

Real-time wireless tumor tracking during breast conserving surgery

Natasja Janssen¹ · Roeland Eppenga² · Marie-Jeanne Vrancken Peeters² · Frederieke van Duijnhoven² · Hester Oldenburg² · Jos van der Hage² · Emiel Rutgers² · Jan-Jakob Sonke¹ · Koert Kuhlmann² · Theo Ruers^{2,3} · Jasper Nijkamp²

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Abstract

Purpose To evaluate a novel surgical navigation system for breast conserving surgery (BCS), based on real-time tumor tracking using the Calypso® 4D Localization System (Varian Medical Systems Inc., USA). Navigation-guided breast conserving surgery (Nav-BCS) was compared to conventional iodine seed-guided BCS (¹²⁵I-BCS).

Methods Two breast phantom types were produced, containing spherical and complex tumors in which wireless transponders (Nav-BCS) or a iodine seed (¹²⁵I-BCS) were implanted. For navigation, orthogonal views and 3D volume renders of a CT of the phantom were shown, including a tumor segmentation and a predetermined resection margin. In the same views, a surgical pointer was tracked and visualized. ¹²⁵I-BCS was performed according to standard protocol. Five surgical breast oncologists first performed a practice session with Nav-BCS, followed by two Nav-BCS and ¹²⁵I-BCS sessions on spherical and complex tumors. Postoperative CT images of all resection specimens were registered to the preoperative CT. Main outcome measures were the minimum resection margin (in mm) and the excision times.

Results The rate of incomplete tumor resections was 6.7% for Nav-BCS and 20% for ¹²⁵I-BCS. The minimum resec-

tion margins on the spherical tumors were 3.0 ± 1.4 mm for Nav-BCS and 2.5 ± 1.6 mm for ¹²⁵I-BCS ($p=0.63$). For the complex tumors, these were 2.2 ± 1.1 mm (Nav-BCS) and 0.9 ± 2.4 mm (¹²⁵I-BCS) ($p=0.32$). Mean excision times on spherical and complex tumors were 9.5 ± 2.7 min and 9.4 ± 2.6 min (Nav-BCS), compared to 5.8 ± 2.2 min and 4.7 ± 3.4 min (¹²⁵I-BCS, both ($p < 0.05$)).

Conclusions The presented surgical navigation system improved the intra-operative awareness about tumor position and orientation, with the potential to improve surgical outcomes for non-palpable breast tumors. Results are positive, and participating surgeons were enthusiastic, but extended surgical experience on real breast tissue is required.

Keywords EM navigation · Tracking · Real-time · Wireless · Breast conserving surgery

Introduction

Breast cancer screening, improved imaging techniques and neoadjuvant systemic therapy (NST) have led to increased numbers of small and non-palpable tumors suitable for breast conserving surgery (BCS). Such tumors require accurate preoperative tumor localization to achieve small resection volumes while ensuring total tumor resection during BCS [1]. Various tumor localization techniques have been developed, such as wire-guided localization (WGL) and radioactive seed localization (RSL) [2–5]. With WGL, a hooked wire is inserted into the tumor and used as a guide during surgery. In RSL, a radioactive iodine seed (¹²⁵I) is implanted into the tumor center using ultrasound- or stereotactic guidance. Intra-operatively, the seed can be detected by the surgeon with a portable gamma probe. However, both WGL and RSL provide only a pointwise approximation for tumors

The authors Natasja Janssen and Roeland Eppenga have contributed equally to this work.

✉ Jasper Nijkamp
j.nijkamp@nki.nl

¹ Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

² Department of Surgical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

³ Nanobiophysics Group, MIRA Institute, University of Twente, Enschede, The Netherlands

with a complex geometry such as ductal carcinoma in situ (DCIS). The surgeon has no information regarding the actual tumor volume or shape surrounding the tip of the guidewire or radioactive seed. This oversimplification leads to significantly higher rates of incomplete tumor resections (20–30%) when compared to palpable tumors, resulting in higher reoperation rates and patient burden [6,7].

Surgical navigation systems can be used to integrate preoperative tumor imaging into the surgical procedure, providing intra-operative localization and guidance toward the actual tumor borders. For example, Ungi et al. [8] developed a system for navigation-guided BCS based on implanting a tracked localization needle into the tumor, and contouring the tumor borders using tracked 2D ultrasound. During surgery a tracked cautery tool was visualized relative to the tumor contour. Initial results on phantoms and six patients with palpable tumors were promising. However, their system has two main disadvantages: a tracked needle is protruding from the breast, and intra-operative ultrasound is needed to define tumor borders.

Wireless tumor tracking is an alternative technique and has already been applied in radiation oncology, using the Calypso's *GPS for the Body*® tumor tracking technology (Varian Medical Systems Inc., Palo Alto, California, USA). Three implanted EM-sensitive Beacon® transponders provide real-time information about tumor position and orientation, assuring a tracking precision and accuracy below 1 mm [9,10]. The Calypso system could be useful in surgical oncology as well, where real-time information about tumor location and orientation is highly important for accurate tumor resection.

In the present study, we present a novel surgical navigation system that facilitates navigation-guided BCS (Nav-BCS), using the Calypso system to track the tumor position in real-time. A surgical instrument is optically tracked and visualized relative to a pre-defined resection volume on pre-operative tumor imaging. We tested the navigation system on breast phantoms and compared it to conventional iodine seed-guided BCS (^{125}I -BCS). Furthermore, the clinical feasibility of the Nav-BCS was tested on real breast tissue, originating from the resection specimen of a patient who underwent a preventive mastectomy.

Materials and methods

Study outline

Five dedicated breast surgical oncologists familiar with ^{125}I -BCS participated in this study. To get acquainted with Nav-BCS, all surgeons first had a practice session on a phantom using the Nav-BCS setup. In the 1st study phase, each surgeon performed one session of Nav-BCS and one ses-

sion of ^{125}I -BCS. Per session, two phantoms were operated: one containing a simple spherical tumor and one containing a complex tumor. The phantom with the simple tumor was always operated first. The 2nd phase of the study was performed in order to detect a possible learning curve in using Nav-BCS. Therefore, all surgeons performed one additional session of Nav-BCS and ^{125}I -BCS on a simple spherical tumor. Besides the phantoms, one Nav-BCS was performed on ex vivo breast tissue, derived from a patient that underwent a preventive breast mastectomy. The primary task in all sessions was to remove the tumor with a resection margin of 1 cm around the tumor, irrespective of the surgery technique or tumor type.

Navigation system overview

The navigation system consisted of a Calypso tracking system, the optical NDI Polaris Spectra Hybrid System (Northern Digital, Waterloo, Ontario, Canada) and in-house developed navigation software.

Calypso system

The Calypso system is able to track three wireless 5DOF Beacon transponders that are excited by an external electromagnetic (EM) field, which is generated by EM source coils integrated in an EM array. The excited Beacon transponders emit a decayed localization signal that can be measured by the same EM array, at a frequency of 8 Hz per transponder [9]. The phantom with the implanted transponders was positioned within the tracking volume of approximately $14 \times 14 \times 19$ cm, at a height of 9 cm above the EM array [10].

Polaris system

As the Calypso system can maximally track 3 Beacon transponders, an additional tracking system is needed to track surgical instruments. For this, we used the optical Polaris system to track a pointer and the EM array. Both the pointer and EM array had an attached optical reference frame (Ref), with 4 mounted passive reflective spheres. The infrared camera of the Polaris system transmits and subsequently detects infrared light which is reflected by these spheres. Because the camera is stereoscopic, the spatial location of the spheres can be determined and therefore also the location and orientation of the optical reference frames, i.e. the pointer and EM array.

Calibration

The coordinate systems of both the EM and optical tracking system (OTS) were registered following a calibration

procedure, using an in-house developed phantom. This calibration phantom consisted of three embedded transponders and 4 optical reflective spheres mounted on the surface. The configuration of the transponders with respect to the optical spheres was known. The calibration phantom was positioned at 48 different locations within the EM tracking volume, collecting both EM and OTS data. The 48 positions covered the entire tracking volume, with 12 locations per layer, at 4 different heights from the EM array. The collected OTS data were first transformed to the coordinate system of the optical reference frame that was mounted on the EM array. Subsequently, the OTS and EM data were used to calculate a transformation matrix describing the transformation between the Ref and EM coordinate system, using a least-squares fitting point algorithm. The root mean square error (RMSE) after registration of both systems was calculated as a measure of calibration accuracy.

Navigation software

The research Calypso system has an OpenIGTLink interface providing TRANSFORM messages over a TCP/IP connection. For readout of the Polaris and Calypso hardware, the PlusServer from the Plus Toolkit (www.PlusToolkit.org) was used [11]. Within PlusServer, the data for the Polaris and Calypso system were combined into one data stream. Data of both tracking systems were communicated using OpenIGTLink TRANSFORM messages. Our in-house developed navigation software uses the OpenIGTLink.dll from IGSTK (www.igstk.org) to receive these messages. Data were acquired with a sampling rate of 8 Hz per transponder and 15 Hz for both the optical reference frame and pointer.

The graphical user interface consisted of 4 different CT views of the phantom: a 2D axial and sagittal view and 3D volume renders in axial and sagittal views (Fig. 1). In these views, also the tumor segmentation and pre-defined resection volume were visualized. The measured real-time Beacon transponder positions were automatically registered to the corresponding transponder positions on CT at every update. The registration accuracy was expressed by the fiducial registration error (FRE) in mm, which represents the root mean square residual error after transformation. The location of the pointer tip was related to the corresponding CT slice and visualized on the 2D axial and sagittal views. On the render viewers, a 3D model of the pointer was visualized. All views were updated with 15 Hz.

Study materials

Breast phantoms

Breast phantoms were constructed from plastisol liquid plastic (M-F Manufacturing, Fort Worth, TX, USA), in a similar

way as the phantoms used by Ungi et al. [8]. The phantoms consisted of mimicked normal ‘healthy’ breast tissue (1/3 added softener), one tumor (no added softener) and a harder skin layer (no added softener). Despite the difference in stiffness between the tumor and the surrounding tissue, the tumors were non-palpable. Magnesium oxide (MgO₂) powder was added to the tumor during the manufacturing process to generate image contrast on CT and ultrasound. Further, the tumors had a different color than the surrounding breast tissue to facilitate direct visual examination of the resection specimen after surgery. Two types of phantoms were produced: containing spherical (approximately 15 mm in diameter) and complex elongated tumors. Aim was to mimic small round-shaped tumors and more extensive tumors like ductal carcinoma in situ (DCIS).

In the phantoms used for Nav-BCS, three transponders were implanted inside or close to the tumor during the manufacturing process. For the ¹²⁵I-BCS phantoms, a radiologist implanted one iodine seed after the manufacturing process, using ultrasound guidance. All phantoms underwent preoperative CT. The tumor was manually delineated on each CT scan using in-house developed software. Secondly, the intended resection volume was defined as an isotropic margin of 1 cm around the tumor. The location of the implanted transponders was determined using thresholding. All transponders were inside the defined resection volume. The tumor delineations and resection volumes for ¹²⁵I-BCS were not shown to the surgeons before start of the surgery as this is also not standard clinical practice.

Surgical procedures

The surgeon started the Nav-BCS sessions by using the pointer and the corresponding navigation views in order to determine the tumor location and extent inside the phantom. The preferred incision lines were drawn on the skin of the phantom using a marker pen. Intra-operatively, the surgeon alternated between resecting the tumor using the scalpel and navigating using the pointer and the navigation views. For ¹²⁵I-BCS, the surgeon preoperatively evaluated the CT in order to determine the tumor location and size, and the position of the iodine seed with respect to the tumor border. Subsequently, the standard clinical gamma probe was used for tumor localization and guidance. Both for Nav-BCS and ¹²⁵I-BCS, the tumor was resected using a scalpel (size 15) instead of the clinically used diathermia probe (because of the lack of electrical conductivity of the phantom material). A plastic retractor was used to avoid disturbance of the EM tracking accuracy, instead of the standard metal retractor used in clinical practice. All other used surgical instruments were similar to clinical practice.

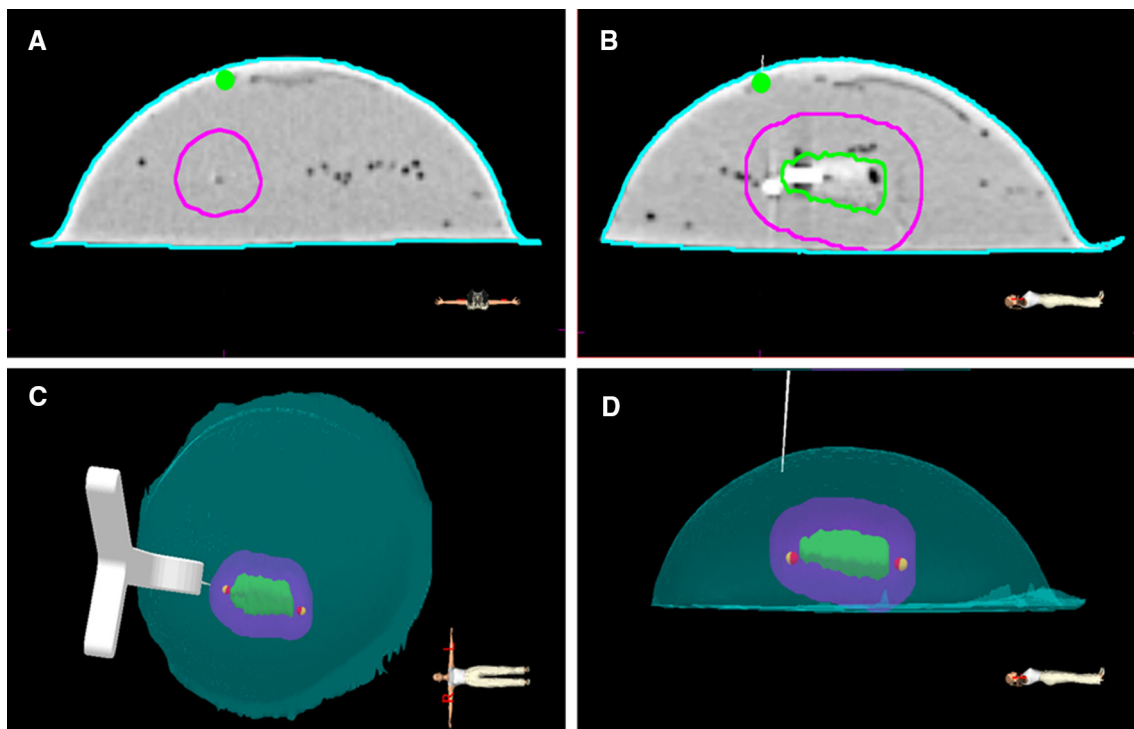


Fig. 1 The navigation interface displays 2D axial (a) and sagittal (b) views and two 3D volume render axial and sagittal views (c+d) of the phantom, including delineations of the tumor (green), the pre-defined

resection volume (pink) and a 3D model of the pointer. The pointer tip location (green dot) determined the corresponding CT slice

Mastectomy specimen

To evaluate Nav-BCS on real breast tissue, a resection specimen of a prophylactic skin sparing mastectomy (breast amputation) was used with the patient's informed consent. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The specimen was placed inside a ring on a plastic plate, in order to maintain the same tissue configuration during implantation of the transponders, CT acquisition and the Nav-BCS (Fig. 2). A radiologist implanted three Calypso Beacon transponders in close proximity of each other in a region of dense breast tissue using ultrasound guidance. A CT was acquired on which a fictive tumor was delineated (around the implanted transponders) and the resection volume defined as 1 cm margin around the tumor. One of the participating breast surgeons operated on the specimen. In contrast to the phantom study, the surgeon was able to use both an optically tracked scalpel and the pointer. The tracked scalpel enabled simultaneous tumor resection and navigation. An optical reference frame with 4 mounted passive reflective spheres was attached to the scalpel and was calibrated before start of Nav-BCS. Three-dimensional models of both

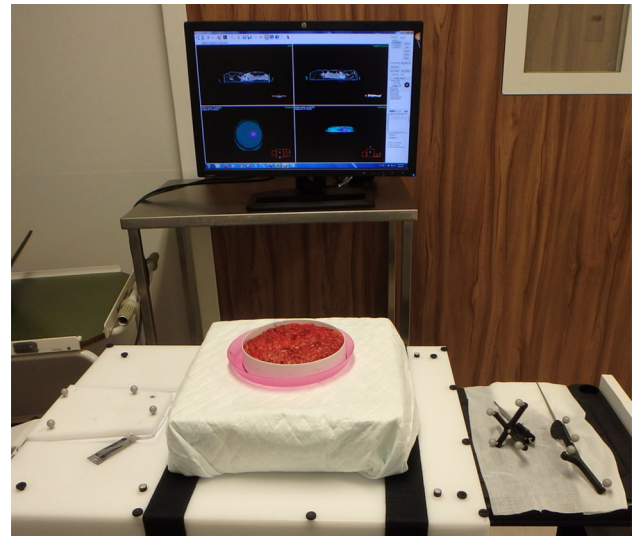


Fig. 2 Navigation setup for tumor resection on real breast tissue specimen that was positioned on top of the EM array, next to an optically tracked scalpel and pointer

the pointer and scalpel were shown on the render views in the navigation software. Postoperatively, the Nav-BCS resection specimen was brought to pathology together with the remaining mastectomy specimen for standard pathological analysis.

Outcome measures

Postoperative CT images were acquired of all resection specimens. In order to compare the preoperative defined resection volume with the actual resection volume, the postoperative CT images were registered to their corresponding preoperative CT using a rigid gray-value registration with mutual information as a cost function. Registration was performed within an ROI including the implanted transponders or the iodine seed. The actual resection volumes were automatically segmented on CT using thresholding. Per phantom, the 3D resection margin was calculated by randomly sampling 4000 points on the surface of the tumor and calculating the shortest vector distance to the actual resection border. With 4000 points, the entire surface is sampled with an average point to point distance of 0.5 mm. The minimum of these vector distances was reported, in which a negative distance indicated an incomplete resection. The rate of incomplete resections was reported per surgery technique. In clinical practice, a variety of definitions for incomplete tumor resections are being used. For this study, we used the definition as described by the American Society of Clinical Oncology (ASCO) guidelines: a minimum of 2 mm is considered to be a safe resection margin for BCS of non-palpable in situ breast carcinomas [12]. Therefore, we derived the percentage of calculated distances between tumor and resection border of less than 2 mm [% (margin \leq 2 mm)]. Other quantitative outcome measures were the mean distance from tumor to resection border, and the excision time. The mean resection margin would be 1 cm in case of an ideal resection. Further, usability of Nav-BCS was assessed using the System Usability Scale (SUS), based on questionnaires filled in by the surgeons [13]. A SUS score above 68 is considered above average, indicating good usability of the system [14].

Differences between minimum tumor to resection border distances and excision times of Nav-BCS and ^{125}I -BCS were tested using a Student's *t* test. A *p* value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software package version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

The calibration between the OTS and EM system was performed once, as the optical reference frame is rigidly attached to the EM array. The calibration resulted in an average RMSE of 0.26 mm. Further, registration of the real-time transponder locations in all operated phantoms with those on CT resulted in an average FRE of 0.21 ± 0.10 mm at the start and 0.30 ± 0.22 mm at the end of Nav-BCS. At the start of every Nav-BCS procedure, the accuracy of the system was

visually checked by moving the pointer over the surface of the phantom.

Phantom study

One of the five practice Nav-BCS resulted in incomplete tumor resection. In the first study phase, the rate of incomplete resections was 1/10 (10%) for Nav-BCS and 3/10 (30%) for ^{125}I -BCS, indicated by the negative minimal distance between tumor and specimen border (Table 1). Three of the four incomplete resections were performed by the same surgeon.

Spherical tumors 1st study phase

The minimal distance (\pm SD) between the spherical tumor and resection border was on average 0.9 ± 2.0 mm for Nav-BCS, compared to 1.1 ± 2.1 mm for ^{125}I -BCS ($p=0.81$) (Table 1). The mean distance between spherical tumors and resection border (\pm SD) was 6.4 ± 0.9 mm for all Nav-BCS and 6.8 ± 1.9 mm for ^{125}I -BCS ($p=0.70$). The percentage of surface points with a margin \leq 2 mm was on average 5.6% for Nav-BCS and 5.7% for ^{125}I -BCS (Table 2).

Complex tumors 1st study phase

The minimal distance (\pm SD) between the complex tumors and resection border was on average 2.2 ± 1.1 for Nav-BCS and 0.90 ± 2.4 mm for ^{125}I -BCS ($p=0.32$). Mean distances between complex tumors and resection border (\pm SD) were 9.0 ± 1.0 mm (Nav-BCS) and 7.5 ± 1.4 mm (^{125}I -BCS) ($p=0.10$). The percentage of surface points with a margin \leq 2 mm was on average 0.6% for Nav-BCS and 2.6% for ^{125}I -BCS.

Spherical tumors 2nd study phase

The results of the first study phase indicate that Nav-BCS of the more challenging complex tumors was performed better than Nav-BCS on the simple spherical tumors, which indicates an ongoing learning curve in using the Nav-BCS system. In the second study phase, the minimal distance between tumor and specimen border was 3.0 ± 1.4 mm for Nav-BCS and 2.5 ± 1.6 mm for ^{125}I -BCS ($p=0.63$). Mean distances increased to 7.7 ± 0.9 mm for Nav-BCS and 8.1 ± 1.7 mm for ^{125}I -BCS ($p=0.66$). Both the minimal and mean distances of both Nav-BCS and ^{125}I -BCS increased in the second study phase, indicating that surgeons were more familiar with resecting the phantoms. The percentage of surface points with a margin \leq 2 mm was 0.2 and 2.4% for Nav-BCS and ^{125}I -BCS, respectively. There were no incomplete tumor resections in the 2nd study phase.

Table 1 The minimum distances in mm between tumor and resection border for the spherical tumors (1st and 2nd study phase), the complex tumors (only 1st phase) and SUS score for the Nav-BCS system per surgeon

# Study phase	Spherical tumors				Complex tumors		SUS Score
	Nav-BCS (mm)	¹²⁵ I-BCS (mm)	Nav-BCS (mm)	¹²⁵ I-BCS (mm)	Nav-BCS (mm)	¹²⁵ I-BCS (mm)	
	1st	1st	2nd	2nd	1st	1st	
Surgeon A	0.2	1.9	5.0	0.8	1.4	3.1	75
Surgeon B	1.0	3.7	3.0	4.9	2.6	3.5	82.5
Surgeon C	−1.2	−2.1	1.9	1.3	0.8	−1.6	57.5
Surgeon D	4.1	0.7	1.4	2.3	3.5	1.0	75.0
Surgeon E	0.2	1.5	3.6	3.2	2.6	−1.3	52.5
Average min ± SD	0.9 ± 2.0 mm	1.1 ± 2.1 mm	3.0 ± 1.4 mm	2.5 ± 1.6 mm	2.2 ± 1.1 mm	0.9 ± 2.4 mm	68.5 ± 12.8
¹²⁵ I-BCS versus Nav-BCS	$p = 0.81$		$p = 0.63$		$p = 0.32$		
1st versus 2nd session	$p = 0.08$		$p = 0.29$				

Bold and negative distances indicate incomplete tumor resections

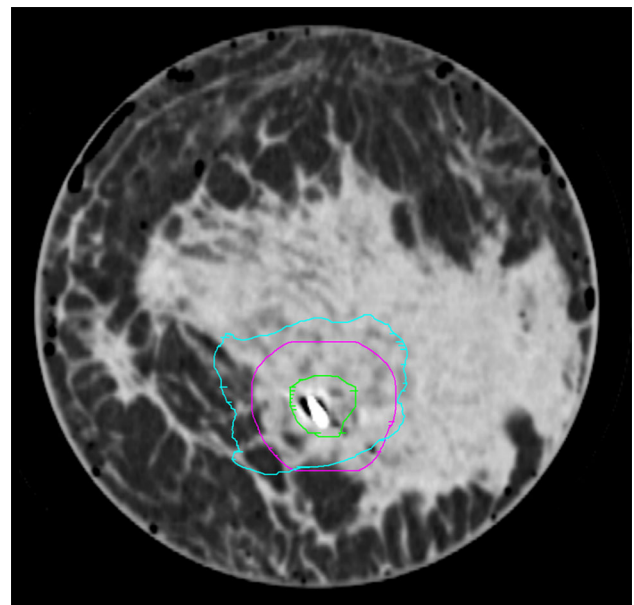
Table 2 The percentage of tumor—surface points with a resection margin ≤ 2 mm

# Study phase	Spherical				Complex	
	Nav-BCS	¹²⁵ I-BCS	Nav-BCS	¹²⁵ I-BCS	Nav-BCS	¹²⁵ I-BCS
	1st	1st	2nd	2nd	1st	1st
Surgeon A	5%	0%	0%	11%	1%	0%
Surgeon B	4%	0%	0%	0%	0%	0%
Surgeon C	13%	25%	0%	1%	2%	6%
Surgeon D	0%	3%	1%	0%	0%	2%
Surgeon E	7%	1%	0%	0%	0%	5%
Mean %	5.6%	5.7%	0.2%	2.4%	0.6%	2.6%

The average SUS score of our navigation system was 68.5 (range: 52.5–82.5) and all surgeons indicated to be enthusiastic about Nav-BCS. Mean excision times for Nav-BCS and ¹²⁵I-BCS of the 1st and 2nd study phase on spherical tumors were 8.6 ± 2.4 min and 6.1 ± 2.3 min ($p = 0.03$). For the complex tumors, these were 9.4 ± 2.6 min for Nav-BCS and 4.7 ± 3.4 min for ¹²⁵I-BCS, respectively ($p = 0.04$).

Mastectomy specimen

Calibration of the optically tracked pointer and scalpel was performed before start of the Nav-BCS of the mastectomy specimen. Shortly after start of the Nav-BCS, the scalpel appeared suboptimal to perform a spherically shaped resection in the real breast tissue. Therefore, the surgeon aimed for a more cubical shaped resection beforehand. Although there was considerable deformation of the real breast tissue during Nav-BCS, tumor resection was complete with a minimum distance between tumor and the resection border of 3.4 mm (Fig. 3). Total excision time was 35.3 min. The registration of the real-time transponder locations during the surgical procedure increased from 0.2 mm at the start to 1.5 mm at the end of the session.

**Fig. 3** Registered postoperative CT of the Nav-BCS resection specimen to the preoperative CT of the original mastectomy specimen. Delineations of the tumor (green), planned resection volume (pink) and actual resection volume (blue) are shown

Discussion

In this study, we presented a novel surgical navigation system based on real-time and wireless tumor tracking using EM sensors, in order to perform navigation-guided breast conserving surgery. Our results indicated that resection of complex tumors improved with navigation guidance, in comparison with conventional iodine seed-guided surgery. Navigation-guided BCS was also feasible and successful in real breast tissue, even with large tissue deformations during the surgery. Further, all participated surgeons were enthusiastic about the navigation system. This preliminary work shows a potential role of the navigation system for resection of diffuse lesions like DCIS, aiming to reduce the high rates of incomplete tumor resections in this patient group.

There are some limitations of our presented study. First of all, we did not investigate the influence of the surgical environment on the EM tracking accuracy [20, 21]. The Nav-BCS procedures were all performed on a plastic table with a minimal amount of surrounding metal and equipment. Previous studies in which an EM navigation system was used for neurosurgical applications showed an increased tracking error due to metallic surgical instruments [22]. This will be part of future investigations. In our approach, we assume that the transponders are representative for the tumor position and orientation and that they do not migrate. In the mastectomy specimen case, we saw that the fiducial registration error increased during surgery, which is probably caused by migration of the transponders. In this case, the transponders were implanted *ex vivo*, with limited fixation. A study by Litzenberg et al. showed that implanted Beacon transponders in the prostate were positionally stable [23]. Also RSL has negligible seed migration independent of the time *in situ* [24]. Therefore, we expect that migration of the transponders when implanted in the breast days to weeks before surgery will be negligible. In this study, we assume that the tumor is rigid and that the pre-defined shape of the tumor can be used during surgery. Depending on the tumor type, this assumption might be invalid. Further improvement of the Nav-BCS system can be achieved if the displacement of each individual transponder is used for real-time adaptation of the defined resection volume.

The most comparable study on a navigation system for breast conserving surgery is by Ungi et al [8], using a tracked localization needle and tracked 2D ultrasound for intra-operative contouring of tumor borders. They showed promising results in terms of less resected tissue and a reduced positive margin rate (12.5%) compared to conventional wire-guided BCS (50%). Direct comparison is challenging, as they aimed to minimize the resection volume by removing the contoured tumor with a safety margin

of 1 mm, while we aimed for a consistent safety margin of 10 mm around the tumor. The 10 mm margin is used in our clinical practice to take geometrical uncertainties into account during ^{125}I -BCS. The 10 mm margin often results in a minimal margin of at least 1 mm, also represented in our results, and seems to be a good balance between the risk of incomplete tumor resections and sparing healthy tissue. Another difference with the study of Ungi et al. is the preparation workload in the operating room (OR). Our navigation system is ready to use without any OR preparation using the preoperative image (CR/MR), transponder positions and corresponding 3D tumor model as input. In the tracked needle and tracked ultrasound setup, on-site tumor delineation is required as soon as the needle is implanted in the OR. This might also require presence of a radiologist in the OR, which is not the case for our setup.

We compared the Nav-BCS to RSL in our study, although wire-guided localization is still common practice in most institutes despite high rates of incomplete tumor resection varying between 13 and 58% [15]. In our institute, RSL was already introduced in 2007 [3]. Seven years of experience with more than 1200 patients has shown the applicability of RSL for localization of non-palpable *in situ* carcinomas, larger invasive carcinomas and axillary lymph nodes, and the use of multiple-seed RSL in patients with extensive/diffuse tumors like DCIS. This last patient group still suffers from high rates of incomplete tumor resection up to 25% [16]. We think that the presented surgical navigation system is an attractive alternative in comparison to both WGL and RSL for this patient group, aiming to reduce the rate of incomplete tumor resections.

To eventually achieve a successful implementation of the navigation system into clinical practice, we consider a multi-disciplinary collaboration to be essential. The first step in this clinical workflow is acquisition of a high-quality image of the tumor. Preferably magnetic resonance imaging (MRI), due to its high image contrast for soft tissues such as the breast. MRI appeared to be superior to CT for visualization of irregularities and spiculations inside the breast tissue, as well as for tumor detection [17]. Currently, acquisition of high-quality breast MRI in supine position has become available, by using a respiratory triggered image protocol [18]. Subsequently, the radiologist can use this supine MRI together with ultrasound for implantation of the three transponders inside the tumor. The next step in the clinical workflow is localization of the implanted transponders relative to the tumor borders and definition of the resection volume. Since the transponders cause small signal voids on MRI images, CT would be the most appropriate 3-D imaging technique for this step. After registration of the MRI and CT images, their combined information can be used by the radiologist and surgeon to delineate the tumor and resection volume. Although such an approach would be desirable,

we are aware that acquisition of an extra MRI and CT for surgical planning could limit adoption of the technology. The minimum imaging information needed is a 3D scan on which the tumor can be segmented (e.g. the diagnostic MRI), and the 3D positions of the transponders with respect to the tumor, which can most easily be acquired with a CT scan.

In contrast to the application of Calypso in a radiotherapy setting, there is no space for the EM array above the patient during the surgical procedure. Therefore, the patient should be positioned on top of the EM array in the operating room to minimize disturbance of the current clinical workflow. Especially in patients with larger breasts, it can be challenging to position the tumor, and thus the implanted beacons, within the tracking volume of $14 \times 14 \times 19$ cm. In a navigation system developed for surgery of pelvic malignancies, a specialized mattress was developed in which an EM field generator could be embedded [19]. Such a mattress should also be designed for the Calypso system. As soon as the patient is positioned, the navigation system can be started and used by the surgeon. In research mode, the Calypso system has an extended tracking volume of $27.5 \times 27.5 \times 22.5$ cm, which will allow for more positioning flexibility. However, before we can use the extended tracking volume, accuracy should be investigated. Preferably, the surgical pointer is replaced by a tracked diathermia probe to mimic current clinical practice as well as possible. Postoperatively, the resection specimen will go to the pathology department for transponder removal and standard histological analysis. Since the first attempt of Nav-BCS on real breast tissue was feasible and successful, we are planning a more comprehensive clinical study to assess the potential clinical impact of our solution.

In our current setup, the navigation system requires implantation of three Beacon transponders, compared to only one iodine seed for simple tumors. In case of extensive DCIS, multiple iodine seeds could be used to indicate the borders of the tumor, which is called bracketing [16]. However, it is hard to assess the radioactive signal from the different sources, and simultaneously imagine the 3D configuration of the tumor position and orientation. With 34% reoperations using this setup, results so far have not been very promising [16]. One major advantage of the Calypso system over RSL is no use of radioactive material and accompanied protocols at the nuclear medicine department.

In conclusion, we think this preliminary work shows a potential role of our navigation system for improvement of intra-operative awareness about tumor position and orientation and has the potential to improve surgical outcomes. All surgeons were enthusiastic about Nav-BCS and indicated that this might be the technology for future surgery of non-palpable tumors. However, extended surgical experience on real breast tissue is needed.

Compliance with ethical standards

Conflict of interest Author Jasper Nijkamp has a research agreement with Varian Medical Systems. However, they did not influence the design or execution of the study.

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