

# Non-sentinel lymph node involvement in patients with breast cancer and sentinel node micrometastasis; too early to abandon axillary clearance

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**Aims:** It has been suggested that patients with T1–2 breast tumours and sentinel node (SLN) micrometastases, defined as foci of tumour cells smaller than 2 mm, may be spared completion axillary lymph node dissection because of the low incidence of further metastatic disease. To gain insight into the extent of non-sentinel lymph node (n-SLN) involvement, SLNs and complementary axillary clearance specimens in patients with SLN micrometastases were examined.

**Methods:** A set of 32 patients with SLN micrometastases was selected on the basis of pathology reports and review of SLNs. Five hundred and thirteen n-SLNs from the axillary clearance specimens were serially sectioned and analysed by means of immunohistochemistry for metastatic disease. Lymph node metastases were grouped as macrometastases (> 2 mm), and micrometastases (< 2 mm), and further subdivided as isolated tumour cells (ITCs) or clusters.

**Results:** In 11 of 32 patients, one or more n-SLN was involved. Grade 3 tumours and tumours > 2 cm (T2–3 v T1) were significantly associated with n-SLN micrometastases as clusters (grade: odds ratio (OR), 8.3; 95% confidence interval (CI), 1.4 to 50.0; size: T2–3 tumours v T1: OR, 15; 95% CI, 2.18 to 103.0). However, no subgroup of tumours with regard to size and grade was identified that did not have n-SLN metastases.

**Conclusions:** In patients with breast cancer and SLN micrometastases, n-SLN involvement is relatively common. The incidence of metastatic clusters in n-SLN is greatly increased in patients with T2–3 tumours and grade 3 tumours. Therefore, axillary lymph node dissection is especially warranted in these patients. However, because n-SLN metastases also occur in T1 and low grade tumours, even these should be subjected to routine axillary dissection to achieve local control.

The sentinel node procedure was pioneered for penile carcinoma.<sup>1</sup> In recent years, it has been introduced for breast cancer, where its main purpose is to gain insight into the status of the axillary basin for the presence of metastatic disease.<sup>2,3</sup> Axillary clearance with its associated morbidity can be avoided if metastatic disease in the SLN cannot be proved. To rely on the SLN procedure in guiding patient management, it is essential that it be thoroughly investigated. Many studies have clearly shown that more sensitive techniques such as serial sectioning, the use of immunohistochemistry, and molecular techniques (such as reverse transcription polymerase chain reaction) dramatically increase the detection rate of metastatic disease in lymph nodes.<sup>4–10</sup> A direct consequence of this enhanced sensitivity is the observed increased incidence of micrometastatic and "occult" disease. Although not all studies agree on this, several papers showed a survival disadvantage for patients with micrometastatic disease.<sup>6, 11–13</sup>

In addition to its application as a staging procedure in guiding further treatment, it has been suggested that the SLN procedure may in certain circumstances serve a secondary function as a means of local disease control by removing metastatic disease.<sup>14, 15</sup> In this setting, it is assumed that the SLN has effectively filtered out early metastatic disease before tumour microemboli have had the chance to spread beyond the initial lymph node. Furthermore, it is assumed by some that certain forms of micrometastatic disease, such as isolated tumour cells, may not have the potential for outgrowth.<sup>4, 16</sup> Accepting these hypotheses implies that metastatic disease in n-SLNs should only rarely be found in cases with SLN micrometas-

tases. To test these assumptions we examined the n-SLNs of patients with micrometastatic SLN disease.

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## METHODS

Identification of the sentinel node was performed by peritumoral injection of 40 MBq (99m)Tc radiolabelled nanocolloid at least 2.5 hours before surgery and intradermal injection of 0.5 ml patent blue dye during surgery. The sentinel node was identified with the guidance of the RMD-CTC4 probe (Radiation Monitoring Devices, Watertown, Maine, USA), aided by visual identification of the blue stained vessel, and was removed under general anaesthesia. After frozen section analysis (superficial level of one half of a bisected lymph node), the remaining SLN tissue was formalin fixed and paraffin wax embedded. Large nodes were trimmed down into smaller pieces and submitted in toto for histology. Sections were cut at four 250 µm intervals with parallel haematoxylin and eosin (H&E) and immunohistochemical (IHC) staining with anticytokeratin antibodies.

**Abbreviations:** CI, confidence interval; H&E, haematoxylin and eosin; IHC, immunohistochemistry; ITC, isolated tumour cell; LN, lymph node; n-SLN, non-sentinel lymph node; OR, odds ratio; SLN, sentinel lymph node

**Table 1** Tumour characteristics of patient set

	Positive n-SLN	Negative n-SLN
No. of patients (%)	11 (34)	21 (66)
Primary tumour		
Ductal	10	17
Lobular	1	4
Size (mm)	26.1 (median, 21)	14.7 (median, 12)
T1	3	19
T2	6	2
T3	2	0
Grade (Bloom and Richardson)		
I	2	5
II	4	12
III	5	4

n-SLN, non-sentinel lymph node.

On the basis of pathology reports, 40 patients were identified who had an SLN micrometastasis. The SLNs and primary tumours of these patients were reviewed. Grading of the primary tumours was performed according to the modified Bloom and Richardson criteria.<sup>17</sup> The sizes of the SLN and n-SLN micrometastases were measured on the microscope stage using the Vernier scale; in equivocal cases, a digital image was acquired and measurements were made using an image analysis application (AutoCyte Link; TriPath Imaging Inc, Burlington, North Carolina, USA). Metastases were divided into three groups, namely: metastases larger than 2 mm (macrometastases); micrometastases (< 2 mm) consisting of groups of four or more cells in close approximation, termed clusters; and micrometastases consisting of isolated single tumour cells or small collections of up to three tumour cells together, designated as isolated tumour cells (ITCs).<sup>16</sup> When multiple micrometastases were present in a single node, the largest metastasis was measured. The sizes of individual metastases were not added together. After reviewing the SLNs, eight patients were excluded from our study (in seven patients the metastasis was over 2 mm in size, one patient did not proceed to axillary node dissection). The remaining 32 patients formed the basis of our study. From these patients, all n-SLNs were cut at 250 µm intervals through the paraffin wax block, resulting in three to 10 additional sections for each block. The sections were immunostained with anticytokeratin antibody CAM 5.2 (Becton Dickinson, Mountain View, California, USA) using a standard peroxidase-anti-peroxidase procedure in an automated immunostainer (Mark V; DPC, Los Angeles, California, USA). Appropriate positive and negative controls were incorporated in each run of the immunostainer. In equivocal cases, H&E stained sections were prepared from retained ribbons for comparison. The presence of micrometas-

tases was scored and compared with the tumour parameters size and grade using the statistical package SPSS for Windows release 10.05 (SPSS Inc, Chicago, Illinois, USA).

## RESULTS

Thirty two patients with breast cancer were identified with a SLN micrometastasis. Forty five SLNs were derived from these patients, ranging from one to four lymph nodes (LNs)/patient (median, one). The primary tumours were 27 ductal type adenocarcinomas "not otherwise specified" and five lobular carcinomas (table 1). Mean tumour size was 19 mm (range, 6–55 mm). The axillary clearances yielded 513 LNs (range, 3–28; median, 14). Because of the poor clinical condition of one patient, only a limited (level 1) LN dissection was performed, yielding four LNs. Metastases in n-SLNs were identified in 24 of 513 LNs (4.7%) from the axilla of 11 of 32 patients, five of whom had initially been diagnosed as not having n-SLN metastases ("occult metastases") (table 2). In addition to eight identified involved n-SLNs in the original reports, 16 extra involved n-SLNs were documented after serial sectioning and IHC. In two patients a macrometastasis was found. Three patients had ITCs only, two patients only had clusters (including one patient with a macrometastasis), and six patients had ITCs and clusters (including one patient with a macrometastasis). The number of involved n-SLNs ranged from one to four (median, two). Within the group of 11 patients with n-SLN micrometastases, 10 carcinomas were of the ductal type and the 11th case was a lobular carcinoma. The mean tumour size in this group was 26.1 mm (range, 12–55). Two of the carcinomas in this group were multifocal (multiple non-continuous foci of invasive carcinoma, not necessarily confined to one quadrant). In the group of 21 patients without n-SLN micrometastases, the mean tumour size was 14.7 mm (range, 6–35), 17 carcinomas were of the ductal type and four tumours were lobular carcinomas. In this group of patients, two patients had only ITCs in the SLN, two patients had ITCs and clusters, and the remaining 17 patients had clusters.

The average tumour size was significantly larger in patients with involved n-SLNs than in those without n-SLN metastases (26.1 mm (SD, 14.3) v 14.7 mm (SD, 7.2); *t* test, *t* = 2.474 (unequal variance); *p* = 0.028). The presence and type of metastasis (ITC v cluster) of n-SLN metastases was analysed with respect to tumour size and grade by calculating relative odds (odds ratio; OR). A significantly greater risk of positive n-SLNs with clusters was found for high grade tumours (OR, 8.3; 95% confidence interval (CI), 1.4 to 50.0). The odds of n-SLN metastases as clusters were significantly greater for carcinomas > 2 cm (OR, 15; 95% CI, 2.18 to 103.0).

**Table 2** Characteristics of tumours and results in 11 patients with n-SLN involvement

Patient	No. of SLNs (pattern of involvement)	No. of n-SLNs	Pattern of n-SLN involvement (n)	Tumour type	Size (mm)	Grade (B&R)
1	2 (SLN1 and SLN2 ITC)	19	ITC+ cluster (4)‡	Ductal	25	3
2	2 (SLN1 ITC+ cluster, SLN2-)	13	ITC (1)	Lobular	50	1
3	1 (cluster)	8	Cluster* (3)‡	Ductal	12	1
4	1 (cluster)	22	Cluster (1)	Ductal	21	3
5	1 (cluster)	10	ITC (1)‡	Ductal	17	2
6	1 (cluster)	11	Cluster* (2)	Ductal	26	2
7	1 (cluster)	15	Cluster† + ITC (4)	Ductal	30	3
8	3 (SLN1 cluster, SLN2 and SLN3-)	4	Cluster (2)	Ductal	20	3
9	1 (cluster)	22	Cluster† (3)	Ductal	21	2
10	1 (cluster)	10	ITC (1)‡	Ductal	55	2
11	1 (ITC+ cluster)	28	Cluster (2)‡	Ductal	10	3

\*n-SLN micrometastasis larger than SLN metastasis; †n-SLN macrometastasis; ‡negative n-SLN status in original report.  
B&R, Bloom and Richardson; ITC, isolated tumour cell; nSLN, non-sentinel lymph node; SLN, sentinel lymph node.

## DISCUSSION

The question arises whether the presence of microscopic tumour deposits in the SLN justifies complete axillary clearance and adjuvant treatment. It may be argued that for staging purposes the object has been achieved by finding metastatic disease in the SLN and that further involved nodes are unlikely to be found. Moreover, the view may be taken that removing an SLN with micrometastatic disease constitutes adequate local control and that axillary clearance is not justified in these cases. Accepting this perspective implies that either metastatic deposits in n-SLNs are highly unlikely or that even if further micrometastatic deposits in n-SLNs are present these will not result in locoregional disease.

To gain insight into possible metastatic disease in the remaining (non-sentinel) axillary LNs we performed serial sectioning with IHC on the n-SLNs of 32 patients with SLN micrometastases. Metastases were grouped as macrometastases (> 2 mm) and as micrometastases (< 2 mm). Micrometastases were further subdivided into "clusters" (four or more cells together) and isolated tumour cells (single cells and groups of up to three cells together). We found that in 11 of 32 patients metastatic disease was present in non-sentinel nodes from the axilla, whereas in seven patients more than one node was involved and in four patients the n-SLN metastasis was larger than the SLN metastasis (including two patients with n-SLN macrometastases). It is possible that erroneous SLN identification had occurred in the patients with macrometastases. Nevertheless, excluding these two patients does not significantly detract from our observation that n-SLN involvement is not uncommon when sensitive techniques are used. Large n-SLN metastases in micrometastatic SLN involvement have been noted previously, including n-SLN metastasis in cases with single cells in the SLN.<sup>7</sup>

"On the basis of our findings and the literature data, we find it premature to conclude that axillary dissection may be avoided in patients with T1–2 tumours and sentinel lymph node micrometastases, as suggested by Chu *et al* and Reynolds *et al*"

In our study, LNs with radioactive tracer uptake were designated as SLNs, the blue dye served only as a visual aid in identification. Other workers have in some instances included blue, non-radioactive nodes as SLNs, a practice that has been challenged.<sup>18–19</sup> From a conceptual viewpoint it could be argued that there can only be a single "true" SLN and that all other nodes are non-sentinel nodes. If this line of reasoning is pursued, two of seven patients from our group without n-SLN involvement would have to be considered as having n-SLN involvement. Conversely, it has been shown that more than one first echelon node (SLN) may be present. In accordance with these observations we chose to accept multiple SLNs.

We found that n-SLN metastases as clusters were associated with tumours > 2 cm in size and with high grade tumours. Other groups have not found tumour grade to be an independent risk factor for n-SLN metastasis.<sup>18–21</sup> This is surprising, because grade has been shown to be associated with an increased risk for nodal metastases in small tumours.<sup>22–23</sup>

The term micrometastasis has only been defined arbitrarily, and its definition varies between studies. A cut off point of 2 mm has been used in many studies and is included in the TNM classification.<sup>16–24–25</sup> Alternatives, such as the area of lymph node involved by tumour and the particular pattern of lymph node involvement, have been suggested.<sup>19–26–28</sup> The importance of micrometastatic disease and the implications for treatment when it is demonstrated hinge upon delineating the biological behaviour of small tumour deposits and small numbers of isolated tumour cells.<sup>12</sup> Experimental studies suggest that most isolated (circulating) tumour cells are not viable and will not result in metastatic disease. Thus, in the

## Take home messages

- Non-sentinel lymph node (n-SLN) involvement is relatively common in patients with breast cancer and sentinel lymph node micrometastases
- Metastatic clusters in n-SLN are found more frequently in patients with T2–3 tumours and grade 3 tumours
- Thus, axillary lymph node dissection is especially warranted in these patients, but because n-SLN metastases occur even in T1 and low grade tumours, these tumours should be subjected to routine axillary dissection to achieve local control
- Further studies are needed with larger series and patient follow up to assess the clinical relevance of these findings

strictest sense, a micrometastasis requires the arrest of tumour cells in the tissue and proliferation.<sup>4–16</sup> Biological characteristics such as viability, angiogenic capacity, and avoidance of the host immune reaction may be equally important factors.<sup>29–30</sup> In addition, it may be necessary to look at the host lymph node response, because this may also influence the ability of a micrometastasis to expand.<sup>26</sup> In this setting, it is interesting to note that Colpaert *et al* found a survival advantage for patients with SLN micrometastases and hypothesised that this may result from an enhanced host immune response.<sup>31</sup>

Whatever the outcome of single tumour cells in the circulation or in organs may be, it should be appreciated that the very fact that they are detected implies that access to the lymphatics or blood vessels has been gained, and that a line of defence has been breached in the metastatic pathway.

The incidence of n-SLN involvement varies in reports and this is in part a result of the sensitivity of the detection method used. Naturally, more intensive analysis of LNs with serial sectioning and immunohistochemistry will reveal more metastatic disease, as has been shown in SLN research.<sup>9–10</sup> Reynolds *et al* did not observe n-SLN metastases in 18 patients with T1 tumours and micrometastases in the SLN. They propose that axillary lymph node dissection may not be necessary in patients with T1 breast tumours and SLN micrometastases.<sup>21</sup> Likewise, Chu *et al* found that less than 5% of patients with T1 tumours and only 6% of patients with T1–2 tumours and micrometastatic SLN disease had n-SLN involvement, and they also suggest that axillary lymph node dissection may not be necessary in these patients.<sup>18–20</sup> However, the methods used in their study, with one or two sections for each n-SLN and without IHC, probably underestimated the extent of n-SLN disease.<sup>20</sup> The same investigators in Giuliano's group later found that 24% of patients with T1–2 tumours and micrometastases in the SLN (either detected by H&E staining or IHC) harboured n-SLN metastases. In that study, two level IHC was used, which may have increased the sensitivity. However, they did find that when lymphatic vascular invasion and extranodal hilar tissue invasion were taken into account only one of 58 patients with T1–2 tumours had an n-SLN metastasis.<sup>32</sup> Another study, examining n-SLN involvement in patients with positive SLNs, found n-SLN involvement in 27% of patients with a single SLN harbouring a metastasis < 1 mm.<sup>28</sup> In our series, three of 21 patients with T1 tumours and an SLN micrometastasis had n-SLN metastases detected by serial sectioning and IHC. On the basis of our findings and the literature data,<sup>28</sup> we find it premature to conclude that axillary dissection may be avoided in patients with T1–2 tumours and SLN micrometastases, as suggested by Chu *et al* and Reynolds *et al*.<sup>18–20–21</sup> Indeed, if n-SLN metastases are relatively common in patients with micrometastatic SLN disease and are likely to be followed by axillary node dissection, then it is imperative that the SLN is meticulously investigated. Therefore, the question that must be answered is how thoroughly this must be done and at what cost.<sup>33</sup> The ultimate test of the importance of

SLN micrometastatic disease and its treatment implications will be disease recurrence and disease related survival. For this issue to be resolved, further studies are needed with larger series and patient follow up. A trial incorporating these aspects organised by the oncology group of the American College of Surgeons is under way.<sup>34</sup>

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