SPIO-Enhanced Magnetic Resonance Imaging for the Detection of Metastases in Sentinel Nodes Localized by Computed Tomography Lymphography in Patients with Breast Cancer


Annals of Surgical Oncology
ISSN 1068-9265
Volume 18
Number 12

DOI 10.1245/s10434-011-1710-7
SPIO-Enhanced Magnetic Resonance Imaging for the Detection of Metastases in Sentinel Nodes Localized by Computed Tomography Lymphography in Patients with Breast Cancer

Kazuyoshi Motomura, MD, PhD, Makoto Ishitobi, MD, PhD, Yoshifumi Komoike, MD, PhD, Hiroki Koyama, MD, PhD, Atsushi Noguchi, RT, Hiroshi Sumino, RT, Youji Kumatani, RT, Hideo Inaji, MD, PhD, Takashi Horinouchi, RT, and Katsuyuki Nakanishi, MD, PhD

1Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; 2Department of Radiology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

ABSTRACT

Background. Superparamagnetic nanoparticle-enhanced magnetic resonance (MR) imaging has been reported to be a promising improvement for diagnostic imaging of lymph node metastases from various tumors. Moreover, sentinel nodes have been reported to be well identified using computed tomography (CT) lymphography (CT-LG) in patients with breast cancer. The aim of this study was to evaluate MR imaging with superparamagnetic iron oxide (SPIO) enhancement for the detection of metastases in sentinel nodes identified by CT-LG in patients with breast cancer.

Methods. This study included 102 patients with breast cancer and clinically negative nodes. Sentinel nodes were identified by CT-LG, and SPIO-enhanced MR imaging of the axilla was performed to detect metastases in the sentinel nodes. A node was considered nonmetastatic if it showed a homogeneous low signal intensity and metastatic if the entire node or a focal area did not show low signal intensity on MR imaging. Sentinel node biopsy was performed, and imaging results were correlated with histopathologic findings.

Results. The mean number of sentinel nodes identified by CT-LG was 1.1 (range, 1–3). The sensitivity, specificity, and accuracy of MR imaging for the diagnosis of sentinel node metastases were 84.0%, 90.9%, and 89.2%, respectively. In 4 of 10 patients with micrometastases, metastases were not detected, but all 15 patients with macrometastases were successfully identified.

Conclusions. SPIO-enhanced MR imaging is a useful method of detecting metastases in sentinel nodes localized by CT-LG in patients with breast cancer and may avoid sentinel node biopsy when the sentinel node is diagnosed as disease-free.

Sentinel node biopsy has become the standard of care that has replaced axillary lymph node dissection as a less-invasive method for axillary staging in breast cancer patients with clinically negative nodes.1–5 Sentinel node biopsy decreases the risk of morbidity in terms of lymph edema, neuropathies, seroma, wound infection, reduced shoulder motility, and chronic pain, but even after sentinel node biopsy, 2–7% of patients are reported to have lymphedema.6–8 Allergic reactions to the dye occur in 0.6% of patients, and anaphylactic reactions occur in approximately 0.1% of patients.6

Although imaging techniques, such as magnetic resonance (MR) imaging and computed tomography (CT), may be much less invasive for axillary nodal staging in patients with breast cancer, there is insufficient accuracy with these conventional methods.9–14 Ultrasonography is a less invasive and costly means of assessing the axilla. While ultrasound facilitates pathological confirmation by guiding fine needle aspiration biopsy, it is reported to have low sensitivity and specificity for nodal staging.15–18

Recently, superparamagnetic nanoparticle-enhanced MR imaging has been reported to be a promising improvement for diagnostic imaging of lymph node metastases from various tumors.19–21 Harisinghani et al. demonstrated that the sensitivity for nodal staging using
ultrasmall superparamagnetic iron oxide (USPIO)-enhanced MR imaging in 334 lymph nodes from 80 patients with prostate cancer was 90.5% on a node-by-node basis, significantly higher than the conventional method using size criteria, which has a sensitivity of 35.4%.10 Rockall et al. compared the diagnostic performance of USPIO-enhanced MR imaging with standard size criteria of MR imaging for nodal assessment in 768 lymph nodes from 44 patients with endometrial or cervical cancer.20 They demonstrated that USPIO increased the sensitivity of MR imaging in the detection of nodal involvement (100% vs. 27%), with no loss of specificity (94% vs. 94%). Stets et al. assessed USPIO-enhanced MR imaging for axillary lymph node metastases in 52 lymph nodes from 9 patients with breast cancer.21 Using precontrast and postcontrast data, they showed the results based on a nodal diameter >6 mm, and visual assessment of signal changes on MR imaging allowed an accuracy of 87%, sensitivity of 81%, and specificity of 92%.

Moreover, sentinel nodes have been reported to be well identified using CT lymphography (CT-LG) in patients with breast cancer.22 In all 40 patients, lymph flow and sentinel nodes were successfully visualized by local injection of the CT contrast agent. Since CT imaging can accurately identify sentinel nodes, it may be possible to perform diagnostic imaging using superparamagnetic nanoparticle-enhanced MR imaging by assessing only sentinel nodes with a mean number of only 1 or 2 per patient.

In the present study, we evaluated MR imaging with superparamagnetic nanoparticle enhancement for the detection of metastases in sentinel nodes localized by CT-LG in patients with breast cancer. Superparamagnetic iron oxide (SPIO) was used as the contrast agent in MR imaging because it is commercially available. Although USPIO has been administered intravenously in clinical studies, SPIO was administered locally in this study, similar to the administration of dye and radioisotope during sentinel node biopsy.

PATIENTS AND METHODS

A total of 102 consecutive patients with clinical T1–2 breast cancers and clinically negative nodes who underwent sentinel node biopsy at Osaka Medical Center for Cancer and Cardiovascular Diseases between January and December 2008 were enrolled in this study. Patients with multiple primary tumors, nonpalpable breast cancer, prior axillary surgery, or who were pregnant were excluded. Patients with a contraindication to CT or MR imaging, or a known allergy to the contrast agents were also excluded. The institutional review board of Osaka Medical Center for Cancer and Cardiovascular Diseases approved the study, and written consent was obtained from all patients.

Sentinel Node Localization Using CT-LG Interstitial CT-LG was performed using a multidetector row helical CT scanner (Light Speed VCT; GE Healthcare, Milwaukee, WI). Contiguous 1.25-mm-thick CT images from the upper thorax to axillary regions were obtained once before administration of the contrast agent. CT scanning with a detector of 0.625 mm, 64 rows was operated at 120 kV, 300–400 Auto-mA, 35-cm field of view, 512 × 512 matrix, section spacing of 1 mm, and a table speed of 55 mm/0.5 s.

Transaxial CT images were reconstructed with a 1.25-mm thick and 1 mm interval. Each patient was placed in the supine position. Three small plastic bullets were placed as landmarks on the upper chest wall on the skin for a merged image of the CT-LG and axial MR images. First, their arms were placed in an elevated position. After local anesthesia with a subcutaneous injection of 2 ml of 2% procaine hydrochloride, a 6-ml dose of iopamidol (Iopamiron 370; Bayer Schering Pharma, Osaka, Japan) was injected intradermally into the skin overlapping the breast tumor and into the subareolar skin. A CT scan was performed after massaging the iopamidol injection site for 1 min. Second, a CT scan was performed in the adducted arm position. Finally, their arms were placed in an elevated position again, and a localizing marker, which is usually used for CT-guided lung nodule biopsy, was attached to the skin at the axilla to identify the sentinel node location over the skin.23 The sentinel node location was identified on the CT image and was indicated precisely by the crossing point of the localizing marker and the CT scan plane lights. The site was marked on the skin surface using an oil pen.

Three-dimensional CT images were reconstructed from the postcontrast CT images at each time point with volume-rendering techniques, and, if necessary, a workstation (GE Advantage Workstation, version 4.3; GE Healthcare) was used to further examine lymph flow and the sentinel node (Fig. 1a).

MR Imaging MR images were obtained using a 1.5T imaging system (Symphony; Siemens, Erlangen, Germany) with a 12-channel matrix body coil. T1-weighted axial images were obtained from the upper thorax to axillary lesions (repetition time in milliseconds [TR], 140; echo time in milliseconds [TE], 1.88; slice thickness, 4 mm; interslice gap, 0 mm; number of acquisitions, 1; field of view, 28 × 28 cm; matrix, 141 × 256). T2-weighted axial images were obtained through the axilla (TR, 4000; TE, 85 effective time; echo train length, 11; slice thickness, 4 mm; interslice gap, 0 mm; number of acquisitions, 1; field of view, 25 × 25 cm; matrix, 250 × 384). Additional nodal imaging sequences included T2*-weighted gradient echo images in the axial plane (TR, 613; TE, 30; flip angle, 30 degrees; slice thickness, 4 mm; interslice gap, 0 mm;
FIG. 1 Three-dimensional CT lymphography reconstructed from the first postcontrast images (a). Contrast agent was injected intradermally into the skin overlying the breast tumor and the subareolar skin. Lymphatic vessels drained into a single axillary sentinel node (arrow). Images of CT lymphography (b) and T2*-weighted axial MR images (c) at the same level were compared to specify the node (arrow) on T2*-weighted axial MR imaging corresponding to the sentinel node (arrow) identified by CT lymphography. If necessary, images (d) of CT lymphography and T2*-weighted axial MR images were merged on a workstation (PEGASYST; ADAC, Milpitas, CA) with the help of small plastic bullets placed as landmarks on the skin.

Each patient was placed in the supine position in the adducted arm position. A 40-μl aliquot of SPIO (Resovist; FUJIFILM RI Farma Co., Ltd., Kyobashi, Tokyo), containing 1.115 mg iron, was diluted in 20 ml normal saline. After local anesthesia with subcutaneous injection of 2 ml of 2% procaine hydrochloride, a 6-ml dose of SPIO, containing 0.3345 mg iron, was injected intradermally into the skin overlying the breast tumor and into the subareolar skin. The injection sites of SPIO were gently massaged for 1 min. At 18 to 24 h after the administration of SPIO, the T1-, T2-, and T2*-weighted sequences used for interpretation of the lymph node status were repeated. The MR imaging interval was determined by referring to the report of the study using USPIO.24 Images of the CT-LG (Fig. 1b) and T2*-weighted axial MR images (Fig. 1c) in the adducted arm position at the same level were compared to specify the node on T2*-weighted axial MR imaging corresponding to the sentinel node identified by CT-LG. If necessary, a merged image of the CT-LG and T2*-weighted axial MR image was obtained on a workstation (PEGASYST; ADAC, Milpitas, CA), with the help of small plastic bullets (Fig. 1d).

Nodes were evaluated on pre-SPIO and post-SPIO images by 1 reader (K.M.). Visual analysis was based on the criteria previously reported by Harisinghani et al.19 In brief, a node was considered nonmetastatic if it showed homogenous low signal intensity and metastatic if the entire node or a focal area did not show low signal intensity on post-SPIO MR imaging compared with the signal intensity on pre-SPIO images (Figs. 2, 3).

Surgery Sentinel node biopsy was performed as described previously.25-27 In brief, intradermal injection of 0.3 ml of 37 MBq (1 mCi) Tc-99m tin colloid the day before surgery and peritumoral injection of 5 ml indocyanine green (ICG, Diagnogreen 0.5%; Daiichi Pharmaceutical Co. Ltd., Nihombashi, Tokyo, Japan) 10 min before surgery were performed, and then the injection site was massaged manually. Hot nodes were identified using a gamma probe (neoc2000; Neoprobe Corporation, Dublin, OH). Lymph nodes located just under the markers using CT images were defined as sentinel nodes and were removed first. All dyed nodes or all nodes with an ex vivo radioisotope count of twofold or greater than the axillary background were removed.

Histopathology Sentinel nodes and dyed or hot nodes were serially sectioned at 2-mm intervals. Hematoxylin and
FIG. 2 (a) CT lymphography demonstrated a sentinel node (arrow). (b) The corresponding node was identified on T2*-weighted axial MR imaging (arrow). The node showed high signal intensity before administration of superparamagnetic iron oxide (SPIO). (c) After administration of SPIO, the node showed strong SPIO enhancement and was diagnosed as benign (arrow). (d) Histologic findings confirmed it as benign.

FIG. 3 (a) CT lymphography demonstrated a sentinel node (arrow). (b) The corresponding node was identified on T2*-weighted axial MR imaging (arrow). The node showed high signal intensity before administration of superparamagnetic iron oxide (SPIO). (c) After administration of SPIO, the node showed no SPIO enhancement and was diagnosed as malignant (arrow). (d) Histologic findings confirmed it as malignant. This node was almost entirely replaced by metastatic tissue (arrowheads).

eosin sections of these nodes were prepared from each 2-mm slice. When these nodes were tumor negative in paraffin sections, an additional 4-μm section was cut and stained with immunohistochemistry (IHC) using the avidin-biotinylated peroxidase complex technique with the mouse monoclonal antibody against cytokeratin (NCL-CK19; Novocasta Laboratories Ltd., Newcastle, UK or AE1/AE3; Thermoelectron Corp., Waltham, MA). Nodes with isolated tumor cells identified by IHC were considered to be metastasis negative in this study, according to the tumor node metastasis categories defined in the 6th edition of the Union for International Cancer Control TNM categories.

RESULTS

The mean age of the 102 patients was 57 (range, 31–79) years, and the mean tumor size was 17.5 (range, 0.2–60) mm. The mean number of sentinel nodes identified by CT-LG was 1.1 (range, 1–3). The mean number of hot and/or dyed nodes removed was 2.0 (range, 1–6). The mean size of sentinel nodes was 10.0 (range, 4–23) mm. All sentinel nodes localized by CT could be identified on MR imaging. Hot spots could be identified over the skin using a gamma probe on all markers of the sentinel node location by CT. No patient with negative sentinel nodes had metastases in other dyed or hot nodes.

A total of 117 sentinel nodes were removed, of which 27 had metastatic deposits. Of these, 11 had deposits smaller than 2 mm. Also, 11 nodes had isolated tumor cells. On a node-by-node basis, 22 of 27 sentinel nodes with metastases were diagnosed as node positive on SPIO-enhanced MR imaging. Of 90 sentinel nodes without metastases, 81 were diagnosed as node negative. The sensitivity, specificity, and accuracy of MR imaging for the diagnosis of sentinel node metastases were 81.5% (95% confidence interval [95% CI], 63–92%), 90.0% (95% CI 82–95%), and 88.0% (95% CI 81–93%), respectively. The negative predictive value (NPV) and positive predictive value (PPV) were 94.2% (95% CI 87–98%), and 71.0% (95% CI 52–86%), respectively (Table 1). On a patient-by-patient basis, 21 of 25 patients with positive sentinel nodes
definitively diagnosed by pathology demonstrated metastases on SPIO-enhanced MR imaging. Of 77 patients with negative sentinel nodes definitively diagnosed by pathology, 70 were nonmetastatic on imaging studies. The sensitivity, specificity, and accuracy of MR imaging for the diagnosis of sentinel node metastases were 84.0% (95% CI 64–95%), 90.9% (95% CI 82–96%), and 89.2% (95% CI 82–94%), respectively. The NPV and PPV were 94.6% (95% CI 87–99%), and 75.0% (95% CI 57–87%), respectively (Table 1). In 4 of 10 patients with micrometastases, the metastases were not detected (Fig. 4), but all 15 patients with macrometastases were identified successfully. Of the 7 false-positive results, 6 were due to a prominent fatty hilum (Fig. 5), and the remaining result was attributable to insufficient uptake of SPIO. For sentinel nodes not less than 10-mm diameter, sensitivity was 90.0% (95% CI 56–100%) and specificity was 95.5% (95% CI 77–100%), and for sentinel nodes less than 10 mm diameter, sensitivity and specificity were reduced to 76.5% (95% CI 50–93%) and 88.2% (95% CI 88–95%), respectively. No adverse events were associated with either CT or MR imaging, such as allergic reactions.

**DISCUSSION**

In the present study, 40% of patients with micrometastases were not detected, although all 15 patients with macrometastases were identified successfully. Excessive dosage or a high concentration of SPIO may conceal small metastatic foci, resulting in low signal intensity of the whole sentinel node (Fig. 4). Micrometastases of 2 mm or smaller would be difficult to detect accurately under this condition. Michel et al. also mentioned that small metastases of 2 mm or smaller cannot be identified using USPIO-enhanced MR imaging because of the limits of spatial resolution in patients with breast cancer. Meta-analysis by nodal size was performed for studies of USPIO-enhanced MRI. For lymph nodes between 5 and 10 mm, sensitivity was 96% and specificity was 99%, and for lymph nodes smaller than 5 mm, sensitivity and specificity were reduced to 41% and 98%, respectively, similar to our results. Because MR imaging has limited resolution in the present setting, micrometastases can be missed more often in small sentinel nodes. On the other hand, the clinical importance of micrometastases for the prognosis is debatable. Hansen et al. reported that patients with sentinel node micrometastases do not have a worse survival than node-negative patients. This is in contrast with a large retrospective study that demonstrated reduced survival in patients with micrometastases. It is necessary to clarify whether micrometastases should be identified intensively or not for the prediction of prognosis and therapy selection. False positives may be due to prominent fatty tissue, focal nodal fibrosis or lipomatosis, and insufficient transition of SPIO to sentinel nodes.

MR imaging using intravenously administered USPIO has been reported to be promising for the evaluation of nodal involvement noninvasively. In meta-analysis, USPIO-enhanced MR imaging is superior to other modalities in the detection of lymph node metastases of various tumors. Despite many such promising results with USPIO-enhanced MR imaging, several issues remain to be solved. One important issue is that many nodes are evaluated on USPIO-enhanced MR imaging as USPIO is probably taken up by all normal nodes of the whole body so it is not known which nodes should be evaluated. Moreover, it has the potential for various adverse events. Bernd et al. presented a comprehensive review of the safety and tolerability of USPIO. At least 1 adverse event considered to be related to USPIO was reported in 18.2% of patients. The most commonly reported USPIO-related events were back pain, pruritis, headache, and urticaria. There were 76 serious adverse events reported in 44 patients (2.6%), although 7 severe adverse events (0.42%) were considered to be USPIO-related (anaphylactic shock, chest pain, dyspnea, skin rash, oxygen saturation decreased, and hypotension).

SPIO is another type of superparamagnetic nanoparticle and consists of iron oxide particles ranging from 50 to 100 nm, with a structure similar to USPIO (particle size, 30 nm). It is commercially available and clinically used as the contrast agent in MR imaging with intravenous administration for the characterization of liver and splenic tumors. Although interstitial administration of

**TABLE 1 Results of MR imaging for the diagnosis of sentinel node metastases**

<table>
<thead>
<tr>
<th>Node-by-node basis</th>
<th>Patient-by-patient basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%) (95% CI)</td>
<td>22 of 27 (81.5%) (63–92%)</td>
</tr>
<tr>
<td>Specificity (%) (95% CI)</td>
<td>81 of 90 (90.0%) (82–95%)</td>
</tr>
<tr>
<td>Accuracy (%) (95% CI)</td>
<td>103 of 117 (88.0%) (81–93%)</td>
</tr>
<tr>
<td>NPV (%) (95% CI)</td>
<td>81 of 86 (94.2%) (87–98%)</td>
</tr>
<tr>
<td>PPV (%) (95% CI)</td>
<td>22 of 31 (71.0%) (52–86%)</td>
</tr>
</tbody>
</table>

CI confidence interval, NPV negative predictive value, PPV positive predictive value
SPIO showed iron oxide uptake in lymph nodes, intravenous administration of SPIO failed to demonstrate iron oxide accumulation within lymph nodes because of their large particle size. SPIO may enter the lymphatic system by increasing interstitial pressure when administered using an interstitial injection, similar to a dye or radiocolloid during sentinel node biopsy. SPIO is well tolerated, with a favorable safety profile when using intravenous administration. Onishi et al. reported that adverse reactions to SPIO occurred in 14.3% of 315 patients. The reported common events were nausea, dizziness, distension, diarrhea, and heartburn, all of which were mild in intensity, and no serious reactions requiring medical treatment were recognized. Moreover, in the present study, SPIO was injected interstitially, not intravenously. It is therefore probable that there would be fewer adverse events with interstitial SPIO injection. No local and systemic adverse events were associated with either CT or SPIO-enhanced MR imaging in this study.

The timing of postcontrast MR imaging was evaluated with a dose and time range study. Hodgins et al. demonstrated that the best imaging timing was 24–36 h after contrast administration. We performed postcontrast MR imaging according to their results, and the time after contrast administration could be cut because contrast agents were locally injected and reached sentinel nodes in a short time. Concerning the concentration of SPIO, we first used 100-fold and 200-fold dilution of SPIO, but even macrometastases were missed in some cases. We then decided to use 500-fold dilution to evaluate this technique. Further study is needed to confirm the best timing and concentration of SPIO to improve the accuracy of this technique.

During sentinel node biopsy, multiple nodes should sometimes be removed as sentinel nodes according to the definition that any dyed nodes and/or hot nodes are sentinel nodes. Most are probably not sentinel nodes, but it is difficult to distinguish sentinel nodes from nonsentinel nodes by the standard procedure of sentinel node biopsy using a dye and/or radiocolloid. It is time consuming, and a considerable volume of axillary fatty tissue is removed during sentinel node biopsy, resulting in complications.
such as lymphedema and neuropathies in these cases.\textsuperscript{6,7} SPIO-enhanced MR imaging may avoid sentinel node biopsy and consequently avoid these complications of sentinel node biopsy. Moreover, only 1 or 2 sentinel nodes are enough to evaluate by SPIO-enhanced MR imaging because CT imaging can accurately identify sentinel nodes by visualizing lymph flow.

When discussing the utility of this technique practically, there is a cost consideration. The small amount of contrast agent per patient and no films may reduce the cost compared with sentinel node biopsy and hospital stay as well as that of pathologic analysis.

In conclusion, SPIO-enhanced MR imaging is a useful method of detecting metastases in sentinel nodes localized by CT-LG in patients with breast cancer and may avoid sentinel node biopsy when the sentinel node is diagnosed as disease-free. Fat-saturated images, a 3-T MR system, and a special coil for MR imaging may be promising to improve accuracy, and further prospective studies using these techniques will be needed to confirm the usefulness of this technique for the diagnosis of sentinel node metastases.

REFERENCES


Sentinel node biopsy for breast cancer: past, present, and future

Kazuyoshi Motomura

Received: 19 September 2012 / Accepted: 15 October 2012
© The Japanese Breast Cancer Society 2012

Abstract Sentinel node biopsy has replaced axillary lymph node dissection as the standard of care in early breast cancers. Sentinel node biopsy represents a highly accurate and less-morbid axillary staging, which allows most patients to avoid unnecessary axillary lymph node dissection and its morbidity. This review provides information including several issues which are still under debate, such as clinical significance of micrometastases, avoidance of axillary lymph node dissection for patients with positive sentinel nodes, accuracy and timing of sentinel node biopsy in patients undergoing neoadjuvant chemotherapy, and how many sentinel nodes are sufficient for removal. Finally, a new topic is introduced: superparamagnetic iron oxide (SPIO)-enhanced magnetic resonance (MR) imaging for the detection of metastases in sentinel nodes localized by computed tomography (CT)-lymphography (CT-LG) in patients with breast cancer. SPIO-enhanced MR imaging is a useful method of detecting metastases in sentinel nodes localized by CT-LG in patients with breast cancer. Patients with clinically negative nodes may be spared even sentinel node biopsy when the sentinel node is diagnosed as disease free using SPIO-enhanced MR imaging.

Keywords Sentinel node · Sentinel node biopsy · Axillary lymph node dissection · Breast cancer · Staging

Introduction

Sentinel node biopsy has rapidly emerged as a minimally invasive, highly accurate method of axillary staging and as an alternative to axillary lymph node dissection as a new standard of care in breast cancer. The concept of the sentinel node was first introduced by Morton and colleagues for early cutaneous melanoma [1]. The sentinel node is the first node draining the primary tumor and the node is the most likely node to contain metastatic disease. This biopsy technique for breast cancer was first validated and demonstrated by Giuliano et al. and Krag et al. Giuliano et al. [2] reported the results of sentinel node biopsy using blue dye alone. Sentinel nodes were identified in 114 (66 %) of 174 patients and precisely predicted the status of the remaining axillary nodes in 96 % of patients. In their next report, Giuliano et al. identified [3] sentinel nodes in 100 (93 %) of 107 patients, with 100 % accuracy for predicting axillary nodal status. Krag et al. [4] were able to identify sentinel nodes in 18 (82 %) of 22 patients using a radioisotope and gamma probe. Motomura et al. [5] reported the results of sentinel node biopsy using indocyanine green (ICG) dye alone. The identification rate and false-negative rate of the ICG-alone technique in 172 patients with breast cancer were 74 and 11 %, respectively. Furthermore, Motomura et al. [6] demonstrated that the combination of dye and radioisotopes is superior to dye alone for sentinel node biopsy. The initial 93 patients had sentinel node biopsy guided by dye alone. The next 138 patients had sentinel node biopsy guided by dye and radioisotopes. Sentinel nodes could be identified in 95 % of 138 patients using dye and radioisotopes, but in only 84 % of 93 patients using dye alone. The sensitivity, specificity, and overall accuracy of the combination method in the prediction of the axillary lymph node status were 100, 100, and 100 %, respectively.
and those of the dye-alone method were 81, 100, and 95 %, respectively. The combination method was significantly superior to the dye-alone method in terms of the identification rate (p = 0.006) and sensitivity (p = 0.011). Subsequently, many studies have confirmed that sentinel node biopsy can accurately predict the status of axillary lymph nodes and is acceptable to replace axillary lymph node dissection in the treatment of early breast cancer [7–13].

Several large-scale prospective trials have been conducted to clarify whether sentinel node biopsy provides adequate axillary staging with a lower rate of morbidity and appropriate local control. The American College of Surgeons Oncology Group (ACOSOG) trial Z0010 is a multi-institutional observational study to determine the prognostic significance of sentinel node and bone marrow metastases [14]. Patients were treated using breast-conserving therapy and sentinel node biopsy with bilateral iliac crest bone marrow aspiration. Of 5,210 eligible patients, 5,119 (98.3 %) had sentinel nodes identified. Of these patients, 3,904 (76.3 %) were tumor negative by hematoxylin–eosin (H&E) staining. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial was designed to compare the survival of sentinel node biopsy alone versus axillary lymph node dissection in clinically node-negative patients. In this trial, 5,611 patients were randomized to two groups: One group (group 1) underwent sentinel node biopsy and axillary lymph node dissection [15]. In the other group (group 2), if sentinel nodes were metastasis free, no further axillary surgery was performed; if sentinel nodes had metastases, axillary lymph node dissection was performed. Overall survival, disease-free survival, and regional control were statistically equivalent between the two groups. Eight-year overall survival was 91.8 % in group 1 and 90.3 % in group 2. Eight-year disease-free survival was 82.4 % in group 1 and 81.5 % in group 2. There were eight regional-node recurrences as first events in group 1 and 14 in group 2 (p = 0.22). The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial was conducted to compare quality-of-life outcomes between patients with clinically node-negative breast cancer who received sentinel node biopsy and patients who received standard axillary lymph node dissection [16]. Patients with sentinel node metastases proceeded to delayed axillary lymph node dissection or received axillary radiotherapy. Lymphedema and sensory loss in the sentinel node biopsy group were significantly less frequent than in the standard axillary lymph node dissection group at 12 months. Moreover, drain usage, length of hospital stay, and time to resumption of normal day-to-day activities after surgery were superior in the sentinel node biopsy group (all p < 0.001), and axillary operative time was also reduced (p = 0.055). Patient-recorded quality of life was significantly better in the sentinel node biopsy group.

There are several reports showing that sentinel node biopsy preserved good locoregional control. Giuliano et al. [17] reported the results of sentinel node biopsy using blue dye alone in 133 patients with breast cancer. At 39 months of follow-up, no local or axillary recurrence was reported for 67 patients with tumor-negative sentinel nodes who were observed without further axillary treatment. Veronesi et al. [18] reported the results of a randomized study comparing sentinel node biopsy with axillary lymph node dissection in breast cancer with a 10-year follow-up. There was no statistically significant difference between the axillary lymph node dissection group and the sentinel node biopsy group in terms of axillary recurrence (2 patients in the sentinel node biopsy group vs. no patients in the axillary lymph node dissection group, p = 0.17). Naik et al. [19] reported 4,008 patients with breast cancer who had sentinel node biopsy; 2,340 patients with tumor-negative sentinel nodes had sentinel node biopsy alone. With a median follow-up of 31 months, axillary recurrence occurred in only 3 (0.12 %) patients. In the ACOSOG Z0010, only 0.5 % of the 3,904 patients with H&E-negative sentinel nodes were found to have regional recurrence with a median follow-up of 8.4 years [20]. Van der Ploeg et al. [21] performed a systematic review and meta-analysis of 48 studies concerning 14,959 patients with tumor-negative sentinel nodes who had no axillary lymph node dissection. With a median follow-up of 34 months, 67 (0.3 %) patients developed an axillary recurrence.

On the basis of the results of many studies, sentinel node biopsy has been accepted to be a safe and effective alternative, associated with a better quality of life, to routine axillary lymph node dissection for nodal staging in breast cancer.

Controversy of sentinel node biopsy in breast cancer

Clinical significance of micrometastases in sentinel nodes

The clinical significance of micrometastases in the axillary lymph nodes is an important issue, but is unknown at present. Several studies have shown that focused analysis of axillary lymph nodes can detect micrometastases missed by routine single-section analysis. In the large retrospective study conducted by the International (Ludwig) Breast Cancer Study Group, 7 % of 736 patients who had tumor-negative axillary lymph nodes on routine H&E single-section analysis were found to be node positive on serial sectioning [22]. Additional occult metastases were identified in 20 % of patients by immunohistochemistry. Patients with occult metastases have a higher disease recurrence rate and a lower overall survival rate than those with occult.
metastasis-free axillary lymph nodes. Hainsworth et al. [23] demonstrated that occult metastases were detected in 12% of 343 patients with node-negative breast cancer using immunohistochemistry. After a median follow-up of 79 months, patients with occult metastases had a shorter time to disease recurrence (p < 0.05) but not to death. Chen et al. [24] reviewed the Surveillance, Epidemiology and End Results (SEER) database for patients with breast cancer between 1992 and 2003. The analysis included 209,720 patients. On multivariate analysis, micrometastases remained a significant prognostic indicator across all patients (p < 0.0001) with a hazard ratio of 1.35 compared to N0 disease and 0.82 compared to N1 disease. Chen et al. concluded that nodal micrometastasis of breast cancer carries a prognosis between N0 and N1 disease, even after adjusting for tumor- and patient-related factors.

The sentinel node is the most likely to harbor axillary lymph node metastases from breast cancer. One of the advantages of sentinel node biopsy is that focused analysis, such as multiple sectioning and immunohistochemical staining, is easy to perform because the mean number of sentinel nodes is only one or two per patient. Such focused analysis can identify more patients with micrometastases. Giuliani et al. [25] reported that sentinel node biopsy with focused histopathological analysis was more sensitive than axillary lymph node dissection with routine lymph node analysis (42 vs. 29%; p < 0.03); 10.3% of axillary lymph node dissection patients and 38.2% of sentinel node biopsy patients had micrometastasis, and there was a highly significant difference between them (p < 0.0005). Dowlatshahi et al. [26] reported that tumor metastases were found in 6 patients (12%) when sentinel nodes were sectioned at 2-mm intervals and stained with H&E, compared with 24 additional patients (46%) when the same sentinel nodes were sectioned serially at 0.25-mm intervals and stained with cytokeratin. Twelve of the 24 patients with occult metastases had colonies of metastatic cells and the other 12 had isolated tumor cells. Motomura et al. [27] also demonstrated that intensive histological examination of sentinel nodes could detect metastases more often than routine H&E examination of axillary nodes obtained by axillary lymph node dissection. The status of multiple sections of each sentinel node examined by H&E and immunohistochemical staining using cytokeratin was compared with one section of each sentinel and non-sentinel node examined by routine H&E staining in 152 patients with breast cancer. Multiple sectioning and immunohistochemical staining of sentinel nodes detected a further 16% of patients with metastases more than routine metastases. Micrometastases were detected in sentinel nodes from 20 patients by immunohistochemistry, 9 of whom had isolated tumor cells and 11 had micrometastases.

On the other hand, the prognostic relevance of micrometastases in sentinel nodes from patients with breast cancer has been under debate since the introduction of sentinel lymph node biopsy. Giuliani et al. [14] demonstrated that immunohistochemical staining of sentinel nodes and bone marrow identifies breast cancer metastases not seen with routine pathological or clinical examination from the data of the ACOSOG Z0010 trial. Of 5,119 sentinel node specimens, 76.3% were tumor negative by H&E staining. Of 3,326 sentinel node specimens examined by immunohistochemistry, 10.5% were tumor positive. Of 3,413 bone marrow specimens examined by immunocytochemistry, 3.0% were tumor positive. At a median follow-up of 6.3 years, immunohistochemically detected metastasis of the sentinel node was not significantly associated with overall survival (p = 0.64). Giuliani et al. concluded that routine immunohistochemical examination of H&E-negative sentinel nodes is not clinically warranted for early breast cancer. Bone marrow metastases were associated with decreased overall survival (p = 0.04); however, Giuliani et al. suggested that the incidence of occult bone marrow metastases was too low to recommend introducing bone marrow aspiration biopsy into routine practice. Weaver et al. [28] reported the results of re-evaluating occult metastases in sentinel lymph nodes obtained from patients with pathologically negative sentinel lymph nodes using both routine staining and immunohistochemical staining for cytokeratin from the NSABP B-32 study. Occult metastases were detected in 15.9% of 3,887 patients. There was a statistically significant difference between patients in whom occult metastases were detected and those in whom no occult metastases were detected with respect to overall survival (p = 0.03), disease-free survival (p = 0.02), and distant disease-free interval (p = 0.04). However, Weaver et al. suggested that the difference in outcome at 5 years was only 1.2% and the clinical benefit of additional evaluation, including immunohistochemical analysis, of initially negative sentinel nodes is doubtful. The results of the ACOSOG Z0010 and NSABP B-32 trials suggest that sentinel node micrometastases found only by immunohistochemistry are not clinically significant. Routine immunohistochemistry is not recommended for the evaluation of sentinel nodes in guidelines published by the American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN) [29, 30]. Hansen et al. [31] conducted a prospective study designed to determine the survival impact of micrometastases in sentinel nodes. The sentinel nodes were examined in 790 patients and they were divided into four groups: pN0(i−), no evidence of tumor (n = 486); pN0(i+), tumor deposit no larger than 0.2 mm (n = 84); pN1mi, tumor deposit larger than 0.2 mm but no larger than 2 mm (n = 54), and
pN1, tumor deposit larger than 2 mm (n = 166). At a median follow-up of 72.5 months, neither patients with pNOi+ nor pN1mi seemed to have a worse 8-year disease-free survival or overall survival than sentinel node-negative patients. As expected, there was a significant decrease in 8-year disease-free survival and overall survival in patients with pN1 disease in the sentinel node. The majority of patients with micrometastases and isolated tumor cells received adjuvant systemic therapy (96.3 and 91.6 %, respectively) in this study. De Boer et al. [32] demonstrated the results of disease-free survival in breast cancer patients with favorable primary-tumor characteristics and isolated tumor cells or micrometastases in the sentinel node. In total, 856 patients with node-negative disease who had not received systemic adjuvant therapy, 856 patients with isolated tumor cells or micrometastases who had not received systemic adjuvant therapy, and 995 patients with isolated tumor cells or micrometastases who had received such treatment were included. After a median follow-up of 5.1 years, as compared with women with node-negative disease, the adjusted hazard ratio for disease events among patients with isolated tumor cells who did not receive systemic therapy was 1.50 (95 % confidence interval [CI] 1.15–1.94); among patients with micrometastases, the adjusted hazard ratio was 1.56 (95 % CI 1.15–2.13). Among patients with isolated tumor cells or micrometastases, the adjusted hazard ratio was 0.57 (95 % CI 0.45–0.73) in the node-positive, adjuvant-therapy cohort, as compared with the node-positive, no-adjuvant-therapy cohort. Disease-free survival was improved in patients with isolated tumor cells or micrometastases who received adjuvant therapy.

Avoidance of axillary lymph node dissection in patients with positive sentinel nodes

Axillary lymph node dissection for all tumor-positive sentinel nodes has been questioned. Several investigators have reported the single-institution results of their studies of sentinel node biopsy without axillary lymph node dissection for a tumor-positive sentinel node in breast cancer (Table 1) [33–40]. Although most included a small number of patients, the axillary recurrence rate was low, 0–2.1 %. Bilimoria et al. [39] reported the results of the retrospective analysis of data from the National Cancer Database. In 2,203 patients with microscopic nodal metastases, there were no significant differences in axillary recurrence or survival for patients who underwent sentinel node biopsy alone versus axillary lymph node dissection. These results suggested that axillary lymph node dissection did not improve the outcomes of breast cancer patients with microscopic nodal metastases. Pepels et al. [41] reported the results of the regional recurrence rate in breast cancer patients with favorable primary-tumor characteristics and isolated tumor cells or micrometastases in the sentinel node with or without axillary dissection. In total, 857 patients with node-negative disease and 1,823 patients with isolated tumor cells or micrometastases in the sentinel node were included. Without axillary treatment, the 5-year regional recurrence rates were 2.3, 2.0, and 5.6 %, respectively. Compared with patients who underwent axillary treatment, the hazard ratio (HR) for regional recurrence in patients who underwent a sentinel node biopsy alone was 1.1 (95 % CI 0.23–4.98) for node-negative disease, 2.4 (95 % CI 0.67–8.48) for isolated tumor cells, and 4.4 (95 % CI 1.46–13.24) for micrometastases. Pepels et al. recommended axillary treatment in patients with sentinel node micrometastases and unfavorable tumor characteristics. Yi et al. [42] reported the results of comparing the outcome of 26,986 patients with positive sentinel nodes undergoing sentinel node biopsy alone versus sentinel node biopsy with axillary lymph node dissection identified from the SEER database (1998–2004). At a median follow-up of 50 months, there were no statistically significant differences in overall survival between them. Of the patients with micrometastases, 50.6 % underwent sentinel node biopsy alone, compared with only 20.4 % of patients with macrometastases. In patients with micrometastases (n = 6,838), there were no statistically significant differences in ipsilateral regional recurrence between those who underwent sentinel node biopsy alone and those who underwent axillary lymph node dissection. Patients with macrometastases (n = 20,148) had a significantly lower risk of developing ipsilateral regional recurrences after axillary lymph node dissection than after sentinel node biopsy alone (0.08 vs. 0.2 %; HR 0.30; p = 0.02). Wasif et al. [43] reported the results from the SEER database (1998–2005). Of 5,353 patients with sentinel node micrometastases, only 60 % of patients underwent axillary lymph node dissection and 40 % of patients had no further axillary surgery. Galimberti et al. [44] reported the recent follow-up results from the International Breast Cancer Study Group (IBCSG) 23-01 trial at the 2011 San Antonio

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Axillary recurrence (%)</th>
<th>Median follow-up months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guenther [33]</td>
<td>2003</td>
<td>46</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Nal [34]</td>
<td>2004</td>
<td>210</td>
<td>1.4</td>
<td>31</td>
</tr>
<tr>
<td>Swenson [35]</td>
<td>2005</td>
<td>67</td>
<td>1.5</td>
<td>33</td>
</tr>
<tr>
<td>Jeness [36]</td>
<td>2005</td>
<td>73</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Park [37]</td>
<td>2007</td>
<td>287</td>
<td>2.1</td>
<td>23</td>
</tr>
<tr>
<td>Hwang [38]</td>
<td>2007</td>
<td>196</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Bilimoria [39]</td>
<td>2009</td>
<td>1,988</td>
<td>0.6–1.2</td>
<td>64</td>
</tr>
<tr>
<td>Spiguel [40]</td>
<td>2011</td>
<td>123</td>
<td>0.8</td>
<td>95</td>
</tr>
</tbody>
</table>
Breast Cancer Symposium to determine whether axillary lymph node dissection is necessary in patients with sentinel node micrometastases. Nine hundred and thirty-one patients with tumors no larger than 5 cm and micrometastases in one or more sentinel nodes were included in this study. After a median follow-up of 49 months, there were no differences between the no-dissection and dissection group in 5-year disease-free survival rates (88.4 vs. 87.3 %) and 5-year survival rates (98 vs. 97.6 %). Axillary lymph node dissection is underused at present even if micrometastases are found in the sentinel nodes.

Moreover, the results of the ACOSOG Z0011 study have recently been reported [45, 46]. This is a prospective study of patients with sentinel node-positive breast cancer with T1 or T2 breast cancers randomized to axillary lymph node dissection or observation of the axilla after sentinel node biopsy. All patients received breast-conserving surgery and whole breast irradiation. Patients with at least 3 positive sentinel nodes and patients receiving neoadjuvant chemotherapy were excluded from the study. After 6.3 years of follow-up, there was no difference in the 5-year locoregional recurrence rate (4.1 vs. 2.8 %), 5-year overall survival rate (91.9 vs. 92.5 %), and 5-year disease-free survival rate (82.2 vs. 83.8 %). Adjuvant systemic therapy was given to most patients. Forty percent of patients had micrometastases or isolated tumor cells and 60 % had macrometastases in the sentinel nodes. Axillary recurrence was similar in each arm, with 0.9 % of patients in the sentinel node biopsy alone group compared to 0.5 % of patients in the axillary lymph node dissection group. Axillary lymph node dissection can be avoided in selected patients who meet the Z0011 study criteria: T1–T2 clinically node-negative disease and one or two involved sentinel lymph nodes, treated with breast-conserving surgery and whole breast irradiation, and no neoadjuvant chemotherapy. The recommendation reflects an upgrade of the NCCN clinical practice guidelines to a category 1 recommendation (Breast Cancer v.1. 2012) [30].

Neoadjuvant chemotherapy and sentinel node biopsy

Neoadjuvant chemotherapy has been used frequently to downsize large breast tumors and preserve the breast in patients who would otherwise require mastectomy [47]. Axillary lymph node dissection has been the standard practice for such patient populations after neoadjuvant chemotherapy. The use of sentinel node biopsy and the timing of the procedure in patients receiving neoadjuvant chemotherapy have become very important issues.

When sentinel node biopsy is performed before neoadjuvant chemotherapy, there is some concern whether the procedure is feasible for patients with a large primary tumor which is being considered for neoadjuvant chemotherapy. Two studies have demonstrated that sentinel node biopsy provided accurate nodal staging in this patient population without neoadjuvant chemotherapy [48, 49]. Moreover, several institutional case series reported the results of this procedure before neoadjuvant chemotherapy in a small number of patients (Table 2) [50-55]. The identification rate of the sentinel node in these studies was almost 100 %, comparable to that accepted for the use of sentinel node biopsy in patients with a small primary tumor. Unfortunately, the false-negative rate cannot be calculated accurately because the status of the sentinel node was compared with that of the axillary lymph node after neoadjuvant chemotherapy, but several reports have demonstrated a false-negative rate of 0 % [50, 52].

The concerns regarding sentinel node biopsy after neoadjuvant chemotherapy are the possible alterations of lymphatics after neoadjuvant chemotherapy, which may decrease the identification rate of the sentinel node. Moreover, chemotherapy may not equally affect the sentinel node and the non-sentinel node, and the non-sentinel node might have residual disease whereas the sentinel node might not, which could lead to an increase of the false-negative rate. However, many studies have recently shown that sentinel node biopsy is accurate for the prediction of axillary lymph node metastases in patients receiving neoadjuvant chemotherapy (Table 3) [56-67]. In the NSABP B-27, a subset of 428 patients underwent sentinel node biopsy after neoadjuvant chemotherapy [58]. The overall identification rate of the sentinel node was 84.8 %, with a false-negative rate of 10.7 %. Xing et al. [59] reported the results of a meta-analysis of studies that examined the results of sentinel node biopsy after neoadjuvant chemotherapy. This study included 1,273 patients from 21 studies. Using Bayesian modeling, estimates of the identification rate and false-negative rate were 91 and 12 %, respectively. Kelly et al. [65] reported the results of a systematic search of the literature on sentinel node biopsy after chemotherapy in breast cancer patients. Twenty-four trials on 1,799 patients were reported. The identification

<table>
<thead>
<tr>
<th>Table 2: Studies of sentinel node biopsy before neoadjuvant chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
</tr>
<tr>
<td>Ollila [50]</td>
</tr>
<tr>
<td>Cox [51]</td>
</tr>
<tr>
<td>Schrenk [52]</td>
</tr>
<tr>
<td>Grupe [53]</td>
</tr>
<tr>
<td>Papa [54]</td>
</tr>
<tr>
<td>Straver [55]</td>
</tr>
<tr>
<td>NS not stated</td>
</tr>
</tbody>
</table>

© Springer
Table 3 Studies of sentinel node biopsy after neoadjuvant chemotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of patients</th>
<th>Identification rate (%)</th>
<th>False-negative rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lang [56]</td>
<td>2004</td>
<td>53</td>
<td>94</td>
<td>4</td>
</tr>
<tr>
<td>Shimazu [57]</td>
<td>2004</td>
<td>47</td>
<td>94</td>
<td>12</td>
</tr>
<tr>
<td>Mamounas [58]</td>
<td>2005</td>
<td>428</td>
<td>85</td>
<td>11</td>
</tr>
<tr>
<td>Xing [59]</td>
<td>2006</td>
<td>1,273</td>
<td>90</td>
<td>12</td>
</tr>
<tr>
<td>Lee [60]</td>
<td>2007</td>
<td>219</td>
<td>78</td>
<td>5.6</td>
</tr>
<tr>
<td>Kinoshita [61]</td>
<td>2007</td>
<td>104</td>
<td>93</td>
<td>10</td>
</tr>
<tr>
<td>Tausch [62]</td>
<td>2008</td>
<td>167</td>
<td>85</td>
<td>8</td>
</tr>
<tr>
<td>Grimmberger [63]</td>
<td>2008</td>
<td>129</td>
<td>94</td>
<td>14</td>
</tr>
<tr>
<td>Classe [64]</td>
<td>2009</td>
<td>195</td>
<td>90</td>
<td>12</td>
</tr>
<tr>
<td>Kelly [65]</td>
<td>2009</td>
<td>1,799</td>
<td>90</td>
<td>8</td>
</tr>
<tr>
<td>Hunt [66]</td>
<td>2009</td>
<td>575</td>
<td>97</td>
<td>6</td>
</tr>
<tr>
<td>Van Deurzen [67]</td>
<td>2009</td>
<td>2,148</td>
<td>91</td>
<td>10.5</td>
</tr>
</tbody>
</table>

How many sentinel nodes are enough?

Sentinel node biopsy using dye and/or radioisotopes often results in the removal of multiple nodes as a sentinel node, although most of them may be non-sentinel nodes. How many and which axillary lymph nodes need to be removed as sentinel nodes for accurate axillary staging is unclear. Wong et al. [68] reported that the false-negative rate was 14% if only the first node had been removed. The 10% rule is one of the most popular definitions of a sentinel node. It is defined as the removal of all sentinel nodes with counts greater than 10% of the most radioactive node. Martin et al. [69] reported that the false-negative rate was 13% if only the “hottest” node was removed, whereas it was 5.8% if the 10% rule was applied. On the other hand, some researchers suggest that a certain number of lymph nodes is sufficient for accurate axillary staging. Zervos et al. [70] reported that 98% of metastatic sentinel nodes were found when the first three nodes were removed. Zakaria et al. [71] reported that 100% of patients with positive sentinel nodes were found when the first four sentinel nodes were removed. When many more nodes are removed, the false-negative rate may fall, but may worsen the morbidity of the sentinel node biopsy.

Recently, sentinel nodes have been reported to be identified well using computed tomography (CT)-lymphography (CT-LG) in patients with breast cancer. Tangoku et al. [72] demonstrated that lymph flow and sentinel nodes were successfully visualized by local injection of the CT contrast agent in all 40 patients. Motomura et al. [73] evaluated whether true sentinel nodes identified by CT-LG accurately staged the axilla in 168 patients with breast cancer and whether it is sufficient to remove true sentinel nodes alone, reported at the 2010 San Antonio Breast Cancer Symposium. The location of true sentinel nodes was marked on the skin surface using a CT laser light navigator system. Lymph nodes located just under the marking were removed first as true sentinel nodes. Then, all dyed nodes or all “hot” nodes were removed. The mean number of true sentinel nodes identified by CT-LG was 1.1 (range 1–3). The mean number of “hot” and/or dyed nodes removed was 1.8 (range 1–6). Pathologic evaluation revealed that 38 (22.6%) of 168 patients had metastasis to at least one node. All of these 38 patients demonstrated metastases to at least one of the true sentinel nodes identified by CT-LG. True sentinel nodes identified by CT-LG accurately staged the axilla in patients with breast cancer. Removal of true sentinel nodes alone may reduce postoperative morbidity and the cost of the procedure by shortening the operative time and decreasing the costs of pathologic analysis. Moreover, it is quite advantageous to know the number and location of sentinel node in the axilla preoperatively.
Future perspectives

Superparamagnetic iron oxide (SPIO)-enhanced magnetic resonance imaging for the detection of metastases in sentinel nodes localized by CT-LG in patients with breast cancer.

Sentinel node biopsy is a diagnostic procedure, not a treatment. If another method, such as imaging, can accurately stage the axilla, it is not necessary to perform sentinel node biopsy as axillary surgery; however, there is insufficient accuracy with conventional imaging techniques such as ultrasonography, magnetic resonance (MR) imaging, and CT.

Recently, superparamagnetic nanoparticle-enhanced MR imaging has been reported to be a promising procedure for accurate staging of lymph node metastases from various tumors. Harisinghani et al. [74] demonstrated the accuracy of ultrasmall superparamagnetic iron oxide (USPIO)-enhanced MR imaging for nodal staging in 344 lymph nodes from 80 patients with prostate cancer. Sensitivity of the procedure was 90.5% on a node-by-node basis, significantly higher than the conventional method using size criteria, which has a sensitivity of 35.4%. Moreover, sentinel nodes have been reported to be identified well using CT-LG in patients with breast cancer, as mentioned above [73]. Motomura et al. [75] evaluated superparamagnetic nanoparticle-enhanced MR imaging for the detection of metastases in sentinel nodes located by CT-LG in 102 patients with breast cancer. SPIO was used as the contrast agent in MR imaging. Sentinel nodes were identified by CT-LG, and SPIO-enhanced MR imaging of the axilla was performed to detect metastases in the sentinel nodes. A node was considered non-metastatic if it showed homogenous low signal intensity and metastatic if the entire node or a focal area did not show low signal intensity on MR imaging. The mean number of sentinel nodes identified by CT-LG was 1.1 (range 1–3). The sensitivity, specificity, and overall accuracy of MR imaging for the diagnosis of sentinel node metastases were 84%, 91%, and 89%, respectively. In four of 10 patients with micrometastases, the metastases were not detected, but all 15 patients with macrometastases were successfully identified. SPIO-enhanced MR imaging is useful for detecting metastases in sentinel nodes localized by CT-LG in patients with breast cancer.

Conclusions

Sentinel node biopsy has been widely accepted as a standard procedure for axillary staging and has affected the management of early breast cancer. Although sentinel node biopsy decreases the risk of morbidity, such as lymph edema, neuropathies, and shoulder motility, a few patients still have such morbidity. Imaging is an another method of staging the axilla and is considered to be much less invasive for axillary staging. Patients with clinically negative nodes may be spared even sentinel node biopsy when the sentinel node is diagnosed as disease free using new imaging techniques such as SPIO-enhanced MR imaging.

Acknowledgments

This work was supported in part by the National Cancer Center Research and Development Fund (22-38).

Conflict of interest

None.

References


47. Kaufmann M, von Minckwitz G, Manousuopoulou EP, Cameron D, Carey LA, Cristofanilli M, et al. Recommendations from an international consensus conference on the current status and