Navigating towards the unseen margins of non-palpable breast cancer
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Chapter 7

General Discussion and Conclusion
Following the introduction and improvement of breast cancer screening programs and the effective use of neo-adjuvant systemic therapies (NST), breast cancer surgeons are currently faced with more small and non-palpable tumors that are suitable for breast conserving surgery (BCS). BCS of such non-palpable breast cancer remains a challenging task for the surgeon, since palpation of tumor borders is not applicable in this patient group. Different tumor localization techniques like wire-guided localization (WGL) and radioactive iodine seed localization (RSL) have been introduced, in order to guide the surgeon towards the tumor location. Nevertheless, patients with non-palpable tumors still suffer from high rates of positive resection margins (17%) in comparison to palpable tumors (3%) [1]. Although several pre-operative images are acquired for diagnosis of the tumor, none of the valuable tumor information regarding the tumor location and extent is actually used for planning or intra-operative guidance of BCS for non-palpable tumors. Furthermore, surgical outcome is still based on pathology which takes several days. In case of positive resection margins, patients require additional post-operative interventions, while a direct feedback loop on surgical margins in the OR could prevent positive resection margins. In this thesis we focused on improving surgical planning, intra-operative guidance and evaluation of surgical outcome of BCS, aiming to improve surgical outcome of patients with non-palpable breast cancer.

**Towards improved planning of breast conserving surgery**

Although WGL is still the most common tumor localization technique in the Netherlands, RSL has already been used in a variety of patient groups in the Netherlands Cancer Institute since 2007. Within our analyzed cohort of patients that underwent single-seed RSL for mostly Ductal Carcinoma In Situ (DCIS) (Chapter 2), we found an average rate of 15.4% incomplete surgery. This result is comparable to the average rate of incomplete surgery (16.9%) for patients with DCIS, as registered by the Netherlands Breast Cancer Audit (NBCA) [1]. Furthermore, in most patient groups we observed a decrease in resection volume over the years, except in these patients with in situ tumors. In an attempt to localize tumor borders instead of only the tumor center, the idea of multiple seed implantation has been introduced. The use of single and multiple seeds was further evaluated in chapter 3. We found lower rates of incomplete BCS in patients with extensive DCIS that had underwent multiple-seed RSL (29.3%) in comparison to patients with only one seed (47.9%), although this difference was not significant. At the same time the median resection weight in the multiple-seed group was more than twice the size of the single seed group.

One could debate how successful single- and multiple-seed RSL has been for localization of (larger) non-palpable breast tumors, since the rates of incomplete surgery remain high in
this specific patient group. At least surgical outcomes improved in comparison to multiple implanted wires in which rates between 56%-58% have been reported [2], [3]. Nevertheless, both single and multiple-seed RSL provide only a point-source approximation towards the tumor center or two or three locations of the tumor borders. Even when multiple seeds are being placed, the surgeon is not aware of the exact tumor volume that is surrounded by the implanted seeds, which is essential to remove non-palpable tumors completely. Furthermore it is essential that the iodine seed is properly implanted, in order to guide the surgeon towards the anatomically correct tumor location. That this is not always the case became also evident in the analyzed patient cohort of chapter 6, in which the iodine seed was implanted off-center or even outside the tumor in 25 of 80 patients that underwent RSL.

Why is the combined information about tumor location, size, volume and location of the implanted iodine seed with respect to the tumor borders, which is available on the pre-operative acquired mammography (XM), ultrasound (US) and if indicated contrast-enhanced Magnetic Resonance Imaging (CE-MRI), left unused during BCS? Until now the pre-operative acquired imaging is only used for diagnosis of the tumor. However XM is acquired with the patient in standing position, US with the patient in supine position and if indicated an MRI in which is acquired with the patient in prone position. The surgeon evaluates the pre-operative imaging shortly before BCS, in order to mentally define the most optimal resection volume. This surgical plan is intra-operatively adjusted and mentally translated towards the actual position of the patient on the operating table. This translation step is inaccurate, not reproducible and also prone for variation amongst different surgeons. This is partly due to the lack of tumor imaging acquired in a setup similar to surgery, i.e. a supine patient position. Secondly, in the current surgical workflow the pre-operative tumor imaging is not integrated into the surgical procedure, enabling visual guidance towards the tumor.

Tumor visualization in a supine patient position can therefore be a step forward to improve surgical planning. The difficulty with breast MRI acquired in a supine patient position is the effect of breathing-induced motion artefacts, resulting in a lower image quality. Therefore we proposed a respiratory triggered scan protocol for supine breast MRI in which data was only acquired during the end expiratory phase of the patient (Chapter 4). Also other strategies have been published in order to overcome breathing-induced motion artefacts, for example acquisition during one or multiple breath holds of the patient. However, with this technique it is difficult to achieve reproducible MR images. Another technique is the use of phase-encode reordering in which the patients breathing cycle is tracked and used to acquire data within specific positions of k-space [4], [5]. However also this technique has not been widely adopted into clinical practice because phase-encode reordering is not standard available for each MR scanner.
Surprisingly, the image quality of the supine triggered MRI in volunteers improved in comparison to standard breast MRI acquired in prone position (Chapter 4). However acquisition time was also considerably longer in comparison to diagnostic MRI. The long acquisition time hampers adequate timing between MRI acquisition and injection and distribution of the contrast agent. As a result, there was less contrast between tumor and surrounding breast tissue in the contrast-enhanced supine breast MRI of the patient compared to prone. There was also more time between the pulses, which provided more relaxation time for the tissue. In order to overcome these issues in the future the acquisition time should be reduced, for example by using parallel image acquisition, compressed sensing reconstruction or the acquisition of multiple fast scans after injection of contrast agent \([6–8]\). Another option to increase the signal contrast between tumor and normal tissue is improved fat suppression by using a spectral attenuated inversion recovery pulse, similar to prone breast MRI. Another option is excitation of additional pulses shortly before each shot is acquired in the triggered MRI, achieving a similar relaxation of spins as in prone MRI in which data is continuously acquired. These suggestions potentially lead to improved tumor contrast in contrast-enhanced triggered supine breast MRI, enabling adequate tumor delineation in order to create a supine 3D tumor model. This would provide the surgeon anatomical insight of the tumor location and volume within the whole breast which can be directly translated during BCS.

There are a few other studies available in which the use of supine breast MRI has been evaluated for surgical planning and guidance. One technique has been proposed in which the supine MRI was used to determine the most optimal incision lines prior to BCS. These lines were subsequently drawn onto the skin of the breast of the patient. They acquired supine MRI during breath hold of the patient \([9]\) or a similar scan protocol as in our study, however without the use of respiratory triggering or other strategies to minimize breathing induced motion artefacts \([10]\). Nakamura et al. acquired supine MRI in order to delineate tumor borders on the coronal maximum intensity projection (MIP) images \([11]\), \([12]\). The tumor borders were subsequently drawn on a transparent sheet and projected onto the skin of the patient during surgery. Although they used a similar T1-weighted scan in order to acquire supine MRI, no strategies were used to minimize breathing-induced motion artefacts. It is difficult to compare image qualities of the supine breast MRI in the reported studies with our results, since no quantitative measures like for example signal-to-noise ratio were reported. Fausto et al. used an electro-magnetic tracked US probe to register the lesion on real-time US to prior acquired axial MR images, based on the size and location of the lesions. No surrounding anatomical landmarks or other lesion characteristics were taken into account. Although the registration process appeared to be accurate and reproducible when the MRI was acquired in supine position, it can be difficult to perform an adequate registration for lesions such as DCIS since...
these are not always visible on US. These techniques are nice illustrations that supine MRI information about tumor borders can be integrated into the operating room. However, the surgeon still lacks guidance towards the tumor borders during the actual resection.

**Towards improved guidance of breast conserving surgery**

Although surgical planning enabled by pre-operative tumor imaging in supine position is of major importance for BCS of non-palpable tumors, intra-operative real-time visualization of the tumor volume could really guide the surgeon towards the actual tumor borders. We introduced and evaluated a novel surgical navigation system for BCS (chapter 5). The novelty of this navigation system was the use of real-time and wireless tumor tracking enabled via three implanted transponders, which has never been reported for breast surgery before. Our phantom study results indicated that especially the resection of complex shaped tumors improved with navigation guidance. This is a promising result since we aimed to mimic extensive DCIS in the phantoms with such complex shaped tumors.

There are still some limitations of our navigation system which hamper direct successful implementation into the clinic. First of all, we assume that the transponders do not migrate and are representative for the tumor position and orientation during the whole navigation-guided BCS. However breast tissue can undergo large deformations during surgery in which the implanted transponders potentially migrate, for example after the skin incision has been made or by manipulation of the breast tissue during surgery. This was also illustrated during the navigated BCS in the mastectomy specimen, where the registration error of the real-time transponder locations with those on pre-operative CT increased from 0.2 mm at the start to 1.5 mm at the end of the surgery. This is still acceptable in clinical practice, regarding the 10 mm safety margin around the tumor which is used to take geometrical uncertainties into account. Furthermore these transponders were implanted ex vivo in the mastectomy specimen, in which adequate fixation within the tissue was not achieved. Litzenberg et al. found that implanted transponders in the prostate showed no significant migration up to 50 days after implantation, with similar uncertainties as implanted gold markers [13]. Also iodine seeds are known to have minimal migration (0.9 mm) between implantation in the breast and subsequent BCS (on average 5 days later) [14]. Such a minimal migration could be applicable for the transponders as well, in case they are implanted a few days before BCS.

Furthermore in our current 3D tumor model we assume that the tumor is rigid although it is plausible that the tumor will deform, especially in softer or non-palpable tumors. Our navigation system can be improved if the pre-defined resection volume is adapted according
to the displacement of each individual transponder. Another solution would be to implant more than 3 transponders in the tumor, in order to measure asymmetrical deformations through the whole tumor volume. Besides adaptations of the surgical navigation system itself, the operating room also needs some adaptations in order to implement our navigation system. Ideally, the patient should be positioned on top of the EM array in the operating room in order to minimize disturbance of the current clinical workflow and to achieve accurate navigation. A special matrass should be designed in which the EM field generator could be embedded, similar to navigation-guided surgery for pelvic malignancies [15]. Furthermore, the impact of several metallic surgical tools on the accuracy of our navigation system should be tested first.

In my opinion, successful implementation of our navigation system in clinical practice is achieved if: (1) our system is intuitive and easy to use for the surgeons, (2) it disturbs the normal clinical workflow in the operating room as little as possible, and (3) if all the preparations can be performed before start of BCS. First of all surgeons have to be convinced of the added value of our novel surgical navigation system in order to adopt this technique in the operating room. Fortunately, the participated surgeons in our study were all enthusiastic about the presented system and indicated that this might be the technology for future surgery of non-palpable tumors. Simultaneously, the continuous 3D representation of the tumor within the patient in relation to the surgical instrument is an entirely different setting compared to iodine seed-guided BCS in which the surgeon is only guided by the radioactive signal of the implanted iodine seed. This ‘3D-thinking’ requires some experience, as was also shown by the ongoing learning curve in using the navigation system between the 1st and 2nd phase in the study (chapter 5). More phantom experiments could be performed in order to train the surgeons and becoming more familiar with the surgical navigation system. A great advantage of the presented navigation system is that all preparations are performed prior to surgery, using the pre-operative tumor imaging, transponder positions and defined 3D tumor model as input. This is substantially different from the proposed navigation system for BCS by Ungi et al. [8], which is the most similar navigation system for BCS reported in literature. With their system the 3D tumor model is prepared within the operating room since it relies on intra-operative US and a tracked wire-guide which is implanted shortly before BCS. Furthermore the use of US in their navigation system excludes many patients with DCIS, since these tumor borders are often not visible on US. On the contrary, for our navigation system additional acquisition of supine MRI and CT is required in order to define a 3D tumor model. This can be suboptimal in terms of complicated radiological logistics and increased costs in the pre-operative workflow of the patient. This could limit wide and fast adoption of this technology in clinical practice. To my opinion the acquisition of 2 extra scans is worthwhile for the potential clinical benefit in terms of reduced rates of incomplete BCS in patients with non-palpable
breast cancer. Less patients will need a radiotherapy boost or even a re-operation in this setting, compensating the additional costs for the supine MRI and CT acquisition and usage of the navigation system on the long term. For cost-effectiveness, the presented surgical navigation system should not be standard for all breast cancer patients but only in patient groups with high rates of incomplete surgery, for example patients with non-palpable breast cancer.

Towards improved evaluation of breast conserving surgery

Within the current workflow a positive resection margin is only detected after the harm already has been done. We aimed to improve direct evaluation of BCS by imaging the excision specimen using μCT (Chapter 6). The results of both our retrospective and prospective study showed that at this point μCT still has a moderate accuracy for adequate evaluation of surgical resection margins, with considerable inter-observer variation. Simultaneously, we did enable local annotation and validation of a suspect positive resection margin on μCT by using the specific scan container, which has never been reported before.

There are still a few hurdles to overcome in order to start a prospective intervention study in which the surgeon resects additional tissue during the same operation in case a positive resection margin is found on μCT. Within this setting it is essential that: (1) μCT has a combination of a high positive predictive value (PPV) and sensitivity in order to correctly identify a local positive resection margin within the excision specimen, (2) the total scan and evaluation time of μCT is still acceptable within the current workflow of BCS and (3) that there is an adequate mapping of the positive resection margin on μCT back to the patient. The most challenging cases in both the retrospective and prospective study were patients with dense breast tissue or patients having DCIS, in which it was difficult to distinguish close from positive resection margins. More experience and the use of dedicated guidelines for μCT evaluation, as was also shown in the 2nd phase of our retrospective study, contribute to improved evaluation of μCT and increased PPV. However, the similar attenuation characteristics of normal tissue and for example DCIS, which grows inside the normal fibro-glandular ducts, result in a similar presentation of both tissue types on μCT. This issue will not be solved by more experience of μCT observers in the future. The use of phase-contrast μCT scanners, μMRI scanners, lower scan voltages or the injection of special contrast agents might be interesting applications to further increase the soft tissue contrast [16]–[20]. However, since current μCT evaluation is mainly based on morphology of the tissue the use of machine learning algorithms for automated margin assessment might be the most potential step forward. Previous studies found that specific machine learning techniques provided a high diagnostic performance.
for prediction of breast tumors on cone-beam CT, surpassing human observers [21]. Wang et al. showed that contrast enhanced cone-beam CT improved the ability of specific texture features to discriminate tumor from normal breast tissue [22]. The use of such innovative machine learning algorithms for automatic margin assessment on μCT should be further explored in the future. Regarding the second requirement; at this point total time for μCT acquisition, reconstruction and evaluation is approximately 20 minutes. The current μCT system only starts scan reconstruction after all projection images are acquired. Recent developed inline reconstruction software, starting with reconstruction as soon as the first projection image is available, provides a reconstructed μCT only a few seconds after μCT acquisition is completed [23]. With this approach acquisition, reconstruction and assessment of surgical resection margins on μCT is possible within 10 minutes, which is already a big step forward. Another fair question to ask is which time frame will still be allowed in the clinic? In other words, how long can BCS be extended in order to scan and evaluate the specimen for positive resection margins? Currently frozen section analysis is performed at the surgeons request in case a positive resection margin is suspected. This technique takes approximately half an hour to provide feedback to the surgeon, which is already longer than the current scan time with μCT. In that perspective reduction of total scan time of μCT is still desirable but not high-priority in order to adopt this technique in the clinic. The last requirement in order to start an intervention study is accurate translation of a positive margin on μCT back to the patient. A simple and straightforward solution would be to ink the location of the suspect positive resection margin onto the specimen and show this to the operating surgeon. The original patient orientation of the excision specimen can be derived via the annotated basal and nipple side onto the specimen, marked with a single and a double suture by the surgeon. This approach would give a rough estimate of the positive margin within the resection cavity of the patient. A more accurate but also challenging solution would be to register the μCT scan with annotated positive margin back to pre-operative MRI of the patient, requiring deformable registration algorithms [24]. One could even use deformable image registration to match the pre-operative defined resection volume on supine MRI towards the excised specimen. With this approach one can evaluate if the whole tumor was included in the specimen, aiming to detect positive resection margins. The accuracy of these methods could be further explored in phantom studies first. Nevertheless, a safe intermediate step for a first intervention study would be to perform a local frozen section at the location of a suspect positive margin instead of a shaved cavity margin, enabling a first step of this technology into the clinic.
Future recommendations

With all the presented solutions to improve pre-operative surgical planning, intra-operative surgical guidance and direct evaluation of surgical outcome in this thesis, the most important question remains: which techniques are most valuable for introduction in clinical practice? In order to improve surgical outcome in patients with non-palpable breast cancer, the surgeon must have intra-operative, real-time and accurate information on tumor borders. The most promising technique discussed in this thesis would be the use of our novel surgical navigation system, together with an improved version of our supine breast MRI as input. The moderate accuracy of μCT at this point disables a first step towards implementation in clinical practice. Furthermore in my opinion, it makes more sense to guide the surgeon towards the tumor borders using surgical navigation than guiding the surgeon towards the location of a positive resection margin via μCT. Therefore, the use of navigation-guided BCS in patients with non-palpable breast cancer might be the promising technique in the future in order to improve surgical outcome in this patient group.

However other interesting techniques are being developed that could change breast cancer management in the future, for example hybrid operating rooms allowing intra-operative MR acquisition within the operating theatre. With such a setup supine MRI can be acquired shortly before BCS and used as input for our presented navigation system, providing intra-operative guidance for the surgeon. Ideally also a supine breast MRI is acquired directly after BCS in order to evaluate if remaining tumor is present within the breast. Such a workflow integrates surgical planning, guidance and direct evaluation of BCS within one surgical operation. Instead of standard BCS performed by the surgeon, one could even think of using surgical robots within such a hybrid operating room, assisting the surgeon during the operation. Within such a setting the robot could move surgical instruments towards the tumor, based on intra-operatively acquired imaging. Although robots have not been introduced for breast surgery until now, this would be an interesting future development.

Use of robots in combination with minimally invasive surgery (MIS) is also an interesting development. MIS has become more popular in comparison to open surgery in the last decades, and could potentially be introduced for BCS of small lesions as well. However the greatest disadvantages of this technique for BCS are the loss of vision and tactile feedback within the patients anatomy during BCS. In order to provide surgical guidance within MIS augmented reality (AR) could be used, projecting a tumor model within the laparoscopic view of BCS [25]. AR is also possible within the field of open surgery, for example by wearing a Google Glass that projects the tumor model within the vision of the surgeon. This approach avoids that the surgeon has to alternate between actual tumor resection within the
patient and intra-operative navigation by looking at a computer screen somewhere else in the operating room. In the future holograms of the tumor might even become available for BCS.

Another interesting field is the use of optical imaging techniques, in combination with tumor-targeted contrast agents. One example is near-infrared fluorescence (NIRF) imaging in which specific fluorophores are administered prior to BCS, intra-operatively detected and visualized with respect to the patients anatomy [26], [27]. In order to excite and localize tumor-specific fluorophores, a specific multispectral camera system has been developed which is suitable within the operating room [28]. This system was evaluated in breast phantoms with different tumors, in which the fluorophores could be detected up to a depth of 21 mm [26]. Furthermore, NIRF-guided BCS appeared feasible in the phantoms, as well as detection of residual tumor in case of incomplete BCS. The use of NIRF has also been studied in real patients, however until now only for detection and guidance of resection of sentinel lymph nodes during BCS [29]. Optical spectroscopy might also be an interesting technique for intra-operative tumor detection and margin assessment. The use of diffuse reflectance spectroscopy (DRS) has been studied in order to evaluate tissue characteristics, aiming to distinguish normal from malignant tissue in lung, colon and breast tumors [30]–[32]. However, with this technique only a limited subset of the whole tumor volume or surgical resection margin can be assessed. Therefore this technique might be more interesting for analysis of suspected positive resection margins within the resection cavity of the patient, in order to evaluate presence of remaining tumor. Finally nanomedicine might become feasible in future breast cancer management of (small) tumors, providing local delivery of drugs into the tumor [33]. Although some progress has been made in developing promising nanoparticles for breast cancer management in the last years, limitations such as increased patient toxicity and high costs have been reported. Therefore it is not likely that the need for accurate BCS will be abandoned within the near future.

Conclusions

The general aim of this thesis was to improve planning, guidance and evaluation of breast conserving surgery in patients with non-palpable breast cancer. Based on the provided work we can conclude that current localization techniques such as RSL, using single or multiple seeds, still have their restrictions in the surgical workflow of BCT for non-palpable tumors. Tumor visualization in supine patient position in combination with a surgical navigation system has the highest potential to improve this current workflow in the operating room. The use of our novel surgical navigation system provides the surgeon intra-operative tumor visualization and therefore awareness of tumor borders. This technology should especially
be used in patients with non-palpable breast cancer or in other patient groups that still suffer from high rates of incomplete surgery. The use of such a navigation system requires different expertise, therefore close collaboration within a multi-disciplinary team is essential for successful implementation in the clinic.
References


