Axillary recurrence rate after tumour negative and micrometastatic positive sentinel node procedures in breast cancer patients, a population based multicenter study ☆

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Abstract

Background: The sentinel lymph node procedure is a widely accepted method for staging of patients with early breast cancer. This study evaluates the incidence of axillary relapse after negative sentinel node biopsy in the seven hospitals in the central part of the Netherlands.
Methods: This study concerns all patients with a T1-2 breast carcinoma who were staged with a sentinel lymph node biopsy in one of the hospitals in the region. Patients with a tumour-free sentinel node without additional axillary lymph node dissection and patients with a sentinel node containing micrometastases were prospectively included and data concerning tumour and primary treatment were recorded. After a median follow-up period of 46 months supplementary data were collected of all patients.
Results: Between January 2002 and December 2003, 541 patients underwent a sentinel node biopsy of which the sentinel node was negative for metastatic disease. During the follow-up period three patients were diagnosed with an axillary recurrence. The incidence of axillary relapse after tumour negative sentinel node biopsy in this study is 0.6% (3/541). In 23 patients a distant metastasis developed. An event occurred in 11% of the patients with a micrometastasis in the sentinel node. This was not significantly different from the patients with a tumour-free sentinel node.
Conclusion: The results suggest that the sentinel lymph node procedure as performed in the region Middle Netherlands is a reliable and accurate instrument for staging of patients with early breast cancer. In our study we observed a non-significant different risk of distant disease in case of micrometastases compared to a tumour negative sentinel node.
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Keywords: Early breast cancer; Sentinel node biopsy; Axillary recurrence rate; Micrometastasis

Introduction

The sentinel lymph node procedure is a widely accepted method for staging of patients with early breast cancer. This procedure is based on the concept that the lymph node upon which the carcinoma drains directly is also the first to be infiltrated by tumour cells. Many studies, mainly single-centre studies, have shown that the sentinel node provides a reliable and valid image of the tumour status of the remaining axillary lymph nodes.[1–3] The number of axillary relapses varies in most studies between 0–1.4% after a median follow-up of 24–79 months.[4,5] These favourable figures have led to the routine use of the sentinel node biopsy in patients with T1-2 breast cancer. This procedure saves the patient from the possible morbidity of an axillary lymph node dissection, provided that the sentinel node is free from tumour.[6]

The tumour status of the axillary lymph nodes is an important prognostic factor in breast cancer and helps to determine the appropriate adjuvant therapy. The pathological work-up of the sentinel nodes consists of serial sectioning of the lymph node and also involves immunohistochemistry using antibodies against cytokeratines which makes it possible to recognize micrometastases (diameter 0.2–2 mm) and isolated tumour cells (diameter < 0.2 mm) as well. The upstaging of breast cancer observed with the introduction of the sentinel lymph node procedure is due

to the detection of more micrometastases.[7] This has raised questions concerning treatment of the axilla with a micrometastasis positive sentinel lymph node as well as questions concerning the clinical relevance of these observations. Van Deurzen et al. concluded that as it is impossible to predict the involvement of the remaining lymph nodes it is justified to perform axillary lymph node dissections in patients with tumour positive sentinel lymph nodes.[8] Others state that axillary lymph node dissection can safely be omitted in patients with submicrometastases.[9] Several studies concerning the biological significance of micrometastases have resulted in opposing conclusions.[8−11] The prognostic and therapeutic implications remain unclear, however, present day protocols usually do not consider micrometastatic disease a N+ classification.

In the Surgical Oncology Group of the Comprehensive Cancer Centre Middle Netherlands (CCCMN) all seven hospitals of the central region in the Netherlands collaborate in developing treatment protocols and in analyzing treatment results. The Surgical Oncology Group developed the protocol for sentinel node staging of patients with early breast cancer and passed it through the CCCMN's Advisory Board for Scientific Research. This protocol has been uniformly used for the validation period for all hospitals. It required informed consent and consisted of an axillary lymph node dissection for every patient after sentinel node biopsy had been performed. As results in this validation period varied remarkably between hospitals (not published data) the Group agreed to prospectively collect and analyse the data of the first two-year cohorts of patients staged solely by the sentinel node procedure in order to identify and analyse the axillary recurrence rate and possible clinical implications of micrometastases in the sentinel node.

Patients and methods

This population based study concerns all patients with a T1-2 breast carcinoma who were staged with a sentinel node procedure between January 2002 and December 2003 in one of the hospitals in the region. Exclusion criteria were the presence of only in situ carcinomas, tumours larger than 5 cm, presence of lymph nodes suspected of malignancy by clinical examination, patients with multifocal disease and patients after neoadjuvant therapy or axillary lymph node dissection. Patients with a tumour-free sentinel node or a sentinel node containing micrometastases were prospectively included and data concerning tumour and primary treatment were recorded.

After a median follow-up of 46 months supplementary data were collected of all patients. The primary endpoint was defined as the occurrence of an axillary relapse after a tumour negative sentinel node without complementary axillary dissection. Secondary endpoints were local recurrence, distant metastasis and death.

Diagnosis, primary and adjuvant therapy

With a palpable lesion the diagnosis of breast cancer was based on clinical examination, radiological imaging and pathological investigation. In case of a non-palpable lesion a stereotactically or ultrasound guided core needle biopsy was performed to confirm the diagnosis.

Treatment of patients with breast conserving surgery was completed with radiotherapy consisting of total breast irradiation up to a dose of 50 Gy and a boost when indicated.

Additional adjuvant radiotherapy, chemotherapy and hormonal therapy was considered for every patient according to national guidelines based on conventional criteria such as SLN status, hormone receptor status, age (pre-/postmenopausal), tumour size and Scarff−Bloom−Richardson (SBR) tumour grade.[12] Patients with a sentinel node containing micrometastases were assessed individually for necessary adjuvant therapy.

In the first year after the primary surgery patients were followed-up every three months by means of clinical examination, the second and next years check-up were performed every six months. A mammography was obtained every year, and additional diagnostic procedures were performed when indicated.

Sentinel lymph node procedure

The technique introduced for visualizing the sentinel node and its identification during surgery has been according to accepted standards as extensively described by Uren et al. and others.[13,14,4] With palpable tumours in addition to the Technetium[99] colloid, patent blue was injected at arrival in the operating room. With non-palpable lesions the dye was injected guided by ultrasound or stereotactically. The procedure used to visualize the axillary and retrosternal sentinel node differed only in minor aspects between hospitals depending on the local resources. During the first part of the study one hospital used a two-day protocol. In order to obtain a possible indication for radiotherapy on a parasternal field, the protocol advised to biopsy retrosternally located sentinel nodes. Details are summarized in Table 2

If the axillary sentinel node(s) seen on lymphoscintigraphy could not be identified intraoperatively an axillary lymph node dissection was performed. All removed lymph nodes were sectioned at 500-micron distance, with at least three sections for each node. At each level two parallel sections were prepared and examined using hematoxylin-eosin and anti-cytokeratin staining to prove or exclude the presence of tumour.

Data collection

Each collaborating surgeon was responsible for the analysis and the contribution of the data for the patients he managed. The Regional Cancer Registry audited the completeness of the two-year cohorts that have been

analyzed. If no data could be retrieved patients were considered 'lost-to-follow-up'.

Results

Between January 2002 and December 2003, 595 patients underwent a sentinel node biopsy of which the sentinel node was negative for metastatic disease. The sentinel node procedure failed in 1.0% (6/595) of cases. In one patient the sentinel node was not visualized and in five patients the sentinel node was not identified intraoperatively. The axillary node dissection revealed axillary lymph nodes without metastatic tumour but these patients were excluded from further analysis. Twenty-seven patients were excluded because of the presence of a ductal carcinoma in situ without invasive growth, 11 were excluded because histologic examination revealed no invasive carcinoma and 10 patients were lost-to-follow-up. A total of 541 sentinel lymph node procedures were analyzed. The median follow-up was 46 months (range 11–64 months).

Patient characteristics

Data concerning the patient characteristics are summarized in Table 1 and Table 2 gives details concerning the sentinel node biopsies. In 38 patients micrometastases were located in the sentinel node. In 70 patients both axillary and retrosternal sentinel nodes were visualized on lymphoscintigraphy. A total of 73 retrosternal lymph nodes were removed. In three patients the retrosternal lymph node could not be identified intraoperatively. None of these three patients developed a local or regional recurrence or distant metastasis.

Axillary recurrences

During the follow-up period three patients were diagnosed with an axillary recurrence. The first patient, a 74-year-old female underwent a total mastectomy because of a pleomorphic carcinoma with a negative hormone receptor status. The axillary sentinel node contained no metastatic tumour. No adjuvant treatment was indicated. Three months after the initial treatment she developed a palpable lymph node in the axilla, which turned out to be a metastasis. She underwent an axillary dissection and radiotherapy. Histology demonstrated nine tumour positive lymph nodes. In view of her age and as systemic disease could not be proven chemotherapy was not considered indicated. Two years after this a CT-scan showed multiple liver metastasis and the patient died 32 months after the initial treatment.

A 76-year-old female presented with an invasive ductal carcinoma with a positive hormone receptor status. She underwent a total mastectomy and intraoperatively one radioactive and blue and one radioactive sentinel node were removed. Histological examination showed no lymph node metastases. No adjuvant treatment was indicated

considering tumour size and SBR tumour grade I. During the follow-up period she presented after 30 months with pulmonary and liver metastasis. A CT-scan also revealed pathological lymph nodes in both axillae. Hormonal therapy was started; no chemotherapy was given considering age and physical condition. Thirty-seven months after the initial treatment the patient died.

A 40-year-old female was diagnosed with an invasive ductal carcinoma with a positive hormone receptor status. She underwent breast-conserving therapy. The axillary sentinel node contained no metastasis. No further adjuvant therapy was indicated considering tumour size and SBR tumour grade I. After 51 months the patient presented with a palpable lesion in the right axilla, which turned out to be a metastasis. Further investigation also revealed bone metastases. Hormonal therapy was started and this patient continues to do well.

Local recurrences and distant metastases

All events are summarized in Table 3. The mean time in which patients presented with a local or axillary recurrence or a distant metastasis was 27 months (range 1–58 months). Twenty-seven patients died, 14 of these deaths were related to metastatic disease. Twenty-three patients developed distant metastasis in bone ($n = 8$), lung ($n = 3$), brain ($n = 1$), intra-abdominal ($n = 1$) or at multiple localisations ($n = 10$).

Looking at the subgroup of patients with micrometastases ($n = 38$) an event occurred in 11% of these patients: three patients developed distant metastases and one patient had a local recurrence. In the group with a tumour-free sentinel node local recurrence and distant metastases was observed in 5% of the patients. These figures are not significantly different (Chi-square χ^2 $p = 0.128$).

Discussion

Axillary recurrence after sentinel node biopsy in our study

The axillary tumour status provides the physician and the patient with important information concerning postoperative treatment and prognosis about T1-2 breast carcinoma. Burak et al. showed that an axillary dissection is an accurate procedure but with considerable morbidity.[6] Considering these facts the aim of this study in the seven hospitals of the Middle Netherlands was to assess the sentinel node biopsy as minimal invasive procedure for staging of the remaining lymph nodes. The results of this study show that the sentinel node biopsy is a valid and safe instrument in T1-2 breast cancer patients with an axillary recurrence rate of 0.6% based on a median follow-up of 46 months. These results are in accordance with the results of follow-up studies showing relapse rates of 0–1.4% after a median follow-up of 22–79 months.[4,5,15–17] It is noteworthy that in the first patient developing an axillary

Table 1
Patient and tumour characteristics (n = 541)

Age (years)	
Mean	58
Range	29–92
Palpable tumour (%)	
Yes	406 (75)
No	135 (25)
Localisation tumour (%)	
Lateral upper quadrant	241 (44)
Lateral lower quadrant	48 (9)
Medial upper quadrant	96 (18)
Medial lower quadrant	42 (8)
Central	110 (20)
Unknown	4 (1)
Biopsy method (%)	
Needle biopsy	492 (91)
Excision biopsy	39 (7)
Unknown	10 (2)
Surgical procedure (%)	
Lumpectomy	390 (72)
Total mastectomy	108 (20)
Both	43 (8)
Tumour size in millimetres (%)	
0–10	117 (21)
11–20	271 (50)
21–30	112 (21)
31–40	19 (4)
41–50	4 (1)
Unknown	18 (3)
Tumour histology (%)	
Invasive ductal	413 (76)
Invasive lobular	51 (9)
Invasive ductulolobular	37 (7)
Tubular	11 (2)
Mucineus	5 (1)
Papillar	5 (1)
Other	19 (4)
Hormone receptor status (%)	
ER+/PgR+	327 (60)
ER+/PgR−	90 (17)
ER−/PgR−	88 (16)
ER−/PgR+	4 (1)
Unknown	32 (6)
Adjuvant chemotherapy (%)	
Yes	113 (21)
No	424 (78)
Unknown	4 (1)
Adjuvant hormonal therapy (%)	
Yes	124 (23)
No	410 (76)
Unknown	7 (1)
Radiotherapy (%)	
After breast conserving surgery	388 (72)
Thorax	3 (1)

Table 1 (continued)

Supraclavicular	8 (2)
Infraclavicular	3 (1)
Parasternal	10 (2)
Axilla	4 (1)
No radiotherapy	148 (27)

recurrence this event occurs three months after the initial treatment. Histology of the axillary lymph node dissection proved nine tumour-containing lymph nodes. This patient underwent an axillary dissection and radiotherapy. This heavy axillary tumour load makes re-routing of the flow of lymph due to blocking of the sentinel node by metastatic tumour a likely explanation. This case illustrates the importance of removing palpably suspicious lymph nodes as well as hot and/or blue sentinel nodes. Furthermore, inappropriate selection of patients for the sentinel node procedure can be avoided if in selected cases clinical examination of the axilla is completed with ultrasound and Fine Needle Aspiration.[18] This patient underwent an axillary dissection and radiotherapy. As systemic disease could not be proven at that time chemotherapy was not considered indicated. In the other two patients the axillary recurrence was observed after 30 and 51 months together with distant disease. Treatment focused mainly on the distant metastasis, therefore, the axillary recurrence had no clinical implications. The majority of events in our study are distant metastases without signs of local or regional recurrence (Table 3). The fact that these metastases occurred in patients with a tumour negative sentinel node signifies that tumour status of the sentinel node is not the only important factor predicting recurrence, but other prognostic factors need to be considered as well.

Data from the literature

The sentinel node biopsy has been accepted as a staging procedure only a few years ago, so no long-term data are currently available. In 2003, Veronesi et al.[17] published a randomised trial comparing patients undergoing a sentinel node biopsy followed by an axillary lymph node dissection with patients undergoing a sentinel node biopsy only followed by an axillary lymph dissection if the sentinel node contained metastatic cells. This latter group consisted of 167 sentinel node-negative patients. An update of this study was published in 2006.[5] After a median follow-up of 78 months one patient was diagnosed with an axillary recurrence, therefore, the axillary relapse rate was 0.6%. Naik et al. analyzed in an impressive single-centre study 4008 out of 6278 consecutive sentinel node procedures after a median follow-up of 31 months.[1] Final pathologic examination required serial sectioning and anti-cytokeratin staining. In 2340 patients with tumour-free sentinel nodes and no axillary lymph node dissection three axillary recurrences were

Table 2
Sentinel node procedure (*n* = 541)

Technique (%)	
Technetium	13 (2)
Patent blue	2 (1)
Combined	526 (97)
Dosage technetium (*n* = 539)	
One day protocol (*n* = 418)	
Mean (range)	74 Mbq (52−100)
Two-day protocol (*n* = 37)	
Mean (range)	208 Mbq (140−314)
Unknown (*n* = 84)	16%
Site of injection technetium (*n* = 539) (%)	
Peritumoral	502 (93)
Intratumoral	8 (1)
Subareolar	3 (1)
Unknown	26 (5)
Site of injection patent blue (*n* = 528) (%)	
Peritumoral	268 (51)
Intradermal	222 (42)
Subareolar	7 (1)
Unknown	31 (6)
Number of removed sentinel nodes	
Mean	1.6
Range	1−5
Number of removed remaining lymph nodes	
Mean	0.3
Ranges	0−3
Number of patients with micrometastasis (*n* = 38) (%)	
Adjuvant axillary dissection	18 (47)
Adjuvant radiotherapy	3 (8)
Both	1 (3)
No adjuvant therapy	16 (42)

observed: one as first event, one coincident with local relapse and one coincident with distant disease, at an axillary relapse rate of 0.1%. These results are achieved in renown centres. In our population based study after a median follow-up of 46 months an axillary recurrence rate of 0.6% was observed. Our results compared well.

Micrometastases and the risk of tumour in non-sentinel nodes

In our study the sentinel node of 38 patients contained micrometastases. In 18 of them an axillary dissection was performed, no positive lymph nodes were obtained. There is an ongoing debate concerning the clinical implications of micrometastases in the sentinel node. Many observational studies have been published but results do not justify uniform conclusions. In 1999, Chu et al. showed that if the sentinel node contained micrometastases there was a 6% chance that the remaining lymph nodes also contained metastases.[19] Others found comparable or higher figures.[8,20,21] No subgroup with regard to size and grade was identified that did not have non-sentinel lymph node metastases. In a large study Van Rijk et al. observed in a subgroup of patients that underwent an axillary clearance subsequent to micrometastasis in the sentinel node in 4% a macrometastasis in non-sentinel nodes.[9] However, in none of these patients this finding indicated additional treatment.

Recently, Noguchi reviewed the literature concerning management of the axilla after a tumour positive sentinel node. He concluded that for the group of patients with macrometastases as well as for the group with micrometastases in the sentinel node it is impossible to identify a subset of patients in whom axillary dissection can be omitted.[22] As there is no significant difference in the risk of metastases in non-sentinel nodes when comparing patients with isolated tumour cells in the sentinel node with those with true micrometastases, some investigators have argued for axillary clearance for patients with isolated tumour cells in the sentinel node as well.

Micrometastases and disease-free survival

In our study we observed a non-significantly different risk of distant disease in case of micrometastasis compared to a tumour negative sentinel node. However, the small number of patients might misrepresent this result. Bettelheim et al. performed serial sectioning of ipsilateral lymph nodes judged to be disease-free after routine histological examination.[23] Their study revealed micrometastases in 9% of 921 patients. These patients had a significantly poorer disease-free and overall survival of five years. Querzoli et al. also re-evaluated the lymph nodes of 377 patients without nodal disease by step-sectioning and immunohistochemistry, out of 702 with an eight year median follow-up.[10] Cumulative incidence curves for metastatic relapse were significantly different for patients with micrometastatic nodal disease compared to true tumour negative axillary status. Kahn et al. studied a cohort of 214 consecutive histologically node-negative breast cancer patients with a median follow-up of eight years.[11] Two 4 µm sections

Table 3
Patterns of relapse

SLN	Local recurrence (%)	Regional recurrence	Distant recurrence (%)	Combined local and regional (%)	Combined regional and distant
Negative (*n* = 503)	5 (1.0)	0	17 (3.4)	1 (0.2)	3 (0.6)
Micrometastasis (*n* = 38)	1 (2.6)	0	3 (7.9)	0	0

SLN: sentinel lymph node.

were cut from all the nodes in formalin-fixed paraffin-embedded blocks, one for H&E and one for anti-cytokeratin-8 staining. Twenty-seven patients had micrometastases and two had isolated tumor cells. Micrometastases were not significantly associated with disease-free or overall survival. There is a difference in the pathology protocol used in this study compared to the studies mentioned earlier that must be taken into account when comparing these studies. But the results of a recent prospective trial have demonstrated that micrometastases have no prognostic implication when there are no further signs of axillary metastases.[24] It appears that the observational studies present opposing results. Studies with cohorts of patients with longer follow-up often lack elaborate histological work-up and their results cannot easily be compared with present day cohorts with micrometastatic nodal disease.[25,26] At present several large prospective multicentre trials that address surgical and management aspects subsequent to sentinel node staging of breast cancer are ongoing.[27–29] It is expected that these studies will provide definitive answers with regard to the clinical relevance of nodal micrometastatic disease in breast cancer, their results must be awaited.

Conclusion

With our study we aimed to investigate the axillary recurrence rate in patients with a tumour negative sentinel node. The results are obtained after a period of midterm follow-up, this may pose a limitation to our study but studies that provided data after 4–5 years follow-up have shown that the majority of the axillary relapses occur within five years of the initial treatment.[30] An important feature of our study is its population-based design. In conclusion, our results show that the sentinel node procedure in the region Middle Netherlands is a reliable and accurate instrument for staging of patients with early breast cancer. Our results also reflect the current incomplete comprehension of the significance of micrometastatic nodal disease in breast cancer.

Conflict of interest

None declared.

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