that all positive non-sentinel nodes would become clinically evident and this would occur at a constant rate over 12 years, we calculated the expected number of axillary events considering the person-years at risk in our series. All analyses were performed with the SAS software version 8.02 (Cary, NC). All *p*-values were two-sided.

Results

Patient and tumour characteristics are summarized in [Table 1](#). A total of 166 (3.2%) patients were <35 years old when diagnosed. A single SN was removed in 2720 (51.7%); 2 were removed in 1569 (29.8%), and 3 or more were removed in 973 (18.5%). The great majority (91.3%) of patients received breast-conserving surgery; 8.7% received mastectomy. Intraoperative radiotherapy with electrons (ELIOT) full-dose (21 Gy) or boost (12 Gy) was given to selected patients undergoing breast-conserving surgery (1389 cases, 26.4%).¹² External beam whole breast irradiation (two tangential fields) was given to 3507 (66.6%). No radiotherapy data are available for 27 cases. Patients undergoing mastectomy did not receive radiotherapy. A total of 3951 (75.1%) patients received adjuvant endocrine therapy. Systemic chemotherapy was given to 627 patients (11.9%); chemotherapy plus endocrine therapy was given to 379 patients (7.2%) according to the protocol in use at our Institute ([Table 1](#)).

After a median follow-up of 7.0 years (range 0–14.8 years; interquartile range 5.4–8.9 years), 906 unfavourable first events occurred in the series ([Table 2](#)). These included local relapse in 227 patients, distant metastasis in 211,

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