Integrating new imaging modalities in breast cancer management
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Radioguided Seed Localisation for breast cancer excision: an ex vivo specimen-based study to establish accuracy of a freehand-SPECT device in predicting resection margins

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Abstract

Purpose
Radioactive seed localisation (RSL) uses an $^{125}$I-iodine- ($^{125}$I)-seed as a marker for the tumour location. The $^{125}$I-seed is implanted into the tumour and enables intraoperative localisation with a conventional gamma-probe. However, specimen margins in relation to the $^{125}$I-seed are estimated based on gamma-probe readings only. A novel device, freehand-SPECT, is capable of measuring the distance from the resection plane to the $^{125}$I-seed. The aim of the present feasibility study is to establish the accuracy of this device in predicting resection margins in ex vivo tumour specimens excised by RSL-guidance.

Materials and methods
In this feasibility study 10 patients with non-palpable breast cancer scheduled for wide local excision with RSL were included. After surgery, the specimens containing the breast tumour and the $^{125}$I-seeds were scanned using freehand-SPECT. Measurements from 5 directions were performed and compared with distances measured by means of an ex vivo CT-scan and related to the pathology report.

Results
The difference between freehand-SPECT and CT measurements was 2.9±2.7mm (mean±SD). One patient had a positive margin based on freehand-SPECT. This specimen contained a focal irradical resection ventral of the tumour based on the pathology report. The smallest distance to the $^{125}$I-seed was 4mm for the freehand-SPECT and 5mm for the CT-scan.

Conclusion
Accurate ex vivo measurements of the tumour resection margins using $^{125}$I-seeds and freehand-SPECT is feasible in patients undergoing breast-conserving surgery. Incorporation of the freehand-SPECT device in RSL protocols may enable a real-time estimation of resection margins, which may be useful for surgeons to adjust resection planes.
Introduction
There are multiple treatment options available for patients with breast cancer. The level of breast-conserving therapy depends on the complete excision of the tumour while maintaining acceptable cosmetics. [1,2] Positive margins after breast-conserving surgery are associated with a 2 to 3 times increase in the chance of recurrence when compared to negative margins; therefore, reexcision of the positive margins or other additional treatment options are required. Reexcision of the margins includes lumpectomy or even mastectomy and can lead to increased psychological trauma to the patient, delay of adjuvant therapy, worsened cosmesis, and increased cost. [3,4] Altogether it is well accepted to aim for complete tumour removal; therefore, novel methods are evaluated for tumour allocation, preoperative imaging and postoperative assessment of the margins.

If tumour localisation is not possible by palpation, an additional marker is implanted to secure accurate localisation during the surgical procedure. Wire guided tumour localisation is currently one of the most used and standardised methods in many institutions. [5,6] Limitations of this technique are dislocation of the wire and discomfort for the patient compared to other techniques. [7,8] A relatively new alternative technique is \(^{125}\)iodine \((^{125}\text{I})\)-seed implantation in the tumour for radioactive seed localisation (RSL). RSL is based on the implantation of an \(^{125}\text{I}\)-seed (27keV) in the centre of the tumour, also allowing intraoperative localisation using a gamma probe. Recent studies conclude that this approach of tumour marking is a safe and reliable method compared to wire guided localisation (WGL). [5,9] RSL or radioactive occult lesion localisation (ROLL), using an intratumoural tracer injection to locate the tumour, demonstrates to be superior to conventional localisation techniques and benefits patients in both outcome and patient comfort. [6] There are several advantages of RSL over ROLL, one of which is the source geometry of the \(^{125}\text{I}\)-seeds. The seed is a fixed metal point source, of which the position with respect to the tumour can be validated using mammography, instead of a gradually diffusing radiotracer that is used in a ROLL procedure. At The Netherlands Cancer Institute over a 1,000 patients have undergone breast-conserving surgery using RSL since 2008.

At The Netherlands Cancer Institute, \(^{125}\text{I}\)-seeds are generally used in women with non-palpable tumours or women who undergo neoadjuvant chemotherapy to enhance detectability of the tumour during surgery. A radiologist implants the \(^{125}\text{I}\)-seed guided by
US-guidance in the tumour, after which the exact location of the seed with respect to the tumour boundaries is confirmed by mammography. Exact knowledge of the $^{125}\text{I}$-seed location within the tumour is required for accurate radioactive tumour resection. At our institute, the surgeon typically aims for a resection 10mm beyond the identified tumour border. Subsequently, the pathologist evaluates the resected specimen to decide whether the resection is conclusive or not.

Nonetheless, even when RSL is used for tumour excision, a percentage of the patients need to undergo secondary surgery for reexcision of the margins. This percentage varies from 10-60% in literature depending on the surgical techniques, additional therapy approaches, and level of experience in clinical institutions. [3,10,11] Accordingly, it will be beneficial if the surgeon is able to estimate the resection margins already during the procedure. At present, there are a number of techniques available for specimen radiography in the operating room. [12] These techniques result in 2 dimensional images of the specimen with the tumour marker. However, this is approach is only valid for WGL or RSL and will not work during a ROLL-procedure. Furthermore, these specimen radiography devices are limited to ex vivo use, and cannot be used to guide the procedure. [13]

Currently, a new imaging modality, freehand-SPECT, has become available that enables quick radioactivity mapping of an $^{125}\text{I}$-seed in order to guide the surgeon’s decision making during the resection. This novel freehand-SPECT system (declipseSPECT, SurgicEye GmbH, Munich, Germany) combines a conventional gamma-probe with an optical tracking system and allows three dimensional (3D) radioactive imaging and navigation. [14–17] A detailed overview and technical description of the system has been published before by Wendler et al. [14,15] Using freehand-SPECT for the localisation of $^{125}\text{I}$-seeds used as breast tumour markers has once previously been described in a preoperative setting. [18] Theoretically, this technique can also be used to measure the distance from the resection plane to the $^{125}\text{I}$-seed. Accordingly, the purpose of this study was to validate $^{125}\text{I}$-seed localisation guided by freehand-SPECT in a perioperative ex vivo analysis in breast cancer specimens. Localisation of the $^{125}\text{I}$-seed within the specimen should allow evaluation of the resection margins relative to the $^{125}\text{I}$-seed and thereby possibly the tumour margins. This approach may eventually lead to
perioperative decision making about additional tissue resection and thereby avoid secondary surgery and associated costs.

Materials and Methods

Patient population

Ten subsequent patients with non-palpable breast cancer, one or two per-/intratumoural $^{125}$I-seed(s) (<8MBq / <0.22mCi) (STM1251, Bard Brachytherapy, Inc. Carol Stream, IL, USA) and scheduled for wide local excision by RSL were included in the study. The radioactive $^{125}$I-seeds (0.8mm x 4.0mm) were implanted into the tumour by a radiologist guided by ultrasound, and verified by mammography. Intraoperatively a handheld gamma-probe (Neo2000, model 2200, Neoprobe Corporation, Dublin, OH) was set to detect a 27-keV $^{125}$I source. The location at the breast with the highest transcutaneous gamma counts was determined and guided the incision. The gamma-probe is then continuously used for $^{125}$I-seed localisation and lesion excision. (Figure 1)

Patients receiving a sentinel lymph node biopsy (SLNB) simultaneously to RSL were excluded in this phase of the study since the scatter of $^{99m}$Tc-nanocolloid could interfere with the $^{125}$I-seed signal. The local ethical committee approved this study.

Positioning of the specimen

After excision, the surgeon marked the specimen by placing 1 suture at the areolar side and 2 sutures at the fascia site. Thereafter, the specimen was weighted and placed on a plate in the same anatomical orientation as it was in the body. The specimen stayed on this plate until its arrival at the Pathology department.

Figure 1: Radioactive seed localisation in the operating room (a) Prior to the incision the gamma-probe is used to localise the place of the $^{125}$I-seed. (b) Continuous use of the gamma-probe for $^{125}$I-seed detection during the tumour excision. (c) A specimen radiograph with the $^{125}$I-seed located central in the specimen.
**Figure 2:** Ex-vivo procedure using the freehand-SPECT (a) Data acquisition. (b) Reconstructed augmented reality image with added display of 2 $^{125}$I-seeds on top of the optical image. (c) Optic image from measurement from 3 o’clock. (d) 3D-visualisation of the $^{125}$I-seed from the probe tip with real time display of the distance.

**Figure 3:** Correlation of freehand-SPECT and CT measurement (a) The distance measured with the freehand-SPECT from 9 o’clock is indicated with the blue arrow. (b) The same distance (arrow) measured on a CT-scan.
Freehand-SPECT acquisition and reconstruction

The plate containing the specimen was fixed on a stable table with a reference target to prevent movements during acquisition. For accurate 3D-volume reconstructions, a surface scan was made by passing the probe over the area of interest without moving the specimen, in three different orientations (e.g. x, y, z planes). This surface scanning takes about 2-3 minutes and the reconstruction for 5mm voxels another 20-25 seconds. (Figure 2a,b) The window level of the image was adjusted until the number of hotspots was equal to the number of $^{125}$I-seeds in situ and the reconstructed hotspot had a realistic size. The 3D-window within the dedicated software of the freehand-SPECT system enables the best navigation to the centroid of the reconstructed $^{125}$I-seed and was used for the spatial measurements. (Figure 2d) Measurements from resection plane to $^{125}$I-seeds were performed in 3D from 5 directions: cranial, caudal, lateral, medial and anterior from the specimen. The distance from the gamma probe tip to the centroid of the reconstructed hotspot was determined for each direction. (Figure 3a) As these measures were performed contemporaneously with the standard surgical procedure there was no prolongation of operation time.

CT-validation

A CT-scan CT (Symbia-T; Siemens, Erlangen, Germany) was obtained before the specimen was send to the Pathology department. The specimens were taken to the CT-scanner for a CT-scan and delivered to the Pathology department within an hour. The same distances as measured by freehand-SPECT were measured in the CT-datasets. (Figure 3b) All the specimens were scanned using a slice thickness of 2mm (130kV, 40mA, B30s kernel). Images were analysed using OsiriX DICOM viewer.

Histopathological analyses

An experienced pathologist conducted histopathological assessment. The specimen was sliced in cuts in the order of 5µm and the margins to the resection planes were measured. An accompanying sketch of the specimen’s anatomical origin together with the suture markers provides the Pathologist with the exact orientation of the specimen. Resection margins were evaluated in all directions. The irradical margins defined at our institute as the presence of malignant cells at the resection border) and the narrowest margins including the distance were reported in the pathology report.
Data analysis
Continuous variables were represented by a mean ± standard deviation (SD). Freehand-SPECT distances were compared to the CT-measures and to the pathology findings, which is considered the golden standard. Differences between the measured distances of the $^{125}$I-seed by freehand-SPECT and on CT-scans were evaluated by Bland-Altman graphs. This resulted in the mean difference and 95% confidence interval (95% CI).

Results
The characteristics of all 10 patients are outlined in Table 1. The mean age of the patients was 53 years, 6 patients underwent neoadjuvant chemotherapy (NAC), and the mean number of days between $^{125}$I-seed implantation and the day of surgery was 77 days. In total, the 10 patients had 12 $^{125}$I-seeds in situ, which resulted in 60 freehand-SPECT and CT measurements (5 per $^{125}$I-seeds). The mean of the absolute difference between the CT and the freehand-SPECT over all measurements was 2.9mm (SD: 2.7mm, range: 0-13mm). These data are displayed in a Bland-Altman plot, which visualizes the mean and ±1.96 times the SD. (Figure 4)
In the 2 patients with 2 $^{125}$I-seeds in situ the findings were equally accurate relative to the other measurements, this was due to the large distance between the $^{125}$I-seeds of 39mm for the first patient, and 55mm for the second patient. Only one patient (Patient 7) had a positive margin at pathological assessment; this specimen contained a focal irradical resection (<4mm) of ductal carcinoma in situ grade III. The narrowest margin to the tumour was at the ventral side (2mm). The smallest distance to the $^{125}$I-seeds measured from ventral side was 4mm for the freehand-SPECT and 5mm for the CT-scan. (Figure 5)
Figure 4: Bland-Altman analysis for the distances in depth measured with the freehand-SPECT and on the CT-scan. The analysis indicates the average of the measurements. The upper and lower dotted lines represent the Bland-Altman limits the 95% confidence interval.

Figure 5: Eccentric $^{125}$I-seed localisation in a case with irradical resection margins (a) The reconstructed hotspot of the radioactive $^{125}$I-seed superimposed on top of the optical image with the tumour lump. (b1) Navigation mode where the camera point of view is from the probe tip, this allows distance measurements from probe tip to the hotspot. (b2) The distance is determined by holding the probe tip to the tissue enabling a distance reading from the probe tip to the hotspot in 3D. (c) CT-image of the tumour lump including the $^{125}$I-seed.
Table 1: Patient characteristics

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<th>Age (years)</th>
<th>NAC* (Y/N)</th>
<th>Tumour type</th>
<th>Irradical (Y/N)</th>
<th>Number of $^{125}\text{I}$-seeds</th>
<th>Days after seed implantation</th>
<th>Specimen weight (g)</th>
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* IDC: Infiltrating Ductal Carcinoma. DCIS: Ductal Carcinoma In Situ. NAC: Neoadjuvant Chemotherapy.

Discussion

This study demonstrates that perioperative assessment of margins from breast cancer specimens by freehand-SPECT is feasible. The freehand-SPECT device is not only able to localise the $^{125}\text{I}$-seed in the specimen, but also capable of determining the distance from the resection plane to the $^{125}\text{I}$-seed by 3D-visualisation. The accuracy of the technique, the 95% confidence interval, was within the aimed surgical resection borders ($< 10\text{mm}$ around the tumour). However due to the limited number of measurements and experience in this technique one should be cautious using this technique and should keep in mind that the measurements can be false positive or false negative. The inaccuracies and limitations of freehand-SPECT while using this approach must be taken into account.

First of all, the low angular specificity and sensitivity of the gamma-probe are limiting factors for the accuracy of the freehand-SPECT technique. Small gamma cameras (SGCs) have a higher angular specificity thanks to better collimation and a larger detector field of view relative to gamma-probes. Handheld SGCs are currently used intraoperative for a number of surgical procedures. The advantage of SGCs is a display of a high-resolution 2D image instead of just a count rate. [19] Acquiring freehand-SPECT acquisitions with an optical tracked SGC allows an increase in the quality and
quantity of the measured data and, therefore, may enable better reconstructions of the radioactivity distribution.

When acquiring freehand-SPECT data, the scanning technique and experience of the user is of great influence on the quality of the reconstruction. For example, the distance of the probe tip to the $^{125}\text{I}$-seed or hotspot during the acquisition is important. Due to the diverging bundle of the gamma-probe, a larger distance to from the probe tip to the hotspot will result in less specific data, this will influence the quality of the reconstructed radioactivity map. Therefore, it is necessary to keep the distance from the probe tip to the hotspot as little as possible at all times. This may one of the reasons, together with the actual scan path, why there is large inter- and intraobserver variance in freehand-SPECT scans. [20] This study was not designed to study a learning curve or examine the intraobserver variation; we also did not find a learning curve in this limited number of cases. This might be the result of the fact that all scans are made by one experienced user. However, to use the freehand-SPECT device a training period is required.

The findings of the present study constitute a step towards the integration of image- and radio-guided surgical navigation in the operating room. Ideally, real-time localisation of the $^{125}\text{I}$-seed and thereby the tumour need to be constantly available during surgery. The freehand-SPECT device enables possibilities for preoperative, intraoperative and postoperative visualisation of radioactivity distribution from $^{125}\text{I}$-seeds and other isotopes. An additional possibility may be dual-isotope imaging of both the $^{125}\text{I}$-seed for tumour localisation, and $^{99m}\text{Tc}$-nanocolloid for lymph node mapping when RSL is combined with a SLNB.

**Conclusion**

In patients with non-palpable breast cancer scheduled for breast-conserving surgery an accurate ex vivo measurement of the tumour resection margins using $^{125}\text{I}$-seeds and freehand-SPECT is feasible. Incorporation of the freehand-SPECT device to RSL protocols may enable a real-time estimation of resection margins, which may be useful for surgeons in adjusting local tumour excisions, and thereby avoid secondary surgery and associated costs.
References


