Original article

Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection

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Background: The sentinel node biopsy technique for breast cancer has been validated extensively in phase I and II studies. However, no data from phase III randomized clinical studies are available. It remains controversial whether a histologically negative sentinel node biopsy without further axillary dissection can be considered to be good clinical practice.

Methods: One hundred consecutive patients with breast cancer who had a negative sentinel node biopsy without additional axillary dissection were studied prospectively between 1997 and 2000 in order to identify tumour recurrence and to assess the morbidity of the sentinel node procedure. Special attention was paid to axillary or locoregional recurrence, distant metastases and overall survival. One year after the procedure patients were sent a questionnaire to assess any functional impairment of the arm or shoulder.

Results: Median follow-up was 24 (range 16–40) months. One patient had an axillary relapse 14 months after the initial diagnosis of breast cancer. She died after 2 years from metastatic disease. There were no other local axillary recurrences. There was a 94 per cent response rate to the questionnaire. Twelve patients developed mild disabilities, of whom two said that they had to change their hobbies, sports or daily activities owing to the sentinel node procedure. No patient developed lymphoedema or needed physiotherapy after the operation.

Conclusion: When strict criteria for the sentinel node biopsy procedure are used, the sentinel node biopsy without further axillary dissection after a negative histological investigation is a safe procedure. It may therefore be considered to be the standard of care for the treatment of patients with breast cancer.

Paper accepted 13 August 2001 British Journal of Surgery 2001, **88,** 1639–1643

Introduction

In patients with operable primary breast cancer, complete axillary dissection is still considered to be the standard of surgical care. However, the minimally invasive sentinel node biopsy provides an attractive alternative to this procedure, because it reduces morbidity substantially. The main reason for performing a complete axillary dissection in breast cancer is for diagnostic purposes. When the axillary lymph nodes are positive for metastatic disease, adjuvant treatment is necessary, while the complete removal of nodal metastases might be therapeutic and contribute to the surgical cure of the patient. Where axillary nodes are negative, the additional value of a complete dissection of all nodal levels is questioned. Such patients are very unlikely to benefit from complete removal of the axillary lymph nodes.

Until now the sentinel node biopsy *only* (no additional axillary dissection if the sentinel node is negative for metastatic disease) has been a matter of debate and some authors are opposed to this procedure as the standard of care[1,2]. Their main concern relates to false-negative sentinel node biopsies and their consequences.

The present study provides data about the quality control and regular follow-up of 100 consecutive patients who underwent a sentinel node biopsy as a sole procedure and who did not have an additional complete axillary dissection.

Patients and methods

From the end of 1997 until June 2000, one hundred consecutive patients with operable primary breast cancer, who underwent a sentinel node biopsy that revealed a negative histological status, were studied prospectively.

Sentinel node biopsy was performed according to a protocol that included only patients with single tumours less than 3 cm in diameter, without clinically suspicious palpable axillary nodes and without clinical signs of distant metastases. Patients were informed about the risk and the technique, after which informed consent was obtained. During the interval in question, 143 patients underwent a sentinel node biopsy of which 43 (30 per cent) were found to be positive.

The biopsy technique has been described previously and includes the use of peritumourally injected technetium-labelled human albumin (Solco R/Nanocoll; Sorin Biomedica Diagnostics, Vercelli, Italy) with lymphoscintigraphy, together with periareolar injection of vital blue dye (Patent Blue V, 2·5 per cent solution; Laboratoire Guerbet, Aulnay-sous-Bois, France)[3,4]. The sensitivity of this procedure was 95 per cent[3]. Harvested sentinel nodes were sectioned serially: small nodes (less than 4 mm) at three levels and larger nodes at six levels. The slides were then stained with haematoxylin and eosin and immunostained with Pan Ab-3 anticytokeratin (Neomarkers, Fremont, California, USA). In the case of a positive sentinel node, patients were offered a complete axillary lymph node dissection. All patients were seen at follow-up after 3 months and subsequently every 6 months. Special attention was paid to possible axillary recurrent disease, locoregional recurrences, distant metastases and new breast cancers.

All patients without recurrent disease or distant metastases were asked to complete a questionnaire assessing postoperative functional disability of the arm and shoulder (*Table 1*). The questionnaires were sent to all patients at least 12 months after the primary surgical procedure.

Table 1 Questionnaire responses

		No. of affirmative responses
1	Do you have any discomfort as a result of the axillary scar?	5 (6)
2	Has the function of your shoulder and/or arm changed since the axillary operation?	10 (11)
3	Did you develop a disability in your arm after the axillary operation?	9 (10)
4	Do you have any (new) pain in the axilla or shoulder since the operation?	12 (13)
5	Did you develop any form of lymphoedema?	0 (0)
6	Has there been a change or loss of sensation in the axilla?	12 (13)
7	Did you have to change your hobbies or sports:	
	Due to the operation in the axilla?	2 (2)
	Due to the breast operation?	10 (11)
8	Was there a need for physical therapy as a result of the axillary operation?	0 (0)

Values in parentheses are percentages. The questionnaire was sent to all patients without (axillary) recurrence or distant metastases (n = 96; response rate 94 per cent (90 of 96))

Results

Table 2 shows the initial patient and tumour characteristics of the negative sentinel node biopsy population without further axillary dissection between 1997 and 2000. Median follow-up was 24 (range 16–40) months. During this period, 99 of the 100 patients did not develop a local axillary relapse.

However, one 46-year-old patient was found to have residual axillary disease at 14 months after the initial sentinel node procedure. An excisional biopsy was performed in June 1998, and an invasive ductal carcinoma grade II with a diameter of 8 mm was diagnosed. The

Table 2 Demographic data of 100 patients with a negative sentinel node biopsy

Age (years)*	59 (33–86)
Menopausal status	
Premenopausal	33
Postmenopausal	66
Male gender	1
Type of surgery	
Ablation	20
Breast conserving†	80
Tumour size (mm)*	15 (3–31)
Histological grade	
I	42
II	23
III	35
Histology of tumour	
Ductal	74
Lobular	16
Mixed or other	10
Receptor status	
Oestrogen receptor positive	73
Progesterone receptor positive	65
Unknown	9
Adjuvant therapy	
Chemotherapy	13
Hormonal therapy	39
Recurrent disease	
Axilla	1
Breast/scar	1
Metastatic disease	
Bone	1
Lung	1
Lung, bone and brain	1
Deaths	
Stroke	1
Metastatic disease	2

*Values are median (range). †All patients received radiotherapy of the breast; no radiotherapy of the axilla was given. Mean and median number of sentinel node biopsies per patient was 2 (range 1–4)

patient then had a sentinel node biopsy (one sentinel node) together with a re-excision of the primary tumour because of a residual ductal carcinoma *in situ*. In September 1998 an additional mastectomy with primary reconstruction using the expander technique was performed. One year later the patient presented with axillary pain and a palpable lesion. A complete axillary dissection showed more than ten positive lymph nodes. Locoregional radiotherapy and hormonal treatment (ovariectomy as well as tamoxifen) was started, but within 2 months the patient developed recurrent disease with pulmonary and bone metastases. In August 2000, 26 months after the initial diagnosis, she died from brain metastases.

Another patient, aged 44 years, developed a local recurrence in the skin 9 months after the initial operation, which was a two-stage mastectomy for widespread invasive lobular carcinoma. At that time, no axillary recurrence was found. She was treated with tamoxifen, leading to a partial remission. Four months later a right colectomy was performed because of an invasive colon carcinoma (pT_2 N_0 M_x). Two months after the colectomy, there was an increase in the local mammary skin recurrence and a clinically suspected and pathologically confirmed axillary lymph node had developed. Locoregional radiotherapy was instigated.

In all, three patients have died: the abovementioned 46-year-old patient from metastatic disease, another 80-year-old patient with bone metastases but without signs of locoregional recurrence, and one 63-year-old patient from a stroke.

Of the 96 patients surviving without residual or recurrent axillary disease, 90 returned the questionnaire (94 per cent response rate). *Table 1* shows the responses. Only a minority of the patients complained of mild functional loss or pain in the shoulder or arm. Remarkably none of the patients developed any form of arm oedema or needed additional physiotherapy because of shoulder complaints. Twelve patients experienced some loss of sensation in the axilla, most probably owing to a lesion of the intercostobrachial nerve.

Discussion

The main purpose of a sentinel node biopsy is to avoid an unnecessary axillary dissection and thus to prevent iatrogenic morbidity. The main criticism of this procedure concerns the consequences of a false-negative biopsy. To date, no randomized controlled phase III clinical trials have been published, while multicentre studies evaluating the method's accuracy compared with complete axillary dissection are still in progress. There is extensive literature available on phase I–II studies that has confirmed the accuracy, feasibility and reliability of the sentinel node procedure[5,6]. There is now a need for quality control and long-term follow-up studies to provide data supporting the sentinel node procedure as an accurate staging method. To date, there are only two studies providing data on patients who had a sentinel lymph node dissection as a sole procedure[7,8]. Both studies, one with a median follow-up of 39 months and the other with less than 2 years' median follow-up, showed no local axillary recurrence in 67 and 285 patients respectively[7,8]. The present series confirms these results.

In their meta-analysis Fraile *et al.*[5] concluded that 'due to limitations of axillary lymph node dissection as the golden standard, sentinel node biopsy can in fact be considered a more accurate method for nodal staging'. Based on extensive reviews and meta-analyses of most of the existing phase I and II studies, the false-negative rate of the sentinel node biopsy (including completion axillary dissection) in breast cancer has been shown to vary between 0 and 17 per cent, with a mean of 8–9 (95 per cent confidence interval 7–11) per cent[5,6].

The sensitivity for the present patient population should have been least as high as a previously shown value of 95 per cent[3] because of the authors' tendency to perform an ultrasonographic investigation (with fine-needle aspiration) of the axilla when there are palpable axillary nodes[9]. By this means, patients with positive axillary nodes are selected who can be excluded from the sentinel node biopsy procedure. This policy, incorporated in 1998, may reduce the false-negative rate and could be the reason why in the present series of 143 patients the positive nodal rate (30 per cent) was less than that published previously (37 per cent)[3].

A 95 per cent sensitivity of the sentinel node procedure means that the expected number of patients with residual nodal involvement after a negative sentinel node biopsy without further axillary dissection is 3 per cent, when the a priori chance of a positive node is 40 per cent. Considering 1000 patients with breast cancer, 400 patients will be truly node positive while 600 will be truly node negative. Assuming a 95 per cent sensitivity, 20 of the 400 patients will not be discovered as being node positive and will wrongly be put in the group of 600 true-negative patients. Thus, of the 620 sentinel node-negative patients, 20 will be falsely negative. Therefore, with a sensitivity of 95 per cent, only 3 per cent (20 of 620) of the patients thought to be negative are truly node positive. When the a priori number of true node-positive patients is smaller, then the number of false negatives will also be smaller.

The present study shows that, after a median follow-up of 24 months, only one patient had axillary residual nodal disease, although this case had a disastrous outcome. Recently, de Boer *et al.*[10] showed that axillary recurrence

after complete axillary dissection for invasive breast cancer occurred in 59 (1 per cent) of 4669 patients at a median interval of 2·6 years. From the NSABP-04 study it is known that three-quarters of patients with breast cancer develop their axillary recurrence within 2 years[11].

Based on the calculations above, approximately three of the 100 patients would be expected to become positive for axillary residual disease at some time. Fortunately, the present data are better than expected. This may be due to adjuvant treatment, which was given to half of the patients (n = 52) based on tumour-related factors according to recent guidelines[12,13], because of the policy of detection of positive axillary nodes by ultrasonography and fine-needle aspiration, or simply because the follow-up period is still too short.

On the other hand, from previous studies it is known that about 20 per cent of patients with breast cancer who receive no treatment of the axilla will develop an axillary relapse[11]. When the incidence of true-positive axillary nodal metastases is about 40 per cent, why then is the relapse rate only 20 per cent after even 10 years of follow-up? Possible explanations for this include the role of the biological behaviour of the tumour, the systemic adjuvant treatment given, the type of surgery and (local) breast radiation[2,7].

The patient questionnaire showed that the morbidity of the sentinel node biopsy procedure is minor. Only a few patients described pain in the axillary scar, or numbness or paraesthesia of the skin. None of the patients developed oedema and only two patients responded that they had to change their hobbies or sports because of the operation in the axilla. After a complete axillary dissection, 30 per cent of patients have some kind of disabling pain, 10–30 per cent develop arm oedema, up to 70 per cent have numbness and 30 per cent have some form of functional impairment[14–16]. In a recent study it was shown that more than 30 per cent of the patients needed physiotherapy after the axillary operation compared with none in the present group[17].

The key question that remains is whether or not it is acceptable to have one fatal recurrence of local axillary disease while avoiding 99 unnecessary axillary dissections. Reflecting on this, one should keep in mind the indications for adjuvant chemotherapy according to recent guidelines: a given therapy with its morbidity should be advised only when an absolute 10-year survival benefit of 5 per cent can be gained[12,13]. Implicitly, this means that it is thought acceptable not to treat 96 patients unnecessarily with chemotherapy if there are four or fewer 10-year survivors to be gained.

It is concluded that when strict criteria for the sentinel node procedure are adhered to, a negative histopathological sentinel node biopsy without further axillary dissection is a correct part of good clinical practice in the treatment of patients with breast cancer and may thus be considered to be the standard of care.

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