Axillary Sentinel Lymph Node Biopsy in Patients With Pure Ductal Carcinoma In Situ of the Breast

Mattia Intra, MD; Paolo Veronesi, MD; Giovanni Mazzarol, MD; Viviana Galimberti, MD; Alberto Luini, MD; Virgilio Sacchini, MD; Giuseppe Trifirò, MD; Oreste Gentilini, MD; Giancarlo Pruneri, MD; Paola Naninato, MD; Fabio Torres, MD; Giovanni Paganelli, MD; Giuseppe Viale, MD, FRCPath; Umberto Veronesi, MD, PhD

Hypothesis: A sentinel lymph node (SLN) biopsy should not be considered a standard procedure in the treatment of all patients with ductal carcinoma in situ (DCIS) of the breast if the lesion is completely excised by radical surgery and there are free margins of resection.

Design: Prospective case series.

Setting: Department of breast surgery of a comprehensive cancer center.


Results: Metastases in the SLN were detected in 7 (3.1%) of the 223 patients, and complete axillary dissection was subsequently performed in all these patients but 1. Of these 7 patients, 5 had only micrometastases in the SLNs; and in the 6 patients treated with complete axillary dissection, the SLN was the only positive node.

Conclusions: Because of the low prevalence of metastases, an SLN biopsy should not be considered a standard procedure in all patients with DCIS. In patients with pure DCIS in whom the lesion is completely excised by radical surgery, an SLN biopsy could be avoided. It could be considered in patients with DCIS undergoing mastectomy, in whom there exists a higher risk of harboring an invasive component using definitive histologic features, like large solid tumors or diffuse or multicentric microcalcifications; in these patients, an SLN biopsy cannot be performed at a later operation. Complete axillary dissection may not be mandatory if the SLN is micrometastatic.

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PURE DUCTAL carcinoma in situ (DCIS) of the breast was infrequently diagnosed in the past, when it accounted for only 1% to 5% of all breast cancers. It usually presented as a palpable lesion, Paget disease, or bloody nipple discharge. Pure DCIS showed a 15-fold increase during the past 10 years, because of the widespread use of mammography for the detection of clinically nonpalpable tumors; now, it accounts for 20% or more of mammographically detected carcinomas and 12% of all newly diagnosed breast cancers. Standard treatment of DCIS is wide resection, with or without postoperative radiotherapy. A total mastectomy can be required in cases of extensive intramammary spread. Axillary dissection is not routinely indicated because of the low prevalence of nodal metastases, which is expected to be less than 2%, and the significant morbidity associated with lymph node dissection.

The sentinel lymph node (SLN) is the first node that receives lymphatic drainage from the primary tumor. In patients with invasive breast carcinoma, an SLN biopsy reduces the morbidity of axillary staging by minimizing lymphatic disruption while increasing the accuracy of staging because it allows a thorough pathologic examination of the SLN. Indeed, the examination of SLNs by serial sectioning and immunohistochemical reactions increases the detection rate of metastases from 9% to 33% in patients with an infiltrating carcinoma.

The techniques of lymphatic mapping and SLN biopsy have also been applied in patients with DCIS, and have resulted in a similar increase in the detection rate of metastases in some series of patients with DCIS. However, to our knowledge, the appropriateness of an SLN biopsy in the management of patients with pure DCIS of the breast has not been established thus far. This study determines the prevalence of
SLN metastases in a large series of patients with pure DCIS of the breast to determine the clinical usefulness of the SLN biopsy in these patients.

METHODS

PATIENTS

Between March 1, 1996, and December 1, 2001, 3391 patients with clinically node-negative breast carcinoma underwent a SLN biopsy at the European Institute of Oncology and were prospectively included in a database. Among these patients, 223 unselected consecutive patients (age range, 30-80 years; average age, 50.1 years) were affected by pure DCIS (patients affected by DCIS with microinvasion were excluded) and were included in the present investigation.

In all the cases of previous surgery or stereotactic biopsy performed elsewhere, all pathologic slides were reviewed at our institution to confirm the diagnosis. All patients were enrolled into the study after they gave written informed consent.

LYMPHOSCINTIGRAPHY

Lymphatic mapping was performed using a radiocolloid technique, as previously described. Briefly, 0.15 to 0.30 mCi (5-10 MBq) of technetium Tc 99m albumin colloid (20-80 nm) (Nanocol; Nycomed Amersham-Sorin, Saluggia-VC, Italy) in 0.2 mL of isotonic sodium chloride solution was injected close to the col; Nycomed Amersham-Sorin-Sorin, Saluggia-VC, Italy) in 0.2 mL of isotonic sodium chloride solution was injected close to the tumor subdermally or peritumorally, the day before surgery or the same day. Lymphoscintigraphy was then performed 15 to 30 minutes after injection and was repeated after 3 hours if no SLNs were evident in early images.

Anterior and anterior-oblique projections of the breast and axilla were obtained to determine the exact position of the SLN. The skin projection of the lymph node was then marked and noted; in all patients, the localization and position was not precise, the distance between the 2 was measured and noted; in all patients, the localization and possible skin contaminations were further checked by scintigraphy. When the occult lesion was detected ultrasonically, the radiotracer was injected, followed by 0.2 mL of radiopaque contrast medium. The needle was then removed, and 5 minutes later, a standard orthogonal mammogram of the proliferative tumor fraction was performed, to highlight the myoepithelial cell component of the lesion. For microcalcifications, opacities, or small opacities) without interfering with the blood flow, radiopaque contrast medium was used to guide the injection. A 22-gauge spinal needle, mounted in the stereotactic frame, was introduced into the lesion and the radiotracer was injected, followed by 0.2 mL of radiopaque contrast medium. If the primary tumor was nonpalpable, we performed a new technique that we called radioguided occult lesion localization (ROLL) to localize the tumor and the SLN using technetium Tc 99m macroaggregates. The day of the surgery or the day before, 0.5 mg of technetium Tc 99m albumin aggregated (10-150 µm) (Macrotec; Nycomed Amersham-Sorin, Saluggia-VC, Italy) in 0.2 mL of isotonic sodium chloride solution was injected close to the tumor subdermally or peritumorally, the day before surgery or the same day. Lymphoscintigraphy was then performed 15 to 30 minutes after injection and was repeated after 3 hours if no SLNs were evident in early images.

The histopathologic diagnosis and classification of DCIS was performed following strictly the criteria of Rosen and Oberman. Grading of DCIS was assessed according to Holland et al. Whenever microinvasion could not be excluded on purely morphological grounds, immunocytochemical reactions for smooth muscle heavy chain myosin and/or p63 were performed, to highlight the myoepithelial cell component of the lesion.

HISTOPATHOLOGIC EXAMINATION

The surgically removed breast lesions were thoroughly sampled for histopathologic examination. In case of microcalcifications, the specimens were sliced and subjected to x-ray examination to ensure complete sampling of all the microcalcification-containing tissue. Specimens without calcifications were extensively sampled, taking at least 1 block per centimeter of the lesion. Samples from the surrounding tissue were also examined; in the case of mastectomy, the areola- nipple complex was also sampled. Tissue sections from all previous needle biopsy specimens (at least 3 sections per core, cut at 110-200-mm intervals) and from all surgical resections performed elsewhere were reviewed.

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The SLN examination was performed as previously described. Briefly, the SLNs were biected fresh along the major axis if larger than 5 mm and fixed in 10% formaldehyde for 6 to 8 hours, before being embedded in paraffin. Lymph nodes less than or equal to 5 mm were embedded uncut. Fifteen pairs of paraffin-embedded sections, 4-µm thick, were cut at 50-µm intervals. If residual tissue was left, additional pairs of sections were cut at 100-µm intervals until the lymph node was entirely sectioned. One section of each pair was stained with hematoxylin-eosin. Whenever needed, to ascertain the nature of atypical cells seen on the hematoxylin-eosin–stained sec-

SURGERY

An SLN biopsy was performed 4 to 20 hours after the injection of radiolabeled albumin. A γ-ray–detecting probe (Neoprobe 2000; Ethicon, Inc, Somerville, NJ) in a sterile glove was used to locate the radioactive lymph node and facilitate its removal. Radioactivity detected by the probe was transduced into digital readout and acoustic signals whose intensity was directly proportional to the level of radioactivity.

In case of breast-conserving surgery, the SLN biopsy was performed through the same incision of the tumor resection in the upper outer quadrants or through a 2- to 3-cm separated axillary incision if the tumor was in another breast quadrant. The SLN was identified and isolated using the probe as a guide. After the SLN was removed, the surgical bed was reexamined for any residual radioactivity. If there was activity again, additional SLNs were identified and removed. If the primary tumor was nonpalpable, we also performed radioguided resection of the lesion (ROLL). This technique allowed the correct removal of the nonpalpable breast lesions (cluster of microcalcifications or small opacities) without interfering with the SLN biopsy because of the capability of the γ-ray–detecting probe of modifying the radiosensitivity. Whenever indicated, we also performed an intraoperative x-ray examination of the resected tissue to ensure complete removal of the lesion. If surgical margins were involved by the tumor at the primary surgery, a second resection or a mastectomy was performed. All the nodes absorbing the radiotracer were classified as SLNs, and all were removed for histopathologic examination.
of the mirror sections were immunostained for cytokeratins using a rapid-staining method (EPOS Anti-cytokeratins/HRP; Dako, Copenhagen, Denmark).

RESULTS

Of the 223 patients, 184 (82.5%) were treated with wide resection and 39 (17.5%) with mastectomy. The SLN biopsy was performed during the same session as surgery on the primary tumor in 85.2% of the patients. In the remaining 14.8% of the patients, the SLN biopsy was delayed after the histopathologic diagnosis of DCIS in the primary breast lesion. Three hundred fifty-six SLNs were identified and examined from the 223 patients: 143 showed 1 SLN, 52 showed 2 SLNs, 13 showed 3 SLNs, and 15 showed more than 3 SLNs (average, 1.6 SLNs). Because an SLN intraoperative diagnosis was not performed, all patients with DCIS, except for 1 with a metastatic SLN, underwent a complete axillary dissection during a second session. One patient with 1 micrometastatic SLN and 3 other first-level nonmetastatic nodes, informed about the risks, refused complete axillary dissection.

PATHOLOGIC FINDINGS

Sentinel lymph node metastases were detected in 7 of the 223 patients with a conclusive diagnosis of pure DCIS without evidence of microinvasion in the original breast biopsy specimen and on reexcision. Patients positive for SLN metastases had their primary tumors reanalyzed by cutting more sections; no focus of microinvasion was found. The SLNs were the only affected nodes in the 6 patients who underwent subsequent complete axillary dissections. No immunohistological investigation was needed for the detection of metastasis.

The biological characteristics of the patients are shown in Table 1. Of the 216 patients whose SLNs were negative for metastases, 47 (21.8%) had their diagnosis made via a vacuum-assisted biopsy device (MammoSite; Ethicon, Inc, Somerville, NJ), whereas 31 others (14.4%) had their diagnosis made via an excisional biopsy. In 178 of these patients, conservative breast surgery was performed; in the other 38 patients, a total mastectomy was performed, with immediate reconstruction in all patients but 3, because of the absence of an indication or patient refusal.

The characteristics of the 7 patients with DCIS whose SLN was positive for metastases are shown in Table 2. Of these 7 patients, 3 had only micrometastases (<2 mm). The risk of lymph node metastases in these patients did not correlate with grade, receptor status, presence of comedo necrosis, predominant histological pattern, or type of surgery. The tumors ranged from 6 to 55 mm (mean, 25.7 mm), and 3 were multifocal. Four patients had their diagnosis made via a vacuum-assisted biopsy device; in 2 others, the diagnosis was made via an excisional biopsy performed at another institution. One patient underwent a breast resection 4 years prior at the European Institute of Oncology for a solid DCIS (grade 2; positive estrogen receptor, 40%; positive progesterone receptor, 40%; and proliferation marker Ki67, 30%) and underwent standard external radiotherapy. Finally, in 2 patients, a dislocation of epithelial cells was shown in the surgical specimen and interpreted as artifactual because of previous surgical or radiological maneuvers.

POSTSURGICAL INTERVENTIONS

All patients whose SLN was positive for metastases, except for 1 who underwent a mastectomy, underwent standard external radiotherapy (5000 rad [50 Gy] to the whole breast and 1000 rad [10 Gy] as a boost to the tumor bed). The other 216 patients whose SLNs were negative for metastases underwent external radiotherapy only in case of high-grade DCIS.

All 7 patients whose SLNs were positive for metastases underwent adjuvant therapy according to the main predictive and prognostic factors. Adjuvant therapy for these patients was as follows: patients 1 and 3, a combination of doxorubicin hydrochloride (Adriamycin) and cyclophosphamide for 4 cycles and a combination of cyclophosphamide, methotrexate, and fluorouracil for 3 cycles; patients 2 and 7, tamoxifen citrate; patient 4, a luteinizing hormone–releasing hormone analogue; patient 5, tamoxifen citrate and a luteinizing hormone–releasing hormone analogue; and patient 6, a combination of cyclophosphamide, methotrexate, and fluorouracil for 3 cycles and tamoxifen citrate. The 216 patients whose SLNs were negative for metastases and

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**Table 1. Main Characteristics of 223 Patients With DCIS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Positive for Metastases (n = 7)</th>
<th>Negative for Metastases (n = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid lesion</td>
<td>4 (57.1)</td>
<td>65 (30.1)</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>3 (42.9)</td>
<td>143 (66.2)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>8 (3.7)</td>
</tr>
<tr>
<td><strong>Comedo DCIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4 (57.1)</td>
<td>160 (74.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>3 (42.9)</td>
<td>56 (25.9)</td>
</tr>
<tr>
<td><strong>Tumor grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (28.6)</td>
<td>41 (19.0)</td>
</tr>
<tr>
<td>2</td>
<td>2 (28.6)</td>
<td>97 (44.9)</td>
</tr>
<tr>
<td>3</td>
<td>3 (42.9)</td>
<td>78 (36.1)</td>
</tr>
<tr>
<td><strong>Hormonal receptor status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>5 (71.4)</td>
<td>158 (73.1)</td>
</tr>
<tr>
<td>Negative</td>
<td>2 (28.6)</td>
<td>58 (26.9)</td>
</tr>
<tr>
<td>Progesterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>5 (71.4)</td>
<td>134 (62.0)</td>
</tr>
<tr>
<td>Negative</td>
<td>2 (28.6)</td>
<td>82 (38.0)</td>
</tr>
<tr>
<td><strong>Proliferative rate (Ki67), %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>4 (57.1)</td>
<td>134 (62.0)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>2 (28.6)</td>
<td>82 (38.0)</td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative surgery</td>
<td>6 (85.7)</td>
<td>178 (82.4)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>1 (14.3)</td>
<td>38 (17.6)</td>
</tr>
</tbody>
</table>

Abbreviations: DCIS, ductal carcinoma in situ; SLN, sentinel lymph node. *Data are given as number (percentage) of patients. Percentages may not total 100 because of rounding. †In 1 patient with an SLN positive for metastases, the information was missing.
who were examined for hormonal therapy enrolled in chemoprophylaxis studies.

The standard of care for patients with a definitive diagnosis of DCIS does not include removal of regional lymph nodes. A less than 2% risk of nodal metastases does not justify a routine axillary dissection considering its potential sequelae. The SLN biopsy considerably increases the rate of detection of lymph node metastasis in patients operated on for invasive carcinoma. Despite the high diagnostic accuracy of the SLN biopsy using the complete serial sectioning technique, in this series of 223 patients with DCIS, the percentage of SLN metastases remained low (3.1%) and consistent with other reports in the literature following complete axillary dissection. Of the 7 patients with SLNs positive for metastases, 5 had only micrometastatic disease in the SLN, and all the patients subjected to complete axillary node dissection did not show additional metastatic lymph nodes.

Other researchers reported a higher rate of metastatic SLNs in smaller series of patients with DCIS. Pendás et al11 found 5 (5.7%) of 87 SLNs positive for metastases (by hematoxylin-eosin staining and immunocytochemistry). Additional sections of the primary tumors, however, revealed 1 patient to have a focus of invasion so that the rate of metastatic SLNs in patients with true pure DCIS decreases to 4.6%. Of the 76 patients with high-risk DCIS described by Klauber-DeMore et al, 12, 9 (12%) had SLNs positive for metastases, compared with only 3 (10%) of 31 patients affected by DCIS with microinvasion. On a retrospective review of the primary tumors associated with metastatic SLNs, additional sectioning revealed that 3 patients with high-risk DCIS had stromal or vascular invasion. An additional patient with a metastatic SLN had a contralateral invasive carcinoma with a metastatic SLN. The actual rate of SLN metastases after exclusion of these 4 patients decreases to 6.6%. Cox et al9 described 195 patients with pure DCIS, of whom 26 (13%) had SLN metastases. Unfortunately, the lack of details on the extent of tissue sampling makes a direct comparison between the data described quite difficult.

An extensive and accurate histological examination of the tumor in patients with DCIS is mandatory to exclude microinvasive foci and, finally, to decrease the prevalence of unexpected SLN metastases. Less thorough sampling and examination of large tumors may miss microinvasive foci: as many as 48% of patients with a DCIS larger than 5.5 cm may exhibit identifiable microinvasion at mastectomy. Despite an accurate sampling and evaluation of the primary tumors, some patients with DCIS will still have unexpected sentinel and/or nonsentinel axillary lymph node metastases, most likely because of missed microinvasive foci.

We did not find any difference when we compared the biological characteristics of the SLN-negative and SLN-positive patients with DCIS: the risk of lymph node metastases in these patients did not correlate with tumor features like size, grade, predominant histological pattern, presence of comedo necrosis, sex corticosteroid hormone receptor status, or type of surgery.

Of the 7 patients with a metastatic SLN, 6 had undergone a previous breast biopsy: 2 had undergone an open surgical biopsy elsewhere (their histopathologic diagnoses were reviewed) and 4 had undergone a biopsy using a vacuum-assisted biopsy device at our institution. In 2 of these 4 latter patients, an artifactual dislocation of tumor cells within the stroma along the needle tract was identified. On the other hand, only 36.1% of the patients with SLNs negative for metastases previously underwent a surgical biopsy (14.3%) and a biopsy with a vacuum-assisted biopsy device (21.8%). The chance of passive transport of dislocated epithelial cells to the SLN following an invasive preoperative maneuver has been reported, but still represents a hotly debated issue, with unsettled clinical implications. However, a preoperative invasive maneuver could remove or hide microinvasive foci in the sampled patients with DCIS.

The low rate of SLN metastases and the lack of features of the primary tumors predictive of lymph node involvement do not recommend routinely performing an
SLN biopsy in all patients with DCIS. In patients with pure DCIS that is completely excised by radical surgery who have free margins of resection, an SLN biopsy could be avoided. But how many times in patients with suspected microcalcifications are we sure of the diagnosis of pure DCIS, even if a preoperative diagnostic maneuver has been performed? A correct diagnosis could be obtained by a large-core breast biopsy using a vacuum-assisted biopsy device (Mammatome) or surgical excision of a single small lesion or a limited cluster of microcalcifications, for which the postoperative specimen x-ray film or pathologic evaluation of the resection margins confirms that the lesion has been totally removed. The core biopsy will be followed by a surgical wide resection in the first case, and the surgical excision will be conclusive in the second. No SLN biopsy will be necessary in both cases. On the other hand, patients with large tumors or diffuse or pluricentric microcalcifications diagnosed as DCIS by a core biopsy and candidates for total mastectomy have a higher risk of harboring an invasive component, which will be eventually identified in the mastectomy specimen. In these circumstances, it would be impossible to perform an SLN biopsy following mastectomy and, therefore, these patients would necessarily undergo complete axillary dissection. Accordingly, for these patients, it seems advisable to perform an SLN biopsy during mastectomy.

CONCLUSIONS

Our study showed that 3.1% of patients with DCIS have occult metastases in the axillary SLNs. No correlations were possible between the many biometric, histologic, and biological characteristics of the primary in situ carcinoma and SLN positivity. In the absence of any predictive criteria, the open question is whether all patients with DCIS should be offered the option of the SLN biopsy to avoid the 3.1% risk of a future axillary dissection for overt axillary metastases. We believe that any women with DCIS should be informed of this small risk and of the easy procedure to perform a biopsy of the axillary SLN, but because of the low prevalence of metastatic involvement, an SLN biopsy should not be considered a standard procedure in the treatment of all patients with DCIS. In patients with pure DCIS in whom the lesion is completely excised by radical surgery and who have free margins of resection, an SLN biopsy could be avoided. It could be considered in patients with DCIS undergoing mastectomy, in whom there exists a doubt of invasion using the definitive histological features, like large solid tumors or diffuse or pluricentric microcalcifications; in these patients, a successive SLN biopsy can not be proposed. Complete axillary dissection may not be mandatory if the SLN is micrometastatic.

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Corresponding author and reprints: Mattia Intra, MD, Department of Breast Surgery, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy (e-mail: mattia.intra@eio.it).

REFERENCES