



## Sentinel node biopsy for breast cancer may have little to offer four-node-samplers: results of a prospective comparison study

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### Abstract

The aims of the study were to determine how often four node axillary sampling (4NAS) encompasses the sentinel node (SN) and to compare the relative sensitivity of 4NAS with sentinel node biopsy (SNB) for axillary node staging. 200 patients with breast cancer were preoperatively injected with 27 MBq 99m-Tc-labelled colloid adjacent to the tumour. At operation, standard 4NAS was performed. Each node was counted *ex vivo* using a probe. A search was then made to find a node with higher counts *in vivo* directed by the probe. If found, it was excised. Each node was submitted separately to pathology. A SN was identified in 191 patients (96%). The SN was contained in the 4NAS in 153 patients (80%) and identified separately in 38 patients (20%). Of 60 node-positive patients, 49 were positive by 4NAS and SNB, the SN was not identified in 2 and in 8 the SN was falsely negative compared with 4NAS. For 1 patient, the SN was positive and the 4NAS negative. SNB performed using radiolabelled colloid has no advantage over 4NAS when nodes are assessed by standard histological technique. © 2001 Elsevier Science Ltd. All rights reserved.

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### 1. Introduction

The technique of sentinel node biopsy (SNB) for staging regional lymph nodes has recently been applied to breast cancer and has received a great deal of publicity. Press releases have heralded the dawn of this “remarkable new technology” [1] and publications on the subject have increased exponentially (this includes two books [2,3]). Whole sessions at international meetings on breast disease are now given over to the SNB [4,5], many teaching courses and conferences devoted solely to SNB have been established and large multicentre trials have been organised. Reputations are being made. No doubt there will shortly be a sentinel node society (if one does not already exist). What then is the justification for all this attention and why has so much energy been focused on this subject?

Axillary lymph node status is a powerful determinant of prognosis and is necessary to define optimum

regional and systemic treatment strategies. Axillary node staging therefore has an essential role in the management of primary invasive breast cancer. Unfortunately, axillary node clearance (ANC), while able to accurately determine node status, is associated with significant morbidity [6,7] and for most patients it will merely confirm that they are node-negative. Several studies validating SNB as an alternative to ANC have been performed and reviewed [8,9]. The majority has found the sensitivity of SNB to be in excess of 90% compared with ANC. SNB is thus proposed as a less invasive and less morbid staging technique and some surgeons have already accepted it as their staging modality.

SNB is an intuitively attractive concept which relies upon identifying the route of lymphatic drainage from the tumour site and targets the first node (or nodes) to be encountered along this path. The means of achieving this are either injection of a blue dye or a radiolabelled colloid around the tumour. The sentinel node (SN) is then identified visually or with the aid of a directional gamma probe. Good results have been reported using each agent individually [10,11] or in combination [12].

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Four-node axillary sampling (4NAS) adds little if any morbidity to the treatment of the primary tumour and no additional cost (unlike SNB). The technique was pioneered in the Edinburgh breast unit and relies on the theory that involved axillary nodes are the ones most likely to be palpable intra-operatively. The lower axilla is mobilised and four nodes are individually identified. This staging modality has been subjected to two randomised trials comparing it with ANC in terms of morbidity, recurrence and mortality [13,14]. These have shown that 4NAS (followed by radiotherapy in node-positive patients) is associated with lower overall morbidity and has equivalent recurrence rates and mortality to ANC.

This study was designed to directly compare SNB with 4NAS and determine their relative sensitivity for axillary node staging.

## 2. Patients

The study population consists of 200 consecutive consenting patients undergoing surgery (mastectomy or wide local excision) for primary invasive breast cancer. All were clinically node negative (T1–2, N0, M0) and had a preoperative diagnosis of invasive breast cancer confirmed by core biopsy or fine needle cytology. All patients presented to and were treated at the Nottingham City Hospital Breast Unit between January 1998 and October 1999.

## 3. Methods

Patients were preoperatively injected with 27 MBq 99m-Tc-labelled colloid (Nanocoll, Amersham Health-care Ltd, Buckinghamshire, UK) in 0.3 ml immediately adjacent to the tumour. The median interval between injection and surgery was 3 h (range: 20 min to 18 h) and preoperative scintigraphy was performed to confirm sentinel node location for the first 15 patients. The policy for managing regional nodes at the Nottingham Breast Unit is shown in Fig. 1. At operation, a standard 4NAS was performed following either wide local excision or mastectomy; through a small incision, accurate dissection of the lower axilla is performed between serratus anterior and the lateral border of latissimus dorsi. The lower axillary contents are then palpated and the four nodes thought most likely to be metastatic are individually dissected free. Rarely, a suspicious node palpable higher in the axilla may also be excised. Node-positive patients were treated by delayed ANC or by axillary radiotherapy according to our protocol (Fig. 1). Internal mammary node biopsy was performed for medial cancers. Each node in the 4NAS (and the internal mammary node if biopsied) was counted *ex vivo*

using a directional gamma-detecting probe (c-Trak, Care Wise Medical, CA, USA). A careful search was then made to find a node with a higher count or an additional SN *in vivo* directed by the probe. If such a node (or nodes) was found it was excised as an additional node. Each lymph node was sliced after fixation at 3–5 mm intervals perpendicular to the long axis. All slices were embedded in one or more paraffin blocks and examined by routine haematoxylin and eosin stained sections. The SN was defined as the ‘hottest’ node and any nodes at least 25% as the ‘hottest’ node with at least 25 counts per 10 s were also classified as sentinel.

## 4. Results

In total, 297 SNs were identified in 191 patients (mean = 1.5 per patient) (range: 1–3). No SN could be found for 9 patients (5%). All SNs were excised as part of the 4NAS (or internal mammary node biopsy) in 80% of patients (153/191). In 20% of patients (38/191) one or more SNs were found in the axilla after performing the 4NAS.

Overall, 60 patients were node-positive (30%). 2 of the 9 patients for whom a SN could not be identified were node-positive. For 8 patients the SN was falsely negative compared with 4NAS (8/57 = 14%). For 1

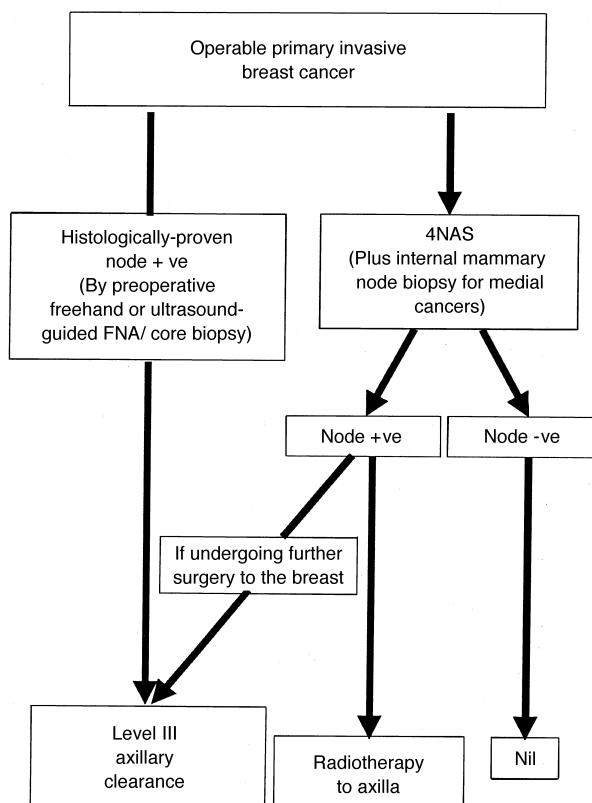


Fig. 1. Protocol for managing regional nodes at the Nottingham Breast Unit. FNA, fine needle aspiration.

Table 1  
Nodal status of 4NAS compared to SN

All SNs excised as part of 4NAS			SN
	+ ve	- ve	
4NAS	+ ve	41	8
	- ve	0	104
All SNs not excised as part of 4NAS			SN
	+ ve	- ve	
4NAS	+ ve	8	0
	- ve	1	29
SN not identified			
4NAS	+ ve	2	
	- ve	7	

SN, sentinel node; 4NAS, four node axillary sampling.

patient, the 4NAS was falsely negative compared with SNB (1/50 = 2%). Table 1 illustrates the breakdown of nodal status. The rate of node positivity was 32% for those patients in whom all SNs were excised as part of the 4NAS and 24% for those in whom a SN was found in the axilla after the 4NAS had been performed ( $P=0.32$ , Chi-squared, relative risk (RR)=1.35, 95% confidence interval (CI)=0.73–2.50). In the latter group, all except one patient had two or more positive nodes (the SN and one or more nodes in the 4NAS).

The 4NAS contained four nodes in 190/200 patients (95%) and less than four nodes in the remainder. An additional node (or nodes) was excised in 77 patients for assessment as a potential SN and in 5 cases the SN was an internal mammary node.

Overall in this study, 10 patients would have been understaged by SNB (17%, 8 false-negative and 2 in whom a SN was not found) and 1 patient would have been understaged by 4NAS (2%) if either technique had been used in isolation.

The pathological staging of patients in this study is detailed in Table 2.

## 5. Discussion

This study suggests that SNB is unlikely to be of value in the discrimination of lymph node status to surgeons

who perform 4NAS. One might even suggest that SNB is an over-elaboration of a rather simple plot. Both of these statements are likely to provoke heated debate as the surgical management of the axilla has long (too long) been a topic guaranteed to incite argument among breast surgeons. While few would contest that full axillary node clearance gives the maximum information on lymph node status, this procedure has not been shown to influence survival [15] and is associated with a definite and significant morbidity [6,7]. However, surgical staging of the axilla remains mandatory for all patients with operable invasive breast cancer.

As patients tend to present earlier, the pathological size of operable primary breast cancers is becoming smaller (mean diameter currently 17 mm in the Nottingham Breast Unit). As a direct consequence, the incidence of node positivity is also in decline. To practice full axillary node clearance for all patients and subject the large majority of these to an unnecessary intervention is unacceptable, hence the enthusiasm with which less invasive staging techniques have been embraced. 4NAS is the only such technique to have been subject to randomised trial and for which long-term outcome has been assessed [13,14]. It is commonly practised in the UK and among surgeons treating screen-detected cancers 4NAS is the preferred staging modality for 39% [16]. The technique is distinguished from lower axillary clearance or other forms of node sampling. The definition of 4NAS (see Methods) is important, as those who malign sampling have generally based their opinion on studies using ill-defined surgical technique or lower axillary clearance [17,18].

With long-term follow-up, two randomised trials have shown no difference between 4NAS (with axillary radiotherapy to node-positive patients) and ANC in terms of recurrence or mortality [13,14]. Morbidity has also been assessed. In the initial trial, which compared 4NAS with ANC after mastectomy, morbidity was assessed in a small sample of patients and was reported as being higher in the 4NAS plus radiotherapy group [19]. However, in the second trial, which compared 4NAS and ANC after breast conserving surgery, a detailed prospective assessment of morbidity was performed using objective and subjective methods

Table 2  
Tumour size, grade and number of positive nodes

	Mean tumour diameter (mm)	Grade			Positive nodes				
		1	2	3	0	1	2	3	4
All patients (200)	19.6 (range: 3–52 mm)	32	70	98	140	28	13	6	13
SN not detected (9)	20.1 (range: 3–35 mm)	2	3	4	7	0	0	0	2
SN false-negative (8)	16.8 (range: 4–29 mm)	2	1	5	0	8	0	0	0
4NAS false-negative (1)	24	0	1	0	0	1	0	0	0

SN, sentinel node; 4NAS, four node axillary sampling.

[14]. This showed that patients treated by 4NAS alone had only a very minor degree of morbidity, which resolved within 6 months. ANC was associated with significantly worse arm swelling which did not improve with time and patients treated by ANC or 4NAS plus radiotherapy had a measurable reduction in shoulder movement and power which in time returned to normal.

This study is the first, to our knowledge, which directly compares SNB with 4NAS. Another study has compared SNB using the blue dye technique with a sampling procedure performed on the ANC specimen *ex vivo* [20]. Nodes were sampled from the ANC specimen in order of their likelihood for harbouring metastases as judged by palpation. The sentinel node was one of the first four such nodes in 86% of cases (compared with 80% contained in the 4NAS in our study). The accuracy of four sampled nodes and the sentinel node for predicting lymph node positivity was 96% and 95%, respectively, compared with ANC.

In our study, the radiolabelled colloid technique was chosen so that the surgeon would be blinded to the SN while performing 4NAS. For this reason, blue dye was also not used. A SN was found in 96% of patients and its sensitivity for predicting axillary node positivity (as defined by 4NAS) was 86%. This is comparable with other studies using radiolabelled colloid [21]. Lymphoscintigraphy was discontinued as it was felt to be an unnecessary procedure. A large, recently published study has supported this view [22]. In addition, lymphoscintigraphy is impractical in a unit such as ours where the large majority of patients are admitted on the day of surgery.

Several validation studies have been published comparing SNB with axillary clearance. In nearly all there has been a percentage of patients in whom a SN could not be identified and a percentage in which the SN was falsely negative. All studies need to be interpreted carefully in this regard, as failure to identify a SN in a node-positive patient is a failure of the technique. This is often not included when sensitivity is calculated. In addition, false-negative rates must be reported as a percentage of the total number of node-positive patients, not all patients. There is also no recognised standard technique for SNB. Timing of injection, amount of radioactivity and use of preoperative scintigraphy are variable parameters in most studies. Indeed the definition of a SN is itself open to debate. While the 'hottest' node may be easy to define, the classification of additional nodes as sentinel differs markedly. The reported mean number of sentinel nodes per patient varies from 1.4 to 3.1 [11,23]. Some studies identify up to eight SNs in one patient [24]. This must inevitably involve considerable axillary dissection, which if radiotherapy is subsequently given may predispose to lymphoedema.

Other criticisms can be levelled at SNB. For instance, it does not by itself give sufficient prognostic information. Patients with four or more nodes involved have a worse prognosis than those with one–three nodes involved [25]. Patients who have a positive SNB would require a second procedure (ANC) to obtain sufficient prognostic information. Apart from the cost and psychological implications, this procedure will be unnecessary in the 38–67% of women who have only one positive node [10,11]. Some series aimed at validating SNB report a 42–53% incidence of node positivity [11,24]. While this may be the overall incidence in some parts of the world, even then it should not be necessary to use a surgical procedure to determine node status for all these patients. For example, a recent multicentre study demonstrated that 36% of node-positive patients (17% of all patients) could be staged preoperatively by ultrasound-guided fine needle aspiration (FNA) of nodes [26]. The use of a similar procedure excluded some patients who were lymph node-positive from our series (Fig. 1), which played some part in the relatively low rate of node positivity (30%) among patients in this study. Breast units preparing to invest in SNB may be better advised to consider preoperative diagnostic techniques.

This study suggests that SNB performed using radiolabelled colloid has little to offer surgeons who perform 4NAS. Even as an adjunct to 4NAS the very slight increase in yield of node positivity (one patient in this study) is unlikely to justify its use. Not assessed in this study is the blue dye technique (alone or in combination with radiolabelled colloid) and whether the SN is more likely to contain micrometastases. These areas are the subjects of further studies by our group and others. We acknowledge that SNB is still in the early stages of refinement and that it may evolve into a more accurate and clinically useful staging procedure. The debate surrounding SNB may also help convince those surgeons who currently perform ANC for all patients that their practice is outmoded [27]. However, the resources and effort currently being allocated to SNB may be more productively spent in other aspects of breast cancer care.

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