Navigating towards the unseen margins of non-palpable breast cancer
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Chapter 1

Introduction and Outline
Breast cancer in numbers

Each year approximately 16,000 patients are diagnosed with breast cancer in The Netherlands [1]. Since the introduction of the Dutch breast screening program in 1989, the incidence rates of (small) invasive and in situ carcinomas has increased over the years (Figure 1). Especially Ductal Carcinoma In Situ (DCIS), which can be considered as a pre-invasive cancer type, is often detected by the screening program and now accounts for approximately 20-30% of all detected breast cancers [1]. Although the incidence rate of both invasive and in situ breast cancer has been increasing over the years, the mortality of breast cancer has remained stable throughout the years: approximately 3400 patients per year (Figure 1) [2].

Figure 1. Absolute incidence and mortality of both invasive and in situ breast carcinomas in the Netherlands.
Breast cancer diagnosis

The diagnostic work-up of breast cancer consists of the following components: clinical breast examination, imaging of the breast and pathological analysis of a small tissue sample. Mammography (XM), also acquired for the screening program, is typically the first acquired imaging modality in patients suspicious for breast cancer. DCIS is often recognized by a cluster of malignant micro-calcifications, whereas invasive breast tumors are typically presented as small masses or distortions of the normal breast architecture on XM. Ultrasound is often the second acquired imaging modality, also used to guide a cytological fine needle aspiration or a biopsy procedure in order to gather a small tissue sample. Cytology can be used to distinguish malignant from benign cells, whereas histology is used for distinction of non-invasive in situ lesions from invasive tumors and for further classification of the tumor. Such tumor classification is based on immune-histochemical (IHC) analysis, in order to determine expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2-neu) on the tumor. Sub-classification of tumors based on their hormonal and HER2-neu expression is essential for subsequent treatment stratification, especially the choice for (neo-adjuvant) systemic therapies. The tumor stage is subsequently determined via the standardized Tumor-Node-Metastasis (TNM) classification [3]. The T stage is related to the size and presence of either in situ or invasive breast cancer, N stands for the location and number of lymph node metastases and M for the presence of distant metastases. This is important for patient-specific treatment selection, prediction of the prognosis and for monitoring of treatment response.

Other acquired imaging modalities are tomosynthesis, magnetic resonance imaging (MRI) and positron emission tomography / computed tomography (PET/CT) [4]. Preferably, dynamic contrast-enhanced MRI (CE-MRI) is acquired in which the breast is visualized before, during and after intravenous administration of a contrast agent. Most breast cancers have a fast uptake of contrast agent during the wash-in phase, visualizing the tumor location, volume and extent within the normal breast anatomy [5]–[7]. MRI has a high sensitivity for tumor detection (91.7%) and is preferably acquired in younger patients which have denser breast tissue than older patients which have more fatty breasts [8]. MRI is generally acquired in prone position using dedicated breast coils.

Breast cancer treatment

The increased sensitivity of mammography, together with introduction of breast screening programs have led to an increased number of early-stage and non-palpable tumors, including both invasive tumors and DCIS. Furthermore the use of neo-adjuvant systemic
therapies (NST) has increased in the last years. These NST regimens have been increasingly tailored to specific patient- and tumor characteristics, resulting in effective downsizing of the tumor before surgery. These developments have led to an increased number of small invasive and non-palpable tumors suitable for breast conserving surgery (BCS) instead of mastectomy [9]–[11]. Main goal of BCS is removal of the whole tumor, surrounded by a margin of healthy breast tissue. Simultaneously, the surgeon aims to spare as much healthy breast tissue as possible to ensure good cosmetic outcome. With mastectomy the whole breast will be removed. Large prospective randomized trials have shown that survival rates between patients that underwent breast conserving treatment, consisting of BCS followed by radiotherapy (RT), and mastectomy were similar [12]–[14]. Therefore more patients are currently being treated with BCS. Also in the Netherlands Cancer Institute BCS has been increasingly performed: 7.1% in 1977 to 60.3% in 2014.

Breast cancer localization

BCS can be a challenging task for the surgeon in non-palpable tumors like DCIS. Therefore, several tumor localization techniques have been developed in the last years. Currently there are three important techniques for tumor localization prior to surgery: wire-guided, ultrasound guided, and radio-guided localization. The most common technique nowadays is still wire-guided localization (WGL), in which a metal wire is pre-operatively inserted into the tumor center using ultrasound or stereotactic X-ray guidance. The surgeon uses the wire as guidance towards the tumor center during the operation. However, WGL is associated with high rates of incomplete tumor removal, varying between 13 and 58% [15]. Other major disadvantages of WGL are possible dislocation of the wire, patient discomfort and poor cosmetic outcome [16]–[18]. With ultrasound (US) guided localization the tumor borders are visualized during the surgical procedure. Although the rates of incomplete surgery with intra-operative ultrasound were lower in comparison to WGL [19], [20], not all tumors are visible on ultrasound, for example DCIS or tumors with a complete clinical response after NST [21]. Therefore, the use of ultrasound is still limited in clinical practice. With radio-guided localization techniques the surgeon is guided by a radionuclide. One method is the Radioactive Occult Lesion Localization (ROLL) in which a small amount of radioactive liquid technetium is injected into the tumor, shortly before surgery. The location with the highest radioactive signal is subsequently localized during surgery with a portable gamma probe. However, the diffuse uptake of technetium in the breast hampers precise tumor localization. In order to overcome this issue, the Radioactive Seed Localization (RSL) has been developed in which a radioactive iodine seed (125I) is pre-operatively implanted [22]–[26]. For localization of unifocal spherical tumors the iodine seed is preferably implanted in the center of the tumor, using ultrasonic or stereotactic X-ray guidance. Similar to ROLL, a gamma probe provides
intraoperative guidance to the radioactive iodine seed and thus the tumor location. With RSL the surgeon is guided by point-source localization of the iodine seed, instead of the diffuse radioactive signal throughout the breast with ROLL. Another advantage of RSL is the long half-life time of iodine (64 days). This makes RSL a suitable localization technique for patients undergoing NST [27]. Even after completion of several courses of NST, which can be several months after seed implantation, the radioactive signal of the iodine seed can still be localized at the time of surgery, guiding the surgeon towards the original tumor location. Several randomized clinical trials and cohort studies have shown that the use of ROLL or RSL results in lower rates of incomplete tumor removal and re-excisions when compared to WGL. Secondly, cosmetic outcome improved [15], [28], [29].

The main disadvantage of WGL, ROLL and RSL is that they all provide a simplified representation of the whole tumor volume. None of these techniques are capable to localize the precise 3D tumor borders, which is essential to guide the surgeon during tumor resection. Another shortcoming of the current workflow is that the available diagnostic information about tumor location, size and 3D volume on the acquired pre-operative tumor imaging is not used to plan or guide during the tumor localization procedure or BCS. The surgeon prepares the operation by evaluating XM, US and preferably CE-MRI, but is subsequently only guided by the implanted wire-guide or iodine seed which is a point-source approximation of the whole tumor volume. Ideally, the available information about tumor location, size and volume on CE-MRI is used for planning and guidance of BCS. However, standard CE-MRI is acquired in prone patient position in order to minimize breathing-induced motion artefacts. Obviously, the patient is operated in supine position. With such a deformable organ, there is considerable displacement and deformation of the breast (3-6 cm) between a prone and supine setup [30]. Visualization of the tumor similar to subsequent treatment could be achieved with breast MRI acquired in supine position. However, supine breast MRI suffers from breathing-induced motion artefacts that significantly decrease image quality. Several techniques have been explored to acquire supine breast MRI of sufficient quality, for example acquisition during one or multiple breath-holds or the use of phase-encode reordering techniques [30], [31]. However both techniques have not been implemented into clinical practice yet, due to issues with reproducible acquisition of breath hold MRI acquisition for example. The lack of accurate tumor visualization in supine patient position disables adequate translation of the pre-operative image findings to the actual patient position during treatment. This is especially problematic for non-palpable tumors like DCIS in which the surgeon also has no tactile feedback about tumor borders during the operation. Consequently the rate of incomplete tumor resections is higher in patients with DCIS in comparison to patients with palpable invasive tumors: 17% vs. 3% of the BCS in 2016 in the Netherlands [32].
Evaluation of breast conserving surgery

In order to evaluate the success of BCS the surgical resection margin is analyzed with a standardized pathology procedure. The first step at pathology is inking of the outer borders of the excision specimen with different colors, indicating the original specimen orientation within the patient. The specimen is frozen and subsequently cut into slices of ~3 mm thick, with simultaneous removal of the wire or iodine seed when present. All slices are fixated with formalin overnight and imaged on radiography the next day. The radiograph is evaluated by the pathologist to identify the tumor distribution and possible malignant micro-calcifications throughout the slices. Furthermore, the tumor size on pre-operative imaging, gross examination and palpation of the total excision specimen are taken into account in order to select the appropriate slices which require further histological examination. This step, thus the selection of the suspicious tumor-containing slices, is indicated by a term called sampling of the excision specimen. The selected slices are embedded in paraffin, of which a few thin slides of 5 μm are drafted and stained with hematoxylin and eosin (H&E). The H&E slides are subsequently evaluated under the microscope by a pathologist, in order to evaluate the surgical resection margins of the excision specimen. According to Dutch guidelines, resection margins are considered negative when no invasive cells or carcinoma in situ cells are present on the inked edge of the excised specimen [33]. Margins are considered focally positive when invasive cells or carcinoma in situ are found over a maximum length of 4 mm on the inked edge of the specimen. Margins are more than focally positive in case tumor cells are found on a length larger than 4 mm or in multiple (small) areas. A variety of definitions for surgical resection margins are being used in different countries, and therefore also the indication for post-operative interventions [34]. In the Dutch guidelines, a re-operation is required in case of more than focally positive resection margins and a radiotherapy boost when focally positive resection margins are found [35]. Although the recurrence rate in the Netherlands is very low in patients that underwent BCT, avoidance of any additional post-operative interventions is desirable. Normally the pathological evaluation takes approximately 3 to 5 days, which means that the quality of the surgical procedure and thus the need for any post-operative interventions is unknown until days after surgery.

Direct evaluation of surgical resection margins while the patient is still on the operating table could improve BCS substantially. Therefore, several intra-operative margin assessment (IMA) techniques have been developed to evaluate the margins during the surgical procedure, for example specimen radiographs, frozen section analysis, cytology, intra-operative ultrasound, and optical imaging [36]–[40]. Only cytology and frozen section analysis appeared to have sufficient diagnostic accuracy for clinical practice [41]. However, none of these techniques were implemented into routine clinical practice because they are operator dependent,
labor-intensive, costly and time-consuming [42]. A novel IMA technique is micro-computed tomography (μCT). This non-invasive technique provides a 3D image of the entire excision specimen, allowing 3D analysis of the resection margins [43]–[45]. The first experience of μCT for evaluation of surgical resection margins was obtained at the Massachusetts General Hospital in Boston (MGH) [44]. In a pilot study of 25 evaluated shaved cavity margins an accuracy of 92% was obtained with μCT. Although they evaluated shaved cavity margins instead of total excision specimen, their initial results with μCT were promising. When embedded in the surgical workflow, μCT imaging of the excision specimen could reveal positive resection margins while the patient is still on the operating table. Such a setup would improve the current protocol in which pathological results are only available several days after surgery.

**Aim and Outline of this thesis**

Following the introduction and improvement of breast cancer screening programs and the effective use of neo-adjuvant systemic therapies, there are currently more small and non-palpable tumors suitable for breast conserving surgery. In the last years several tumor localization techniques have been introduced in order to guide the surgeon during surgery. Nevertheless, especially patients with non-palpable tumors still suffer from high rates of positive resection margins. Although much effort is put in visualizing the tumor on different imaging modalities, all valuable diagnostic information is not used for planning or guidance of the surgical resection. Furthermore surgical outcome is only available several days after surgery, which in case of positive resection margins require additional post-operative interventions.

The general aim of this thesis is to improve surgical outcome in patients with non-palpable breast cancer. The different parts in this thesis are focused on improving planning, guidance and evaluation of breast conserving surgery in these patients.

The first part of this thesis is focused on optimizing surgical planning of patients with non-palpable breast cancer that undergo BCS. **Chapter 2** evaluates the role of radioactive seed localization (RSL) as a tumor localization technique in improving breast- and axilla-conserving surgery in patients with breast cancer in the Netherlands Cancer Institute. A retrospective review was performed of all consecutive RSL procedures between November 2007 and April 2014, focusing on the rates of incomplete tumor removal and the median resection volume over the years. In **Chapter 3** the use of single and multiple-seed RSL is compared in patients with extensive DCIS. Multiple-seed RSL enables localization of the tumor borders, instead of
only the tumor center in case of single-seed RSL. Both patient groups were compared with respect to surgical outcome and re-operation rates. Besides improved tumor localization we aimed to improve surgical planning by tumor visualization in a supine patient position, similar to BCS. Chapter 4 describes the development and evaluation a novel breast MRI scan protocol acquired in supine position, using a respiratory triggered scan protocol to minimize breathing-induced motion artefacts.

The second part of this thesis is focused on optimizing surgical guidance in patients with non-palpable breast cancer. The pre-operative tumor imaging can be integrated into the surgical procedure by using surgical navigation systems, providing intra-operative localization and guidance towards the actual tumor borders. Chapter 5 describes the evaluation of a novel navigation system used for navigation-guided BCS. The innovative part of this navigation system was the use of real-time wireless tumor tracking, which has never been reported for breast surgery before. Navigation-guided BCS was tested and compared to conventional iodine seed-guided BCS by several surgical oncologists on phantoms with different tumor types and on real breast tissue of 1 patient.

The third part of this thesis was focused on improving the evaluation of BCS by imaging the excision specimen on μCT, a novel imaging technique that provides 3D assessment of surgical resection margins. Chapter 6 analyzes the feasibility and diagnostic accuracy of μCT for positive margin assessment in excision specimen from patients undergoing BCS. First a two-phase multi-observer study was performed in order to analyze inter-observer variation and the effect of guidelines on μCT evaluation. Secondly, we performed a prospective study in which the accuracy of μCT for local assessment of positive resection margins was analyzed, validated by pathology.

The fourth part of this thesis includes a general discussion (Chapter 7), followed by an English and Dutch summary.
References


