Integrating new imaging modalities in breast cancer management
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Introduction and outline
Breast cancer in numbers

In the Netherlands each year 14,400 women are diagnosed with invasive breast cancer and 2,500 women with an in-situ carcinoma. [1] World wide this was estimated to be 1.7 million new cases in 2012. [2,3] The chance of getting breast cancer in a women’s life is 12-13%, making this the most prevalent cancer for women in the Netherlands. Early diagnosis by the national screening program, every 2 years for women in the age of 50-75, improves the prognosis for women with breast cancer. [3] Two requirements for screening with the purpose to reduce the mortality are: I. the time of diagnosis should advance and II. early treatment should have advantages over treatment at the time of clinical presentation. [4] With these assumptions in mind, women in the western world receive mammograms when reaching a certain age. Nowadays, incidence-based mortality studies with longer follow-up periods among European women invited for screening show a general reduction of breast cancer mortality. [5] However, discussion remains on whether or not this reduction is caused by screening, or that other factors, such as changes in systemic treatment or improvements in diagnostic imaging, may also be held responsible. [6] The five-year relative survival rate varies per stage and subtype of breast cancer and varies from 100% for stage 0 and I to 22% for stage IV disease. [7] Despite the good prognosis of this disease it remains the single most substantial cause of cancer death in Western women only exceeded by lung cancer. [8]

Breast cancer diagnosis and staging

Clinical breast examination

The clinical breast examination based on palpation and inspection of the breast and adjacent lymph nodes is the most basic form of diagnosis performed either by the patient herself, general practitioner, or by the breast cancer specialists.

Imaging

For screening purposes next to self-investigation and clinical examination, mammography is the standard procedure. For diagnostic purposes regular used imaging methods are mammography, tomosynthesis, ultrasound (US), magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT). [3] The suspicion of the lesion is indicated by means of a Breast Imaging-Reporting and Data System (BI-RADS) score. Based on this score further diagnosis of the lesion will take place by means of pathological assessment.
Pathology
For further diagnosis more information about biological properties of the lesion is required. In experienced hands, fine needle aspiration cytology (FNAC) can be used for fast track diagnosis. In general 80-90% of all lesions can be with high certainty diagnosed (including the imaging). In case of inconclusive FNAC, image directed multiple core biopsies for histology are warranted. Biopsies are also obtained if further knowledge of the cancer is required, for instance distinction between in situ or invasive cancer, hormonal receptors, genetic profiling, or to direct up front systemic therapies. [3]

Sentinel lymph node biopsy
In case of an invasive component in early breast cancer a sentinel node biopsy (SNB) is indicated for local staging of the disease. Sentinel nodes (SN) are defined as lymph nodes upon which the primary tumour drains directly. The tumour status of the first tumour draining lymph node is a strong predictor for the patient outcome. Morton et al. first introduced the SN procedure for melanoma more than three decades ago and this procedure is standard of care for lymphatic staging in invasive breast cancer. [9,10] A negative SN prevents the need for axillary clearance and in this way reduces patient morbidity without compromising survival. [11,12] For SN mapping, preoperative scintigraphic images are acquired. These images allow SN marking on the skin of the patient. Intraoperatively these SNs are pursued by a gamma probe for gamma detection, and, if required, using additional blue dye as an optical tracer.

Breast cancer treatment
After tumour staging, the treatment strategy is determined together with the patient. Treatment is based on three pillars:
1. Achieving local control of the cancer in the breast by means of breast conserving surgery, ablative surgery, and/or radiotherapy.
2. Identification and treatment regional lymph node metastasis.
3. Estimating prognoses and accordingly improve prognosis by systemic treatment such as chemotherapy, hormone therapy, or immune therapy. [13,14]

Adjuvant and neoadjuvant systemic treatment
Adjuvant and neoadjuvant systemic treatment (NST) are non-invasive treatment options for breast cancer. Neoadjuvant, primary systemic or pre-surgical therapy is given prior to surgery. NST has the advantage of: I. treatment response monitoring to evaluate whether a switch of therapy or final treatment is required, and II. the tumour
size can be diminished, allowing for breast conserving surgery (BCS). NST is indicated for early stage II tumours up to locoregional extensive breast cancer stage III and depends on tumour characteristics, age, and performance. Systemic treatment shrinks the tumour and kills distant isolated tumour cells. In this way, for example, irresectable tumours can frequently be surgically treated or, instead of mastectomy, breast-conserving surgery (BCS) is feasible. Adjuvant therapy, such as chemotherapy, hormone therapy, or immune therapy is given after primary therapy to increase disease-free survival. The Immunohistochemistry characteristics of the cancer determine the regimen given to the patient. [3,13,14]

Surgical treatment
Primary breast conserving surgery is recommended when good cosmetic results and locoregional tumour control can be expected in stage I and II breast cancer. Axillary clearance is indicated only in case of massive nodal involvement insufficiently reacting on systemic treatment. As a consequence to extensive screening programs the rate of non-palpable lesions increased and surgical localisation techniques needed to be introduced. The percentage of BCS increased in The Netherlands Cancer Institute from 7.1% to 60.3% in the period from 1977 to 2014. For adequate BCS, precise tumour excisions should be performed to prevent extensive tissue removal with the known unfortunate results for cosmetic outcome. At present, three important techniques are used to localise the tumour prior to excision: wire-, ultrasound- (US)-, and radioguided (i.e. guided by a radionuclide) localisation, which are applied according to local preferences or legislation. [15-17] Radioguided techniques by means of radioguided occult lesion localisation (ROLL) or radioactive seed localisation (RSL) are both recently introduced and bring advantages for both surgeon and patient. The introduction of these techniques comes with great logistical advantages and leads to new opportunities for intraoperative use to further simplify the surgical procedure.

Innovations in breast cancer localisation and imaging

Radioactive seed localisation
RSL is a localisation technique for breast conserving cancer surgery; it is introduced as a replacement for the commonly used wire-guided localisation technique with several advantages. Patients with non-palpable malignancies or patients scheduled for upfront systemic treatment receive an $^{125}$iodine ($^{125}$I)-seed, which is implanted image directed
(US or stereotactic) at the radiology department. The $^{125}\text{I}$-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 $^{125}\text{I}$-seed marks the location of the tumour site prior to therapy. [18] In extensive ductal carcinoma in situ (DCIS) or multifocal carcinoma, multiple $^{125}\text{I}$-seeds are used to delineate borders of the involved area or mark the different foci. [19] As a result, $^{125}\text{I}$-seeds may demonstrate accurate single lesion, multiple lesion, or larger lesion excisions without excising redundant tissue to allow BCS.

In some centres, including our centre, patients that have a positive lymph node are marked with an $^{125}\text{I}$-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. [20-22]

Transcutaneous measurements with the gamma probe determine the location of the maximum $^{125}\text{I}$-gamma counts, which is marked on the skin, and subsequently the incision is made at this site. The gamma probe is further used to guide the excision of the $^{125}\text{I}$-seed and lesion. Correct $^{125}\text{I}$-seed removal is confirmed by a measurement of no $^{125}\text{I}$-signal in the wound and an $^{125}\text{I}$-signal measurement in the excised specimen. (Figure 1)

![Figure 1](image_url)

Figure 1: (a) Implantation of an $^{125}\text{I}$-seed by US guidance. (b) Post-implantation mammography to validate the implantation location. (c) Intraoperative $^{125}\text{I}$-seed localisation while using a gamma probe.

**Freehand-SPECT**

DeclipseSPECT (SurgicEye GmbH, Munich, Germany) is a device empowering minimal invasive image-guided surgery. The device is primarily designed for two types of image guidance: freehand-SPECT imaging with subsequent navigation and navigation based on preoperative images. Image acquisition and visual feedback are important aspects of robotics in surgery, it is important to stimulate the development of innovative
techniques and, thereby, increase performance beyond the limitations of a person’s inherent physical abilities. Indisputably, in case of proper integration, this will lead to better health- and patientcare now and in the near future. [23-30] The declineSPECT device consists of a conventional gamma probe with an additional reference target attached to a specific site on the gamma probe, a camera system and an image processing system. Through a calibration procedure the relation between the gamma probe tip and the reference target was determined. An optical camera and two infrared cameras enable real-time three-dimensional (3D) tracking of the specific trackers. The patient gets a reference tracker attached to a rigid part of the body to permit tracking of both the tracker and the patient. [23-30] (Figure 2)

Figure 2: Left the declineSPECT with the gamma probe, camera head, and display-screen. Right the workflow on the screen representing the 2D and 3D navigation mode. (SurgicEye GmbH, Munich, Germany)

Portable gamma camera

In current nuclear medicine practice, imaging is routinely performed with either conventional gamma cameras, nowadays commonly equipped with CT scanners, or with PET/CT scanners. In addition to these large devices, several intraoperative small
field of view (SFOV) portable gamma cameras (PGC) have become available over the past years for intraoperative imaging. With these devices, high-resolution images of small surface areas can be obtained and local radioactivity distribution patterns can be assessed with a relative short image acquisition time. A PGC aids the surgeon to localise radioactive targets during surgery and it can be used to guide certain interventions, such as SN mapping and biopsy. In recent years this technique has been successfully demonstrated for various purposes in our and in other clinical institutes. [31-34]

**Aim and Outline of this thesis**

The aim of this thesis is to implement new 3D imaging modalities for breast cancer imaging and BCS and thereby demonstrate feasibility and effectiveness for these procedures. This is focussed on radioguided techniques used for localisation and visualisation of the primary tumour.

**Part 1: Current status intraoperative breast cancer imaging techniques**

In 2008 a novel technique for breast tumour localisation is introduced in the NKI-AVL. RSL is introduced in 1999 in the USA by Gray et al. and in 2007 by Riet et al. in the Netherlands as radioactive $^{125}$I-seed tumour marker for breast lesions. [35,36] Chapter 2 provides a meta-analysis describing the results of all RSL procedures performed and described worldwide. This demonstrates the adaptation rate in different countries and the clinical results of this procedure. Chapter 3 contains a description of all our experiences with PGCs for radioguided surgery. This overview demonstrates the advantages of implementing this device in daily clinical practice for radioguided procedures. Chapter 4 is a technical and clinical evaluation about the introduction of $^{125}$I-markers in standard breast cancer surgery protocols where also another important radioguided procedure is used. SNBs are often combined with surgery of the primary lesion. When these two radioisotopes are used simultaneously, some practical issues with differentiation among the isotopes arise and should be taken into consideration during planning and surgery to maintain safe procedures.

**Part 2: Progresses in image-guided interventions and surgery using freehand-SPECT**

The aim of this part of the project was based on the introduction of freehand-SPECT for visualisation and navigation in the operating theatre to improve the current radioguided intraoperative methods for resection of non-palpable breast cancer. This
aspect was focussed on $^{125}$I-seed guided breast conserving procedures only. This application of freehand-SPECT was a novel way to utilize this device and not demonstrated before. Chapter 5 starts with a proposed training protocol for freehand-SPECT acquisitions to improve scanning accuracy and intra-observer variation. When an accurate scan protocol with appropriate training was in order, clinical use of the system was justified.

For $^{125}$I-seed localisation and navigation within the breast a short freehand-SPECT acquisition with an optical tracked gamma probe can be used. A 3D reconstruction of the radioactivity distribution visualises the location and guides the direction to pinpoint the target. Chapter 6 uses this technique to estimate the distance to the $^{125}$I-seed in resected breast cancer specimens and thereby predict the status of the resection margins. Accordingly, freehand-SPECT was used to guide $^{125}$I-targeted $^{99m}$Tc-albumin nanocolloid administrations used for SN procedures. This procedure with accompanying results is described in Chapter 7.

Chapter 8 is a study where the additional value of freehand-SPECT is evaluated in an intraoperative setting for RSL procedures. RSL procedures using multiple markers can be of specific difficulty while using a gamma probe only in terms of separating the markers transcutaneous because of relative positioning. Chapter 9 provides an overview with all augmented reality procedures in nuclear medicine and molecular imaging. This mainly consists of freehand-SPECT for various radioguided procedures. This overview demonstrates in which phase of the introduction we currently are.

Part 3: Novelties in breast cancer imaging techniques
In this part we go into more detail about preoperative imaging by means of large field of view gamma cameras for SN mapping and intraoperative primary breast cancer lesion localisations using $^{99m}$Tc-nanocolloid. Chapter 10 is a study where we re-evaluate the value of a SPECT/CT scan and a reinjection in case of a non-visualisation on planar imaging in SN imaging. This was initiated because of the observation that an increasing number of patients presented a non-visualisation on planar imaging, most likely because of the changed population of included patients (recurrent breast cancer and NST patients are subjected to SN procedures now). Chapter 11 provides a literature overview of a commonly used radioguided breast cancer localisation technique used for non-palpable lesions. This technique is becoming popular around
various institutes worldwide and therefore reviewed and compared to the techniques that are used in the Netherlands Cancer Institute.

Part 4: Summary and future
Finally all findings are summarised and we provide our opinion about future developments of the integration of new imaging modalities.
References


