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Non-Sentinel Lymph Node Metastases Associated With Isolated Breast Cancer Cells in the Sentinel Node

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There are many reports on the frequency of non-sentinel lymph node involvement when isolated tumor cells are found in the sentinel node, but results and recommendations for the use of an axillary lymph node dissection differ among studies. This systematic review was conducted to give an overview of this issue and to provide recommendations for the use of an axillary lymph node dissection in these patients. We searched Medline, Embase, and Cochrane databases from January 1, 2002, through November 27, 2007, for articles on patients with invasive breast cancer who had isolated tumor cells in the sentinel lymph node (according to the sixth edition of the Cancer Staging Manual of the American Joint Committee on Cancer) and who also underwent axillary lymph node dissection. Of 411 selected articles, 29 (including 836 patients) were included in this review. These 29 studies were heterogeneous, reporting a wide range of non-sentinel lymph node involvement (defined as the presence of isolated tumor cells or micro- or macrometastases) associated with isolated tumor cells in the sentinel lymph node, with an overall pooled risk for such involvement of 12.3% (95% confidence interval = 9.5% to 15.7%). This pooled risk estimate was marginally higher than the risk of a false-negative sentinel lymph node biopsy examination (ie, 7%–8%) but marginally lower than the risk of non-sentinel lymph node metastases in patients with micrometastases (ie, approximately 20%) who are currently eligible for an axillary lymph node dissection. Because 36 (64%) of the 56 patients with isolated tumor cells in their sentinel lymph node also had non-sentinel lymph node macrometastases, those patients with isolated tumor cells in the sentinel lymph node without other indications for adjuvant systemic therapy might be candidates for axillary lymph node dissection.

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Axillary lymph node status is one of the most important prognostic factors for breast cancer patients (1). A sentinel lymph node biopsy examination is a safe and accurate initial staging method for lymph nodes of patients with early-stage breast cancer and has largely replaced axillary lymph node dissection as the preferred staging method (2). Selective targeting of the sentinel lymph node with enhanced pathological analysis (ie, step sectioning and immunohistochemistry) has led to an increased rate of identifying positive lymph nodes (3,4). However, the clinical significance of small groups of metastatic cells in lymph nodes is unclear.

The sixth edition of the Cancer Staging Manual of the American Joint Committee on Cancer (AJCC), which was first published in 2002, distinguishes between isolated tumor cells (clusters with diameters of ≤0.2 mm) and micrometastases (tumor cell clusters of >0.2 but ≤2 mm) on the basis of cluster size, reflecting the increased use of the sentinel lymph node biopsy method for lymph node staging. According to the first publication (5), the category no regional lymph node metastases (pN0) was given an additional description “i” [pN0(i+)] for metastatic cells visible by immunohistochemistry only. That is, pN0(i+) indicated that lymph node metastases were not detected on hematoxylin-eosin–stained lymph node sections but were detected by immunohistochemistry and that each tumor cluster had a diameter of no more than 0.2 mm. These definitions were clarified in the 2003 revision (6), so that the i description referred to the presence (i+) or absence (i−) of isolated tumor cells (clusters with diameters of ≤0.2 mm) regardless of detection method. These patients have been assigned to the N0 group for staging and treatment purposes because “the unknown benefits of providing treatment for these small lesions would not outweigh the morbidity caused by the treatment itself” (7).

Although there is agreement that patients whose sentinel lymph node contain micro- and/or macrometastases (ie, those in the N1 category) should be subjected to axillary lymph node dissection, controversy exists as to whether there is a benefit associated with axillary lymph node dissection for patients whose sentinel lymph node contains isolated tumor cells. Several studies (8–10) report an association between the size of metastases in the sentinel lymph node and non-sentinel lymph node involvement. Before the introduction of the current definition of isolated tumor cells, such groups...
of metastatic cells were included in the micrometastases category (pN1a) and thus usually integrated into the group of metastases detected by immunohistochemistry only. A meta-analysis by Cserni et al. (11) reported an overall risk of non–sentinel lymph node involvement of 9%, when sentinel lymph node metastases were detectable by immunohistochemistry only. Since the introduction of the current definition of isolated tumor cells, a growing number of studies (12–14) have assessed the detection rate of non–sentinel lymph node metastases in patients who have isolated tumor cells in their sentinel lymph node, but the results and recommendations from these studies for the use of axillary lymph node dissection have varied. This systematic review was conducted to give an overview of these results and provide recommendations regarding the role of an axillary lymph node dissection in patients with isolated tumor cells in their sentinel lymph node.

**Patients and Methods**

**Literature Search Strategy**
The electronic databases of Medline, Embase, and Cochrane were searched from January 1, 2002, through November 27, 2007, by use of variations of free text and controlled terms for breast cancer and sentinel lymph node and non–sentinel lymph node involvement. The year 2002 was selected because the sixth edition of the AJCC Cancer Staging Manual was published this year. Articles published in English, German, French, or Dutch were considered. Two reviewers (C. H. M. van Deurzen and M. de Boer) independently evaluated titles and abstracts of the identified papers. The full text of potentially relevant articles was then reviewed.

**Study Inclusion Criteria**
To be included in this review, studies had to meet three inclusion criteria. First, patients had to have invasive breast cancer. Second, patients must have had a sentinel lymph node biopsy procedure followed by an axillary lymph node dissection. Third, isolated tumor cells had to be classified according to the sixth edition of the AJCC Cancer Staging Manual (tumor cell clusters with a diameter of ≤0.2 mm). Studies were excluded that reported on a sentinel lymph node biopsy procedure after neoadjuvant chemotherapy, microinvasive breast cancer, or sentinel lymph node tumor deposits without size definition according to the sixth edition of the AJCC Cancer Staging Manual.

**Data Extraction and Statistical Analysis**
Data extraction was carried out independently by two reviewers (C. H. M. van Deurzen and M. de Boer). Any disagreement was resolved by consensus. Data were extracted by use of standardized data extraction forms. We documented sample size, inclusion and exclusion criteria, primary tumor characteristics, definition of isolated tumor cells, sentinel lymph node biopsy protocol (blue dye and/or colloid and the injection site), processing methods for sentinel lymph nodes and non–sentinel lymph nodes, level of axillary lymph node dissection, and number of patients with isolated tumor cells in their sentinel lymph node and with non–sentinel lymph node metastases. The AJCC classification of non–sentinel lymph node metastases, including isolated tumor cells (cell clusters with diameters of ≤0.2 mm), micrometastases (tumor cell clusters >0.2 but ≤ 2 mm), and macrometastases (tumor cell clusters >2 mm), was also recorded. In some instances, corresponding authors were contacted for additional information.

We calculated 95% confidence intervals (CIs) for the risks of non–sentinel lymph node involvement within the studies by use of the Rothman spreadsheet (15). A random-effects meta-analysis with an exact likelihood approach was used to calculate pooled risk estimates of non–sentinel lymph node involvement and 95% confidence intervals (16). The extent to which one or more study characteristics explained between-study heterogeneity was explored by use of metaregression analysis (17). The following variables were considered: the number of levels of the sentinel lymph node or non–sentinel lymph nodes that were stained with hematoxylin–eosin and/or by immunohistochemistry. Systematic differences between small and large studies were assessed by use of a funnel plot (18). Statistical analyses were performed with SAS version 9.1. All statistical tests were two-sided.

**Results**
The initial electronic search identified 411 potentially relevant articles of which we screened the title and abstract. After that screening, the full texts of 144 articles were obtained. After full text review and exclusion of overlapping series, 29 articles that met the inclusion and exclusion criteria for this study were identified and used for data extraction. The main characteristics and results of these studies are summarized in Table 1. These studies were heterogeneous regarding study design, size, inclusion criteria for sentinel lymph node biopsy examination, sentinel lymph node biopsy technique, and histopathological work-up. Overall, these 29 studies included 836 patients, of whom 108 had non–sentinel lymph node involvement.

Sentinel lymph nodes were usually identified by use of blue dye in combination with radioactive colloid that was injected peritumorally. The detection rate of non–sentinel lymph node metastases ranged from 0% through 27%, with a pooled risk for non–sentinel lymph node metastases of 12.3% (95% CI = 9.5% to 15.7%). Data on the size of non–sentinel lymph node metastases and whether such metastases were considered in the treatment of the patient were scarce. In 10 of the 17 studies with non–sentinel lymph node involvement, information was available on the type of metastases that was classified according to the sixth edition of the AJCC Cancer Staging Manual. The pooled risk of non–sentinel lymph node macrometastases, after a positive sentinel lymph node was found, in these studies was 63.5% (95% CI = 38.1% to 83.1%). The funnel plot did not indicate systematic differences in the frequency of non–sentinel lymph node metastases between large studies and smaller studies (Figure 1). However, the range of non–sentinel lymph node metastases (5%–19%) in larger studies (ie, those with >30 patients) was smaller than the range (0%–27%) in smaller studies (ie, those with <30 patients).

Metaregression analysis revealed that the number of assessed levels of the sentinel lymph node or non–sentinel lymph nodes stained with hematoxylin–eosin and/or immunohistochemistry (ie, defined as the number of lymph node sections assessed by pathological analysis) did not contribute substantially to between-study heterogeneity in non–sentinel lymph node involvement. Because
Table 1. Overview of breast cancer studies reporting on the detection rate of non-sentinel lymph node involvement after axillary lymph node dissection in patients with isolated tumor cells in their sentinel lymph node*

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>No. of patients</th>
<th>Inclusion criteria for SLN procedure</th>
<th>SLN</th>
<th>Non-SLN</th>
<th>Positive non-SLNs†</th>
<th>No. of positive non-SLNs§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delaloye et al. (19)</td>
<td>2</td>
<td>cT &lt;3 cm</td>
<td>10–12</td>
<td>NR</td>
<td>M</td>
<td>0</td>
</tr>
<tr>
<td>Barranger et al. (20)</td>
<td>1</td>
<td>cN0</td>
<td>4</td>
<td>NR</td>
<td>M</td>
<td>0</td>
</tr>
<tr>
<td>McCready et al. (21)</td>
<td>17</td>
<td>cN0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Dabbs et al. (22)</td>
<td>63</td>
<td>NA</td>
<td>3</td>
<td>NR</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Menes et al. (13)</td>
<td>31</td>
<td>cN0</td>
<td>5</td>
<td>NR</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Zinganet al. (23)</td>
<td>5</td>
<td>cN0, cT &lt;3 cm</td>
<td>Ser Sec</td>
<td>Ser Sec</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Changsri et al. (24)</td>
<td>22</td>
<td>NA</td>
<td>3</td>
<td>NR</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Leidenius et al. (25)</td>
<td>19</td>
<td>NA</td>
<td>4</td>
<td>NR</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Vale et al. (26)</td>
<td>116</td>
<td>cN0, cT ≤3 cm</td>
<td>≥15</td>
<td>NR</td>
<td>3–6</td>
<td>17</td>
</tr>
<tr>
<td>Schrenk et al. (27)</td>
<td>44</td>
<td>cN0</td>
<td>≥4</td>
<td>NR</td>
<td>M</td>
<td>4</td>
</tr>
<tr>
<td>de Widt-Levert et al. (28)</td>
<td>13</td>
<td>cN0, cT1</td>
<td>≥3</td>
<td>≥3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Klevesath et al. (29)</td>
<td>4</td>
<td>cN0, cT ≤4 cm</td>
<td>3</td>
<td>NR</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Calhoun et al. (30)</td>
<td>61</td>
<td>NA</td>
<td>M</td>
<td>NR</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Krauth et al. (31)</td>
<td>19</td>
<td>cN0, cT1-2</td>
<td>Ser Sec</td>
<td>NR</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Choi et al. (32)</td>
<td>2</td>
<td>cN0</td>
<td>21</td>
<td>2</td>
<td>M</td>
<td>0</td>
</tr>
<tr>
<td>Houvenaeghel et al. (12)</td>
<td>187</td>
<td>cT0-2</td>
<td>2–6]</td>
<td>NR</td>
<td>M</td>
<td>30</td>
</tr>
<tr>
<td>van Rijk et al. (33)</td>
<td>54</td>
<td>NA</td>
<td>3</td>
<td>NR</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Amin and Hoda (34)</td>
<td>21</td>
<td>NA</td>
<td>3</td>
<td>1</td>
<td>M</td>
<td>4</td>
</tr>
<tr>
<td>Falconeri et al. (35)</td>
<td>19</td>
<td>pT1-2</td>
<td>&gt;15</td>
<td>NR</td>
<td>M</td>
<td>0</td>
</tr>
<tr>
<td>Ryden et al. (36)</td>
<td>6</td>
<td>cN0, cT &lt;3 cm</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bolster et al. (37)</td>
<td>48</td>
<td>cN0, cT1-2</td>
<td>≥3</td>
<td>NR</td>
<td>1–2</td>
<td>7</td>
</tr>
<tr>
<td>Groen et al. (38)</td>
<td>18</td>
<td>cN0, cT1-2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Langer et al. (39)</td>
<td>11</td>
<td>cN0, pT ≤3 cm</td>
<td>&gt;3</td>
<td>NR</td>
<td>M</td>
<td>1</td>
</tr>
<tr>
<td>Faist and Chenrko (40)</td>
<td>4</td>
<td>cN0, cT &lt;4 cm</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>0</td>
</tr>
<tr>
<td>Herbert et al. (41)</td>
<td>4</td>
<td>NA</td>
<td>5</td>
<td>NR</td>
<td>M</td>
<td>0</td>
</tr>
<tr>
<td>Cserni et al. (42–44¶)</td>
<td>22</td>
<td>ILC (43)</td>
<td>≥5</td>
<td>5</td>
<td>1–2</td>
<td>3</td>
</tr>
<tr>
<td>van Deurzen et al. (45)</td>
<td>23</td>
<td>cN0</td>
<td>≥5</td>
<td>5</td>
<td>1–2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>836</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>108</td>
</tr>
</tbody>
</table>

* SLN = sentinel lymph node; H&E = hematoxylin–eosin; IHC = immunohistochemistry; ITC = isolated tumor cells; NR = not routinely; M = missing data; NA = not applicable; Ser Sec = serial section; Micro = tumor cell cluster of >0.2 but ≤2 mm; Macro = tumor cell cluster with diameter of >2 mm; cT = clinical tumor stage; cN0 = clinically no regional lymph node metastasis; cT1 = clinical tumor diameter ≤2 cm; cT1-2 = clinical tumor diameter ≤5 cm; cT0-2 = clinically no evidence of primary tumor through a clinical tumor diameter ≤5 cm; pT1-2 = pathological tumor diameter ≤5 cm; pT = pathological tumor diameter; cT = clinical tumor diameter; ILC = infiltrative lobular carcinoma; pT ≤1.5 cm = pathological tumor size ≤1.5 cm.

† Number of lymph node sections assessed by pathological analysis.

§ Total number of patients with isolated tumor cells in the sentinel lymph node and non-sentinel lymph node metastases (including isolated tumor cells and micro- and macrometastases).

¶ Different protocols were used.

|| Three overlapping reports from the same author, results after excluding overlapping patients.
the included articles did not further specify clinicopathologic features of patients with a sentinel lymph node containing isolated tumor cells, we could not formulate recommendations for the use of axillary lymph node dissection for patients with sentinel lymph node involvement.

Discussion

In this systematic literature review, we have summarized the available studies reporting on the risk of non-sentinel lymph node involvement after isolated tumor cells were found in the sentinel lymph node. The overall incidence of non-sentinel lymph node involvement ranged from 0% to 27%. The pooled overall risk of non-sentinel lymph node involvement was 12.3% (95% CI = 9.5% to 15.7%), and 63.5% (95% CI = 38.1% to 83.1%) of non-sentinel lymph node metastases were macrometastases.

This study had several limitations. First, the studies included in the analysis did not specify the clinicopathologic details of those patients with isolated tumor cells and non-sentinel lymph node involvement. Therefore, with the currently available data, we cannot generate recommendations for the use of an axillary lymph node dissection in subgroups of patients with isolated tumor cells in the sentinel lymph node. Second, many of the included studies in this analysis did not further classify non-sentinel lymph node metastases (ie, isolated tumor cells or micro- or macrometastases). Therefore, the risk calculation for macrometastases in the non-sentinel lymph node was based on a relatively small number of studies.

The large range of non-sentinel lymph node involvement may stem partially from differences in study design, inclusion criteria for a sentinel lymph node biopsy procedure in this study, sentinel lymph node biopsy technique, and/or the processing and interpretation of metastatic deposits. First, included studies may be limited, in part, by their retrospective design because not all patients with a sentinel lymph node containing isolated tumor cells may have undergone an axillary lymph node dissection. The subgroup of patients with a sentinel lymph node containing isolated tumor cells who underwent an axillary lymph node dissection may have been selected because they appeared to have more aggressive primary disease. Second, exclusion criteria for sentinel lymph node biopsy procedure differed by the largest included clinical tumor diameter (ie, 3 or 5 cm). Third, the sentinel lymph node biopsy protocol differed by the type of substance injected (colloid and/or blue dye) and injection site (subdermal, peritumoral, or periareolar), although the influence of these variables was probably minimal. Fourth, the included studies used different protocols for sentinel lymph node and non-sentinel lymph node analyses, with a wide range in the number of slides, depth of section intervals, and use of immunohistochemistry. The detection rate of isolated tumor cells in the sentinel lymph node decreased with less extensive pathological work-up (ie, analysis of a low number of lymph node sections or a lack of routine use of immunohistochemistry) and some sentinel lymph nodes classified as having isolated tumor cells may, in fact, have had micrometastases at deeper levels; these variations would be expected to affect the risk and type of non-sentinel lymph node involvement observed. The risk of non-sentinel lymph node involvement was affected by the size of the sentinel lymph node metastases; the larger the metastasis in the sentinel lymph node, the higher the risk of non-sentinel lymph node involvement. Because pathological sampling involves assessment of a fraction of the lymph node volume only, there may be discordance between the detected sentinel lymph node metastatic size and its true size. In this systematic review, however, the number of assessed levels (defined as the number of lymph node sections assessed by pathological analysis) of the sentinel lymph node and non-sentinel lymph nodes stained with hematoxylin–eosin and by use of immunohistochemistry could not explain the between-study heterogeneity. Non-sentinel lymph nodes are generally examined less extensively without the routine use of immunohistochemistry, and this practice may underestimate the actual risk of small non-sentinel lymph node metastases after isolated tumor cells are found in the sentinel lymph node. The use of immunohistochemistry in the work-up of non-sentinel lymph nodes increases the detection rate of (small) non-sentinel lymph node metastases (46), so omitting immunohistochemistry for non-sentinel lymph nodes is likely to result in a relatively high percentage of non-sentinel lymph node macrometastases. However, Changsri et al. (24) reported only on isolated tumor cells in non-sentinel lymph nodes, by examining a single section of the non-sentinel lymph node by hematoxylin–eosin only. In their study, all patients with isolated tumor cells in their sentinel lymph node also had isolated tumor cells in their non-sentinel lymph nodes. They concluded that additional metastases in non-sentinel lymph nodes of patients with isolated tumor cells in the sentinel lymph node should also be of a small size, which is in contrast with the results of this systematic review. Finally, the heterogeneity of the results of these studies could be due to various interpretations of the current definition of isolated tumor cells, which do not permit a reproducible distinction between micrometastases and isolated tumor cell (47–49).

In, to our knowledge, the largest study of isolated tumor cells in the sentinel lymph node followed by axillary lymph node dissection (n = 187), Houvenaeghel et al. (12) reported a 16% rate of non-sentinel lymph nodes involvement. This retrospective
multicenter study reported no statistically significant difference in the risk of non–sentinel lymph node involvement between sentinel lymph nodes that contained isolated tumor cells (16%) and those that contained micrometastases (14.3%). However, they reported a 9.9% detection rate of non–sentinel lymph node involvement in a large group (n = 212) of sentinel lymph nodes containing micrometastases that had an unknown diameter (which also included isolated tumor cells). No mention was made as to whether additional non–sentinel lymph node metastases were associated with therapeutic decision making. They found that the only proposed subgroups of patients for whom axillary lymph node dissection could be avoided were patients with a small primary tumor (pT1a or pT1b) or with pT1 tubular, colloidal, or medullary tumors, with a risk for non–sentinel lymph node involvement of 5% or less.

In the second largest study (n = 116), Viale et al. (14) reported non–sentinel lymph node involvement in 15% of patients whose sentinel lymph node contained isolated tumor cells; this non–sentinel lymph node involvement was further classified as isolated tumor cells (6%) or micrometastasis (18%) or macrometastasis (76%). They included clinically lymph node–negative patients with early breast cancer (breast tumor diameter of ≤3 cm). The 6.7% difference in the detection rate of non–sentinel lymph node involvement between sentinel lymph nodes containing isolated tumor cells (14.7%) and micrometastases (21.4%) was not statistically significant. The identification of these non–sentinel lymph node metastases, which were mostly macrometastases, affected further systemic therapy in most patients whose sentinel lymph node contained isolated tumor cells or micrometastases. They concluded that the current categories, which were introduced by the sixth edition of the AJCC Cancer Staging Manual, cannot safely be adopted to tailor axillary surgical treatment for patients undergoing a sentinel lymph node biopsy procedure. A predictive model that was based on features associated with non–sentinel lymph node involvement could not identify a subgroup of patients with less than 13% non–sentinel lymph node involvement. From these results, Viale et al. recommended axillary lymph node dissection if there was any evidence of sentinel lymph node involvement in all settings except clinical trials. However, it must be emphasized that their assessment of the sentinel lymph node (by frozen sections and without routine immunohistochemistry) was likely to have decreased the detection rate of isolated tumor cells in the sentinel lymph node, which would, therefore, affect the detectable rate of non–sentinel lymph node involvement.

The decision of whether or not to proceed with an axillary lymph node dissection after finding isolated tumor cells in the sentinel lymph node was based on the risk of the procedure itself and on the risk and clinical significance of leaving residual disease in the axilla. The size of metastatic tumor material in the sentinel lymph node was one of the strongest predictors of non–sentinel lymph node involvement, although other characteristics (increased tumor size, more than one positive sentinel lymph node, and lymphovascular invasion in the primary tumor) also have statistically significant predictive value (50). From the studies included in this systematic review, the pooled risk of non–sentinel lymph node involvement among patients whose sentinel lymph node contained isolated tumor cells was approximately 12.3%, which is only marginally lower than the risk of non–sentinel lymph node involve-
References


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