Improvement in intramammary sentinel lymph node removal using a novel prototype hand held probe during breast conservative surgery

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Summary
Intramammary sentinel lymph node excision during breast conservative surgery was performed, in this case report, using a prototype intraoperative gamma probe. In contrast to the four axillary sentinel lymph nodes that were subnormal, the excised intramammary sentinel lymph node was massively invaded by cancer cells. Therefore this finding had profound implication for the staging of the tumor and for treatment selection. This case report illustrates that an efficient intraoperative gamma probe is useful to locate and remove intramammary sentinel lymph node in breast cancer patients treated with breast conservation.

Introduction
The precise knowledge of lymph node (LN) status is essential for breast cancer management since it is the most accurate prognostic factor [1]. Accordingly finding involved LN influences the selection of adjuvant therapy. The traditional staging procedure, axillary clearance, carries a significant risk of side effects, and therefore is being replaced in selected patients by the sentinel lymph node (SLN) procedure [2]. Indeed, the SLN procedure is now widely used in the staging of breast cancer patients. The SLN is the first node where lymphatic drainage and cancer cells colonization occur [2–4]. Nevertheless the technique of SLN detection deserves to be improved to avoid false negative and to increase intramammary SLN (ISLN) detection. The proportion of intra-mammary LN (ILN) is a controversial subject. According to several studies and depending on the detection method used, the presence of ILN can be hardly ever or frequently detected. For example, in a prospective study, 199 potential ILN (13%) were found on 1500 mammograms [5]. In retrospective studies, when extensive histological examination of the breast was performed after mastectomy, the percentage of ILN was found between 4% (3 out 77) [6] and 28% (45 out of 158) [7] of the breast cancer cases studied, respectively. A further study highlighted the prognostic significance of ILN involvement [8]. In this study, 100 stage I patients were considered and 25 had detectable ILN. A morphological examination of these 25 ILN showed that 6 were involved and 19 were normal [8]. The survival rate at 10 years was 33% for the metastatic and 76% for the normal ILN carriers [8]. The same study showed that ILN involvement did not adversely affect the prognosis of stage II patients [8]. This report implies that among stage I patients the involvement of ILN should systematically be investigated. To date, protocols to detect SLN are diverse and may include preoperative injection of a radio-pharmaceutical compound alone or with intraoperative dye-injection [9]. These protocols also improve the detection of ISLN. In this study we report a first experience using a prototype gamma probe to detect a hidden ILN.

Patient and methods
A 49-year-old Caucasian woman presented a mass in the upper outer quadrant of her left breast. The core biopsy revealed the presence of a differentiated infiltrating ductal carcinoma. SLN detection was performed using a preoperative injection of a radioisotope solution (400 μCi of technetium 99m colloidal, Nanocis, Oris, France) at the four cardinal points in the subareolar area. Lymphoscintigraphy was realized 3 h
after injection (Adac, Philips, Netherlands). A breast conservative surgery was performed. To facilitate SLN identification, methylene blue (1 ml, concentration 1%, Aguettant, France) was injected into subareolar area at the 4 cardinal points. Two intraoperative gamma probes were used to locate radioactive SLN, a cadmium telluride (CdTe) probe (Eurorad, France) and a prototype probe named CAROLIReS developed by the IReS institute [10]. This probe is based on a fast scintillating yttrium aluminium perovskite (YAP) crystal [11]. According to its high gamma-ray detection efficiency, this prototype allows the open diameter to be small enough (< 4.0 mm) to confer to the probe a good selection in the search of SLN with a high spatial resolution. The cylindrical moving collimator of the system has two positions and acts as an efficient shielding against noise. The activity of nodes was measured during the resection with the 2 intraoperative probes and was further confirmed using a gamma-ray counter (Table I). The pathological examination of the nodes was performed by haematoxylin–eosin (H&E) staining. The nodes that appeared to be free of cancer cells were further subjected to immunohistochemistry (IHC) using an antikeratin antibody (AE1/AE3 Dako) that allows the detection of isolated or small clusters of epithelial cells.

**Results**

While mammography (Figure 1a) failed to show ILN, lymphoscintigraphy showed an ISLN as a spot confined to the lower inner quadrant of the breast together with four spots in the axillary area (Figure 1b). The four axillary SLN were first removed using the detection probes and their total activity counting in Hertz was found to be between 1780 and 14600. All were stained with the dye. No dye was visible in the lower internal quadrant and excision of the ISLN was not possible using the CdTe probe since this probe could not discriminate the ISLN radioactive signal from the background signal remaining at the radioisotope injection points. Using a prototype CAROLIReS probe, localization of ISLN radioactive signal was possible since its shielding avoided the background noise. The node was then removed without damaging the breast.

Because ISLN are difficult to identify preoperatively and often small and impalpable, they are difficult to excise when conservative surgery is considered. Nevertheless, this case report shows that an efficient intraoperative gamma probe is helpful to find Hertz was 380 (Figure 1c). Extemporaneous histological examination of the excised SLN showed the absence of cancer cells in the four axillary SLN by H&E staining (Table I). In addition, Keratin immunodetection revealed the presence of few epithelial cell clusters in one axillary SLN. However, the precise significance of these cells is unclear. Therefore, this node was not considered as positive. On the contrary, the ILN was invaded by cancer cells (Figure 1c) and lumpectomy and axillary clearance were performed. Finally, this patient was staged node positive and treated with adjuvant chemotherapy, radiotherapy and anti estrogenic therapy.

**Discussion**

Technical difficulties are often responsible for the poor detection of ILN. The low ILN incidence might essentially be owned to their difficult identification and localization [12]. The common SLN detection protocols use preoperative radioisotope injection and/or intraoperative dye-injection. These methods also improve the detection of ISLN as reported in the literature [13–15]. Nevertheless, when conservative surgery is considered, a significant technological improvement is needed to delineate accurately the ISLN within the breast. Here we show how an ISLN identified preoperatively with lymphoscintigraphy and can be removed in a breast conservative manner. During surgery, although axillary SLN were easily detected using a CdTe probe, this probe failed to localize ISLN since it could not discriminate the ISLN radioactive signal from the background signal remaining at the radioisotope injection points. Using a prototype CAROLIReS probe, localization of ISLN radioactive signal was possible since its shielding avoided the background noise. The node was then removed without damaging the breast.

<table>
<thead>
<tr>
<th>SLN localization</th>
<th>Probe CdTe&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Probe CAROLIReS&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Gamma-ray counter&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Methylene blue&lt;sup&gt;d&lt;/sup&gt;</th>
<th>H&amp;E&lt;sup&gt;d&lt;/sup&gt;</th>
<th>IHC&lt;sup&gt;e&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Axillary 1</td>
<td>+</td>
<td>26</td>
<td>1780</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Axillary 2</td>
<td>+</td>
<td>70</td>
<td>3180</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Axillary 3</td>
<td>+</td>
<td>47</td>
<td>3780</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Axillary 4</td>
<td>+</td>
<td>120</td>
<td>14600</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Intramammary</td>
<td>–</td>
<td>7</td>
<td>380</td>
<td>–</td>
<td>+</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND – not done.

<sup>a</sup>Clear signal (sign +), no discrimination between signal and noise (sign –).

<sup>b</sup>Activity monitored in Hertz in the small solid angle defined by the collimator.

<sup>c</sup>Total activity counting in Hertz in 2π solid angle.

<sup>d</sup>Detection of cancer cells using histological examination with haematoxylin–eosin – cancer cells (sign +), absence of cancer cells (sign –).

<sup>e</sup>Detection of epithelial cells using immunohistochemistry staining of keratin.