Integrating new imaging modalities in breast cancer management
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Intraoperative 3D navigation for single or multiple $^{125}$I-seed localisation in breast-preserving cancer surgery

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Abstract

Background
Mammographic screening has led to the identification of more women with non-palpable breast cancer, many of them to be treated with breast-preserving surgery. To accomplish radical tumour excision adequate localisation techniques like radioactive seed localisation (RSL) are required. For RSL a radioactive $^{125}$iodine-seed ($^{125}$I-seed) is implanted central in the tumour to enable intraoperative localisation using a gamma-probe. In case of extensive tumour or multifocal carcinoma, multiple $^{125}$I-seeds can be used to delineate the involved area. Preoperative imaging is performed different from surgical positioning; therefore exact $^{125}$I-seed depth remains unknown during surgery.

Methods
Twenty patients (mean age 56.8y) with 25 implanted $^{125}$I-seeds scheduled for RSL were included. Sixteen patients had 1 $^{125}$I-seed implanted in the primary lesion, 3 patients 2 $^{125}$I-seeds, and 1 patient 3 $^{125}$I-seeds. Freehand-SPECT localised $^{125}$I-seeds by measuring gamma counts from different directions all registered by an optical tracking system. A reconstruction and visualisation algorithm enabled 3D navigation towards the $^{125}$I-seeds.

Results
Freehand-SPECT visualized all $^{125}$I-seeds in primary tumours and provided pre-incision depth information. The deviation between the freehand-SPECT depth and the surgical depth estimation was 1.9mm (SD 2.1mm, Range 0-7mm). 3D freehand-SPECT was especially useful identifying multiple implanted $^{125}$I-seeds since the conventional gamma-probe has more difficulty discriminating $^{125}$I-seeds transcutaneous.

Conclusion
Freehand-SPECT with 3D navigation is a valuable tool in RSL for both single and multiple implanted $^{125}$I-seeds in breast-preserving cancer surgery. Freehand-SPECT provides continuous updating 3D imaging with information about depth and location of the $^{125}$I-seeds contributing to adequate excision of non-palpable breast cancer.
Background

The use of mammographic screening in nationwide programs has led to an increase in the number of women with non-palpable breast cancer lesions. [1,2] Currently, more than 25% of the radiological suspicious breast lesions are considered clinically non-palpable. [3] Accordingly, in many patients, accurate pre- and intraoperative localisation of these non-palpable lesions is important for adequate breast-conserving surgery. Similarly, adequate localisation is indispensable to allow breast-conserving surgery in patients with locally advanced breast cancer following successful neoadjuvant systemic treatment (NST). At present, three important techniques are used to localize the tumour prior to excision: wire-, ultrasound (US)-, and radioguided (i.e. guided by a radionuclide) localisation, which are applied according to local preferences. [3-5] When there is no clinical evidence for lymph node involvement, these approaches are often combined with a sentinel node (SN) biopsy procedure. [6-8]

At The Netherlands Cancer Institute radioactive seed localisation (RSL) is used for non-palpable breast tumour localisation during surgery and over 1,500 $^{125}$iodine- ($^{125}$I-) seeds have been implanted since 2008. For RSL, a 3.7 to 10.7 MBq $^{125}$I-seed with a half-life time of 60 days is preoperatively implanted into the malignant lesion using US guidance. If the lesion is only visible on mammography, placement of the $^{125}$I-seed is performed under stereotactic guidance. Immediately hereafter, correct position of the $^{125}$I-seed is confirmed by an additional mammogram. This technique is used for localisation of non-palpable lesions in primary surgery and for the setting where NST is given to allow breast-conserving surgery after tumour downsizing. For this latter category marking of the tumour before the start of the NST is required to enable accurate breast conserving surgery afterwards. An important advantage of $^{125}$I-seed markers is that they do not migrate and can remain for longer periods of time within the breast. [9,10] This $^{125}$I-seed acts as a radioactive point source and can be localized within the breast by means of a gamma probe, with adjustment for the $^{125}$I gamma energy. In case of extended areas of ductal carcinoma in situ (DCIS) or multifocal lesions, multiple $^{125}$I-seeds can be placed to delineate the area of a larger lesion or different foci. [11,12]

Recently, a novel freehand single-photon emission computed tomography (SPECT) system (declipse®SPECT, SurgicEye GmbH, Munich, Germany) for three-dimensional (3D) tomographic radio-guided imaging and navigation has been introduced. This innovative device combines a conventional gamma probe with an optical tracking system. An algorithm links the measured counts from the location of the gamma probe
in space and, accordingly, reconstructs a 3D radioactivity map for visualisation. [13,14] Previously we determined the accuracy of this visualisation for preoperative $^{125}$I-seed localisations to facilitate the SN tracer injection. [15] Accordingly, we used the same technique to identify margins intraoperative by assessing the $^{125}$I-seed localisation within the breast cancer specimen. [16] After these initial results we started an intraoperative validation of the method using the freehand-SPECT technology, which also includes intraoperative navigation during the RSL procedure. The number of centres that use RSL is still increasing and popularity rises mainly because of the simplified logistics. [17] The way to implement and apply RSL is still developing, and its different applications with single or multiple seeds, in primary surgery or surgery after NST, or the use of $^{125}$I-seeds to mark axillary lymph nodes, make it an interesting procedure for further technical optimisation. The purpose of the present study is to validate $^{125}$I-seed localisation guided by freehand-SPECT in patients with non-palpable breast cancer in breast preserving surgery. To better determine the additional value of the freehand-SPECT technique we also included more complex cases where multiple $^{125}$I-seeds were used.

**Methods**

This single-institution prospective feasibility study was approved by the institutional review board of the Netherlands Cancer Institute, Amsterdam, The Netherlands.

**Patient population**

In this study 20 patients scheduled for radioguided breast cancer surgery with single or multiple implanted $^{125}$I-seeds were included. In total 28 $^{125}$I-seeds (STM1251, Bard Brachytherapy, Inc., Carol Stream, IL, USA) were localized intraoperative using freehand-SPECT in breast cancer surgery. Informed consent was obtained from all individual participants included in the study.

**Standard clinical RSL protocol**

Patients with non-palpable malignancies or patients scheduled for upfront systemic treatment receive an $^{125}$I-seed implanted at the radiology department. The $^{125}$I-seed is introduced through an 18 gauge needle under ultrasound or stereotactic guidance, after which the location is confirmed by mammography. In case of NST the $^{125}$I-seed marks the location of the tumour site prior to therapy. Pathological confirmation of the response is required because even after a complete radiological response about half of the patients have residual microscopic cancer. [18] In extensive DCIS or multifocal
carcinoma, multiple $^{125}$I-seeds are used to delineate the borders of the involved area or mark the different foci.\[11\]

In a small percentage of the patients a positive lymph node is marked with an $^{125}$I-seed prior to NST. This node is staged after NST in a ‘Marking Axillary lymph nodes with Radioactive Iodine seeds’ (MARI) procedure to determine further treatment.\[10,19,20\]

For MARI procedures $^{125}$I-seeds with less radioactivity are used, an apparent radioactivity of approximately 1MBq instead of 8MBq (normal activity for RSL procedures) $^{125}$I is used.

*Freehand-SPECT acquisition and reconstruction*

Freehand-SPECT is an imaging modality based on data acquisition gathered with a conventional gamma probe (Crystal Probe, Crystal Photonics GbH, Berlin, Germany). By combining counts measured with data about the location and orientation of the probe, acquired by a tracking system that tracts a reflective reference target attached to a specific site on the probe, a SPECT image can be reconstructed. Through a calibration procedure, the relation between the gamma probe tip and the reference target is then determined.\[21\]

To acquire an adequate 3D volume reconstruction from the count data, a surface scan was made by hovering the probe over the area of interest in three different orientations (e.g. x, y and z planes). Every 5 seconds the system provides an updated reconstruction of the radioactivity map. When counts are measured from enough angles an image appears with a reliable projection of the $^{125}$I-seeds. (Figure 1)

The window level was adjusted by using a touch screen to set a visualisation threshold, similar to the ones used in conventional nuclear medicine, until the number of hot spots equals the number of $^{125}$I-seeds *in situ*. The so-called 3D window enables the best navigation towards the $^{125}$I-seed (Figure 1). The visualisation display provides a real-time display with the distance of the probe tip to radioactive source.

*Surgical RSL procedure*

Transcutaneous measurements with the gamma probe determine the location of the maximum $^{125}$I-gamma counts, which is marked on the skin, and accordingly the incision is made at this site. The gamma probe is further used to guide the excision of the $^{125}$I-seed and lesion. Correct $^{125}$I-seed removal is confirmed by a measurement of no $^{125}$I-signal in the wound and an $^{125}$I-signal measurement in the excised specimen.

*Statistics for data analysis*
Continuous variables were represented as mean ± standard deviation (SD). The difference between the measured depth of the $^{125}$I-seed by freehand SPECT and determined by the surgeon was visualized by means of a Bland-Altman graph. [22] The distance determined by the surgeon was based on assessment of pre-operative images and experiences during surgery by means of a measurement with a ruler at the moment of the final part of the excision.

![Figure 1: Intraoperative $^{125}$I-seed localisation. (A) Localisation with conventional gamma probe. (B) Selection of the volume of interest by pointing the freehand-SPECT at the specific area. (C) A continuous updating reconstruction of the $^{125}$I-seeds is visualized by hovering the gamma probe over the breast. (D) 3D visualisation mode with the point of view displayed from the tip of the gamma probe to enable navigation to both seeds. In the upper right corner the distance from the tip of the gamma probe to the radioactive hot-spot is displayed.](image)

**Results**

The patient characteristics are described in Table 1. All 25 $^{125}$I-seeds in the breast were identified in 20 patients while using freehand-SPECT and accordingly excised (16 x 1 $^{125}$I-seed and 4 x multiple $^{125}$I-seeds). Freehand-SPECT acquisition took approximately 1-
2 minutes per procedure. Immediate and continuous image reconstructions allowed real-time image assessment and direct knowledge about where further scanning is required. The deviation between the depth indicated by freehand-SPECT and the depth indicated by the surgeon based on estimation was 1.9mm (SD: 2.1mm, Range: 0-7mm). This was visualized by means of a Bland-Altman graph. (Figure 2) Freehand-SPECT was able to pinpoint the place and direction of the solitary $^{125}$I-seeds on the skin (n=16), which was in all solitary seeds identical to the position as indicated by the acoustic feedback of the conventional gamma probe.

In cases with multiple seeds (n=4), the freehand-SPECT gamma probe indicated the exact area where the $^{125}$I-seeds were located (n=3), in one case identification of separate seeds was not possible. Since these cases are of special interest, the usability of freehand-SPECT in three of these cases will be discussed in greater detail in the following sections, the fourth case was a straightforward successful procedure and therefore not separately described.

**Table 1**: Patient characteristics; n=20 patients; n= 28 $^{125}$I-seeds

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD, Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56.8 (10.6, 39-73)</td>
</tr>
<tr>
<td>Tumour type</td>
<td>IDC: n=14 ILC: n=2 DCIS: n=3 Other: n=2</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>Primary surgery: n=13 Surgery after NST: n=7</td>
</tr>
<tr>
<td>Number of $^{125}$I-seeds</td>
<td>Single $^{125}$I-seeds n=16 Multiple $^{125}$I-seeds n=4; 3 x 2 $^{125}$I-seeds 1 x 3 $^{125}$I-seeds MARI: $^{125}$I-seeds: n=3</td>
</tr>
<tr>
<td>Weight of the breast specimens (g)</td>
<td>21.5 (13.5, 4-60)</td>
</tr>
<tr>
<td>Tumour size (mm)</td>
<td>12.4 (9.7, 0-40)</td>
</tr>
<tr>
<td>$^{125}$I-seed location (total 28 seeds)</td>
<td>2 x lower outer 19 x upper outer 1 x lower inner 3 x upper inner 3 x axilla</td>
</tr>
<tr>
<td>Combination with sentinel node procedure</td>
<td>12 x Yes 8 x No</td>
</tr>
<tr>
<td>Radical procedure</td>
<td>17 x Yes 3 x No</td>
</tr>
</tbody>
</table>

CASE 1: A 71 year-old women that presented with a 10mm infiltrating ductal carcinoma (IDC) at 10 o’clock and a 7mm papilloma at 11 o’clock both in the right breast. Both lesions were marked with an $^{125}$I-seed, the spatial distance between the seeds was 2.3cm in the medial-lateral-oblique (MLO) mammography projection. Both markers were detected with the conventional gamma probe based on acoustic signal, although its exact separation was very difficult to accomplish. By contrast, with freehand-SPECT, both markers were clearly differentiated by creating an image of the radioactivity distribution within 20 seconds and this information could be used reliably after 90 seconds for depth measurements. (Figure 1) By aiming with the probe at the different seeds it was determined that the depths from the skin were 11 and 15mm. The surgeon estimated the depths at approximately 18 and 19mm at the time of excision.

CASE 2: In this 55 year old women three $^{125}$I-seeds were implanted in the left breast in an estimated 7mm area of DCIS at 10 o’clock, a 8mm area of tubular IDC at 1 o’clock, and an 8mm tubular IDC at 12 o’clock. The spatial distance between the two most outer seeds was 6.1cm in the MLO mammography projection. Surgically these three markers could be clearly visualized by using freehand-SPECT supporting the conventional gamma probe, which enabled accurate annotation on the skin of the locations for precise excision. (Figure 3) Unfortunately, after pathological examination,
two of the lumps had tumour deposits in the resection borders and a mastectomy was considered the better option for this patient.

Figure 3: (A) Cranial-caudal mammogram with three $^{125}\text{I}$-seeds in situ and a hydro marker located more ventral. (B) A continuous updating reconstruction of the $^{125}\text{I}$-seeds is visualised by hovering the freehand-SPECT over the breast. (C) 3D visualisation mode displayed from the point of view of the tip of the gamma probe. In the upper right corner the distance from the tip of the gamma probe to the radioactive hot-spot is indicated. (D) Ex vivo overview image of the three excised lumps.

CASE 3: A 68-year-old woman with a 3cm grade II area of DCIS. Two $^{125}\text{I}$-seeds were implanted to bracket the lesions. The spatial distance between these two seeds was 2.9cm in the MLO mammography projection. Both with the gamma probe and freehand-SPECT it was not possible to discriminate between the two markers, because of their relative position they projected as one oval lesion in the inner upper quadrant of the breast. The oval shape and size of the freehand-SPECT reconstruction clearly indicated that it was not a reconstruction of a single marker and it did visualize the orientation of the two markers. It also identified by its shape the area of the DCIS (Figure 4A). Ex vivo it was possible to confirm the correct excision of the area of DCIS by displaying the location of both $^{125}\text{I}$-seeds separately within the specimen. (Figure 4B)

Additional $^{125}\text{I}$-seeds in axillary nodes (n=3) were only identifiable in 1 case due to the low levels of radioactivity (approximately 0.25 MBq at the time of surgery). The sensitivity of the gamma probe attached to the freehand-SPECT system was too low for reliable identification of the axillary $^{125}\text{I}$-seeds (the gamma probe used with the freehand-SPECT alone did not measure any counts from this low radioactive $^{125}\text{I}$-seed as well). The standard intraoperative gamma probe, NeoProbe 2000 (Johnson &
Johnson Medical, Hamburg, Germany) was, due to its higher sensitivity, able to measure the faint signal from these $^{125}$I-seeds transcutaneously.

Figure 4: (A) Two $^{125}$I-seeds implanted in an area of DCIS are projected as one larger area in an oval shape. Note that due to the proximity of the two seeds a reconstruction with separate $^{125}$I-seeds is not possible. (B) After excision of the lesion the $^{125}$I-seeds are identifiable in the specimen by 3D imaging demonstrating correct excision and clear margins.

Histopathological analyses

In the group of 7 patients who underwent upfront systemic treatment, one patient with initial IDC had a complete pathological remission. Two of these 7 patients had tumour in the inked margin and required additional treatment. The 3 positive axillary nodes marked with an $^{125}$I-seed still contained macro metastasis after NST. All patients except for one with primary treated breast cancer (n=12) had clear margins after pathological assessment (only one patient with 3 lesions, which was discussed in Case 2 had tumour deposits in the resection borders).

Discussion

Image guided surgery increases in use given that more options are available and surgeons prefer to see the situation before making decisions. In this light, freehand-SPECT already demonstrated useful applications in various areas of radioguided interventions. [23-25] RSL is increasingly applied for breast-conserving tumour excision and freehand-SPECT might be the next important area where this technique can be used to improve and simplify the surgical procedure, especially when multiple $^{125}$I-seeds are used.

In our experience when a single seed is implanted, the surgeon can easily locate and excise the tumour using the conventional gamma probe. However, in case of multiple seeds, due to its 45-degree diverging viewing angle the conventional gamma probe has difficulties in discriminating two seeds from each other. After incision, and in closer proximity to the $^{125}$I-seeds, the gamma probe is able to pinpoint $^{125}$I-seeds more exactly.
In the present study we demonstrated that it is feasible to use freehand-SPECT for pre-incision $^{125}$I-seed localisation, even when multiple $^{125}$I-seeds are used. Knowledge of $^{125}$I-seeds depth and visual information of their relative locations in the actual position of the patient previous to the surgical procedure allow more accurate planning of the tumour approach and placement of the incision and thereby may benefit the outcome of the surgical procedure. However, to determine the real consequences for the patient a randomized controlled trial should be initiated. The information on the depth and the relative location compared to other markers is unique to the freehand-SPECT device and is an additional aspect introduced during the RSL procedures that could further aid the surgeon in tumour localisation and excision.

The average error between the pre-excission estimates of the depth with the freehand-SPECT and the estimates of the surgeon after excision was 1.9mm, with a range of 0-7mm. Like other scintigraphic imaging methods, freehand-SPECT provides a reconstructed representation of a 3D count distribution, which can have some degree of inaccuracy. Nonetheless, these deviations found within this setting fall within the expected range on the accuracy of freehand-SPECT as described in earlier literature reports. We previously compared depth measurements using freehand-SPECT with US and found an error of 0.05mm ± 2.4mm (range -3.5 to 5mm) for detecting solitary $^{125}$I-seeds [15], which we consider to be acceptable for this intraoperative procedure. A bias might have been introduced since the surgeon was not blinded for the freehand-SPECT results. Another important finding in the present study was the ability of the device to distinguish between two or more point sources, an aspect that has not been documented before. In our small number of cases we detected the limitations of this method in terms of separating $^{125}$I-seeds. The distance between two seeds to be visually discriminated should approximately be 2 cm or greater but this highly depends on the spatial orientation of the seeds relative to skin surface and the scan planes. Another limitation in our surgical setting is that the surgeons use the NeoProbe 2000 and not the Crystal Probe, which is compatible with the declipseSPECT system. For a more natural procedure only one gamma probe should be used. This will decrease the time required to acquire freehand-SPECT scans because all data gathered during normal probe handling will be used to update the freehand-SPECT reconstruction. This principle of tumour targeting with $^{125}$I-seeds can also be used for delineation of other structures. While combining this with freehand-SPECT image guided surgery can be accomplished in different complex areas such as head and neck surgery or excision.
of pulmonary nodules. In addition to the surgical possibilities, freehand-SPECT may be useful in imageguided interventions such as core biopsies. A recent study describes the combination of freehand-SPECT together with an US device where the freehand-SPECT is superimposed over the US image. The US probe is tracked and therefore real-time co-registration of the two modalities is possible. This leads to the possibility of radioguided fine needle aspiration of specific targets further supported by ultrasonography. [26]

**Conclusion**

Freehand-SPECT with 3D navigation is feasible in RSL for both single or multiple implanted $^{125}$I-seeds. Peroperatively, the modality is able to provide continuous updating 3D imaging and information about the depth, location and possible displacement of the $^{125}$I-seeds, contributing to adequate excision of non-palpable breast cancer. 3D navigation may become an important tool in breast-preserving cancer surgery.
References


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