Diagnosis and minimally invasive treatment of early stage breast carcinoma

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Diagnosis and minimally invasive treatment of early stage breast carcinoma

Diagnostiek en minimaal invasieve behandeling van het vroegstadium mammacarcinoom

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Voor Saskia

Contents

Chapter 1	General introduction and outline of the thesis	9
Part 1	**Imaging**	
Chapter 2	Accuracy of contrast-enhanced breast ultrasound for pre-operative tumour size assessment in patients diagnosed with invasive ductal carcinoma of the breast *Cancer Imaging 2007*	17
Chapter 3	MONET study: MR mammography: Randomized Controlled Trial to study efficiency of MR mammography in reducing the number of invasive interventions in nonpalpable breast cancer. *Submitted*	27
Part 2	**Tumour localization**	
Chapter 4	Surgical outcome of patients with core biopsy proven nonpalpable breast carcinoma. A large cohort follow up study. *Ann surg Oncol 2009*	39
Chapter 5	Radio guided occult lesion localization (ROLL) for non palpable invasive breast cancer *J Surg Oncol 2008*	53
Chapter 6	The efficacy of 'Radio guided Occult Lesion Localization' (ROLL) versus 'Wire-guided Localization' (WGL) in breast conserving surgery for non-palpable breast cancer: a randomized clinical trial – ROLL study *BMC Surg 2008*	65
Part 3	**Sentinel node biopsy**	
Chapter 7	Comparison of the 1- versus 2-day protocol for lymphatic mapping and sentinel lymph node biopsy in patients with nonpalpable breast cancer. *Eur J Nucl Med Mol Imaging 2009*	75
Chapter 8	Axillary staging in breast cancer patients with exclusive lymphoscintigraphic drainage to the internal mammary chain. *Accepted for publication in the World journal of Surgery*	85

Part 4 Minimally invasive treatment

Chapter 9	Minimally invasive ablative therapies for invasive breast: An overview of current literature *World J Surg 2007* *European Journal of surgical oncology 2007*	97
Chapter 10	Ultrasound guided laser induced thermal therapy for small palpable invasive breast carcinomas. A feasibility study *Ann Surg Oncol 2009*	113
Chapter 11	General discussion, conclusions and future perspectives	125
Chapter 12	Summary	135
	Nederlandse samenvatting	139
	Dankwoord	143
	List of publications	149
	Curriculum vitae auctoris	152

Chapter 1

Introduction

Background

Breast carcinoma is the most common malignancy in women with a life time risk of 1 in every 9 women[1]. Over the past decades there have been significant improvements in diagnosing and treating breast carcinoma. The transition from the extensive radical Halsted operation to breast conserving surgery (BCS) and, in the late nineties, the replacement of axillary dissection (AD) by sentinel node biopsy (SNB) in the staging of breast carcinoma were the most striking[2, 3]. These improvements in the surgical treatment of breast carcinoma patients lead to less morbidity and a shorter hospital stay. Nowadays the majority of the breast carcinoma patients is treated in day-care[4].
An improvement in the early detection of breast carcinoma was the implementation of nationwide screening programs. Due to these screening programs and the improvements of the mammography modalities the number of early stage, nonpalpable breast carcinomas increased as well[5]. Each year around 4000 suspicious nonpalpable breast lesions are detected in the national screening program, supplemented with another 3000 nonpalpable lesions detected in women with a high genetic risk or a history of breast cancer patients. Eventually 55% of these lesions prove to be malignant (i.e. *in situ* or invasive carcinomas)[6].
Furthermore the excision biopsy procedure for the BI-RADS classifications[7] 3, 4 and 5 lesions was replaced by large core needle biopsy (LCNB)[8]. Therefore a large group of women is spared a wide local excision, associated morbidity and disappointing cosmetic results[9-11].

Imaging

Of course there is still room for improvement in both diagnosing and treating breast carcinoma. Part of the triple assessment of suspicious breast lesions is mammography, ultrasound and breast biopsy. The diagnostic accuracy of mammography alone is around 80% and increases to 91% when ultrasound examination is added to the work up[12]. On the other hand mammography and ultrasound are known to underestimate actual histopathological tumour size[13]. Possibly, tumour size underestimation leads to irradical excisions. Contrast enhanced ultrasound (CEUS) could be a more accurate modality in estimating histopathological tumour size. One of the improvements in pre treatment imaging could be contrast enhanced ultrasound (CEUS). It is a known modality in characterizing liver lesions and determining the extent of these lesions. In **chapter 2** the value of contrast CEUS versus gray scale ultrasound in the preoperative tumour size assessment of breast carcinomas is described.
Furthermore, there is an increased interest in magnetic resonance imaging (MRI) as a diagnostic modality. Sensitivies of up to 90% and specificities of up to 72% are reported[14] and apart from this tumour size estimation and detection of multicentricity, multifocality and bilateral disease could be improved[15-17]. Using dynamic contrast enhanced MRI, lesion morphology, lesion enhancement and contrast enhancement pattern over time can be assessed. Therefore invasive components in *in situ* carcinomas can be detected[18, 19]. This could lead to better pre-operative treatment planning and possibly in less surgical interventions. In **chapter 3** the additional value of preoperative MRI in reducing the number of re-excisions in the surgical treatment of patients diagnosed with nonpalpable breast carcinoma is described

Tumour localization

Due to the increased incidence of nonpalpable breast carcinomas new localization methods are subject of research as well. These carcinomas are currently predominantly localized using a guide wire (WGL) and patients undergo WGL lumpectomy in combination with a SNB. However the WGL has several known disadvantages like wire displacement, patient discomfort and the surgical technique can be challenging due to differences in approach of the radiologist placing the wire and the surgeon performing the operation[20-22]. Using WGL, the orientation of the tumour in the breast is often challenging. In **chapter 4** the surgical outcome in a large cohort of patients diagnosed with a nonpalpable breast carcinoma is analyzed.

Furthermore, the lymph drainage patterns in the breast could be disrupted by an intratumourally placed wire, resulting in a lower success rate of the SNB[23]. Examples of new localization methods are iodium seed localization[24], ultrasound localization[22] and radioguided occult lesion localization (ROLL)[20]. In **chapter 5** our initial experience with ROLL in the surgical treatment of patients diagnosed with an invasive nonpalpabel breast carcinoma is described and in **chapter 6** the protocol of a large randomized controlled trial comparing ROLL to WGL in order to determine the added value of ROLL in the surgical treatment of these patients.

Sentinel node biopsy

A large randomized trial done by Veronesi *et al* comparing axillary dissection to SNB, showed an accuracy of the sentinel node status of 96.9%, a sensitivity of 91.2% and a specificity of 100%. Furthermore, the patients in the SNB group had less pain and post operative morbidity than the patients in the axillary dissection group. The patients with a negative sentinel node had no local recurrence after a median follow up of 46 months[25]. Although the SNB is a patient friendly and reliable alternative to axillary dissection the type of nuclear protocol, the definition of the true SNB and the surgical decision making after drainage to the internal mammary chain only are still subject to discussion[26-29]. In **chapter 7** the successrate of the 1-day protocol and the 2-day protocol for the sentinel node biopsy in patients with an invasive breast carcinoma is compared and in **chapter 8** axillary staging in patients with lymphoscintigraphic drainage to sentinel lymph nodes in the internal mammary chain only is described.

Minimally invasive treatment

The ultimate goal would be to treat breast carcinoma patients minimally or non-invasively in an outpatient setting. Local tumour ablation using radiofrequency ablation (RFA), laser induced thermal therapy (LITT), cryo ablation, microwave ablation and focused ultrasound have been described as possible minimally invasive modalities[30-34]. RFA and LITT have already proven to be good alternatives to surgery in irresectable colorectal liver metastases and hepatocellulary carcinoma[35, 36]. If these modalities prove to be reliable, ultimately they could be applied in the curative treatment setting for breast carcinoma as well, likely resulting in an improved cosmetic result. The current status in literature on the locally ablative modalities in the treatment of breast cancer is described in **chapter 9**.

The available minimally ablative modalities are cryosurgery, radiofrequency ablation (RFA), laser induced therapy (LITT), focused ultrasound (FUS) and microwave ablation. In **chapter 10** the initial results of ultrasound guided laser induced thermal therapy for small palpable breast carcinomas are described. In this study the influence of tumour size and the presence of surrounding *in situ* carcinoma on completeness of ablation is described. Furthermore the feasibility of ultrasound as a treatment guidance modality is presented.

Outline of the thesis

The studies presented in this thesis are guided by the following research questions:

- *Is contrast enhanced ultrasound a feasible alternative to gray scale ultrasound in preoperative tumour size assessment of breast carcinoma?* **(chapter 2)**
- *Can pre-operative breast MRI reduce the number of re-excisions in patients diagnosed with nonpalpable breast carcinoma?* **(chapter 3)**
- *What is the number of re-excisions and conversions to mastectomy in wire guided surgery of nonpalpable breast carcinomas?* **(chapter 4)**
- *Is radio guided occult lesion localisation (ROLL) a good alternative to wire guided surgery (WGL)?* **(chapter 5 and 6)**
- *What is the success rate of the SNB in a 1-day protocol versus a 2-day protocol?* **(chapter 7)**
- *Is axillary staging in patients with exclusive drainage to the internal mammary chain necessary?* **(chapter 8)**
- *What is the current status of minimally invasive treatment of early stage breast carcinoma?* **(chapter 9)**
- *Can ultrasound guided laser induced thermal therapy safely and completely ablate palpable invasive breast carcinomas clinically smaller than 2 cm?* **(chapter 10)**

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Part 1 Imaging

Chapter 2

Accuracy of contrast-enhanced breast ultrasound for pre-operative tumour size assessment in patients diagnosed with invasive ductal carcinoma of the breast

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Abstract

Background
Our aim was to assess the feasibility and accuracy of contrast-enhanced ultrasound (CEUS) of the breast with SonoVue microbubbles for pre-operative size measurement of invasive breast carcinomas.

Methods
Seven patients diagnosed with 9 invasive breast carcinomas prospectively underwent gray-scale ultrasound and CEUS of the breast according to a standardized protocol. CEUS of the breast was performed by a Philips iU22 scanner equipped with a 4-8 MHz linear array transducer. We used a single dose of 2.4ml SonoVue as contrast agent. Breast lesion morphology was scored according to the sonographic BI-RADS lexicon criteria and classified accordingly. The greatest tumour dimensions on gray-scale ultrasound and CEUS of the breast were finally compared with the greatest histopathologic tumour sizes.

Results
Gray-scale ultrasound underestimated the histopathologic tumour size in 6/9 cases (67%), whereas CEUS of the breast underestimated tumour size in only 3/9 (33%) cases. CEUS of the breast was significantly more accurate for tumour size assessment. Greatest tumour dimension as measured with gray-scale ultrasound of the breast was within 2mm of the pathologic tumour size in only 2/9 cases (22%), whereas CEUS of the breast accurately assessed tumour size within 2mm of pathologic tumour size in 6/9 (67%) of the cases ($P<0.05$).

Conclusions
CEUS of the breast proved to be a feasible and safe procedure. It is more accurate than gray-scale ultrasound of the breast for pre-operative size assessment of invasive ductal breast carcinomas.

Introduction

Breast ultrasound has become a standard breast-imaging procedure in addition to mammography, for work-up of patients referred with a palpable mass or with a suspicious lesion detected on the mammogram[1]. Grayscale breast ultrasound offers the ability to visualize the breast tumour in three dimensions and permits direct measurement of tumour size without magnification. To standardize lesion characterization on ultrasound, the American College of Radiology (ACR) developed a lexicon of sonographic descriptors of breast masses with
attendant assessment categories, i.e. the sonographic Breast Imaging Reporting and Data System (BI-RADS) lexicon[2].
Technologic advances over the last decade have fuelled research in the field of minimal-invasive image-guided ablation techniques for treatment of patients with limited stage breast cancer. Techniques that have been studied include radiofrequency ablation, cryoablation, focused ultrasound and laser ablation of breast tumours[3, 4]. Different imaging modalities are used to guide the instruments, to monitor the therapeutic procedure and to assess treatment response. Of all imaging modalities, gray-scale breast ultrasound is most often used for breast tumour visualization and real time monitoring of the ablation process[3].
Accurate assessment of breast tumour size is important for planning surgical and minimal-invasive image-guided ablation procedures. Extensive surgical treatment may result in poor cosmetic results, whereas small tumour-free margins may influence the local recurrence rate[3, 5, 6].
Several previous studies have assessed the accuracy of gray-scale ultrasound for breast tumour size measurement[7-14]. Overall, these studies concluded that gray-scale ultrasound of the breast is a reliable method for determining tumour size and favours mammography, but in general true tumour size is underestimated with this technique[7-14].
In recent years, ultrasound contrast agents have been developed that increase blood echogenicity and improve ultrasound image quality by detection of slow and lowvolume blood flow in small tumour vessels (55 mm). Contrast-enhanced ultrasound (CEUS) of the breast has recently been studied for characterization of indeterminate breast lesions[15-20].
Since breast tumours are strongly vascularized and display neo-angiogenesis in the vital border, it is hypothesized that CEUS of the breast may also be a more accurate modality than greyscale ultrasound for delineation of breast tumour boundaries and tumour size assessment[20]. This prospective feasibility study was designed to assess the accuracy of CEUS of the breast for preoperative tumour size measurement in patients diagnosed with invasive ductal carcinoma of the breast.

Materials and Methods

Seven consecutive female patients, 49 years of age (range 42-57 years), with 9 breast lesions were prospectively included in this study. All patients were referred to our department for ultrasound examination and ultrasound (US)-guided large-core needle biopsy of a suspicious breast lesion (BI-RADS IV and V) detected on mammography between June 2005 and June 2006.
The diagnosis of invasive ductal breast cancer was confirmed in all patients by US-guided large-core needle biopsy (14 gauge). Eligible patients for pre-operative tumour size measurement with contrast-enhanced ultrasound (CEUS) of the breast had no history of previous breast surgery. Patients were

excluded if use of the ultrasound contrast agent (SonoVue, Bracco Spa, Milan, Italy) was contra-indicated, due to a history of cardiac failure, right to left shunt, severe pulmonary hypertension, uncontrolled systemic hypertension, adult respiratory disorders and hypersensitivity[15]. Written informed consent was obtained from all patients and the study was performed in accordance with a protocol approved by our institutional panel.

All eligible patients prospectively underwent both greyscale ultrasound and CEUS of the breast according to a standardized protocol. High-frequency gray-scale ultrasound examination of the breast was performed first with a Philips iU22 scanner (Philips Medical Systems, Best, the Netherlands) equipped with a 11MHz linear array transducer. The probe was held orthogonal to the skin. Breast lesion morphology was scored according to the sonographic BI-RADS lexicon criteria[2] and classified accordingly. Tumours size (expressed in millimeters) was documented in three dimensions (length, width,and height). For measurements, the tumour edge was defined as the end of the hypoechoic mass before the hyperechoic transition border (so called 'echogenic interface') between tumour and healthy surrounding tissue (Figure 1)[13]. The maximum dimension on gray-scale ultrasound was finally compared with the maximum histopathologic tumour size.

Additionally, patients underwent CEUS of the breast according to the following protocol. Nonlinear harmonic imaging using a Philips iU22 scanner (Philips Medical Systems, Best, the Netherlands) equipped with a 4-8MHz linear array transducer was performed at baseline with a low mechanical index of 0.1, chosen to avoid gas bubble destruction. SonoVue was provided as lyophilized powder contained in a septum-scaled vial. A suspension of sulfur hexafluoride (SF6) microbubbles was obtained by adding 5ml saline (0.9% sodium chloride) to 25 mg of the powder, followed by hand agitation[19]. We used a single dose of 2.4 ml SonoVue as contrast agent (SF6 volume in a 2.4 ml

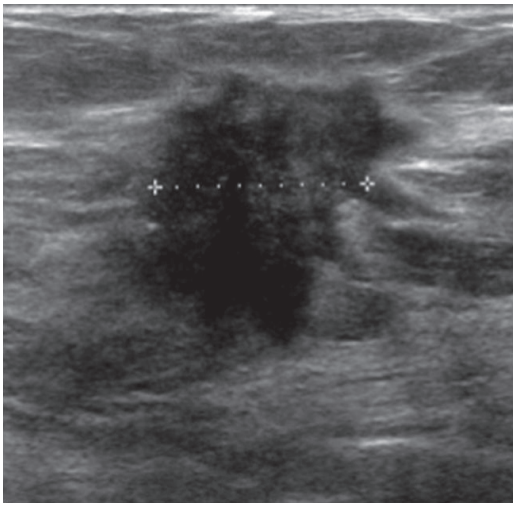

Figure 1. Gray-scale ultrasound image of an irregular, not parallel oriented, spiculated breast lesion, classified as BI-RADS V in the upper outer quadrant of the left breast. For measurements (see lines), the tumour edge was defined as the end of the hypoechoic mass before the hyperechoic transition border (so-called 'echogenic interface') between tumour and healthy surrounding tissue.

dose in 0.02 ml), which was intravenously administrated via a 20 gauge canula placed in an arm vein followed by a flushing of 10 ml standard saline. Directly after SonoVue administration the microcirculation was studied by recording with clip function for 60 s, without chancing the transducer. QLAB software (Philips Medical System, Best, The Netherlands) was used to quantify enhancement on the CEUS images in time. By using the region of interest quantification method we assessed time intensity curves of vascular enhancement at the margin of the tumour. When enhancement was at peak level (around 10 s) breast tumour size was recorded and measured again in three dimensions. For the measurements, the tumour edge was defined as the end of the hyperechoic mass at the time of maximal contrast enhancement of the lesion (Figure 2). The maximum dimension of the tumouron CEUS of the breast was finally compared with the maximum histopathologic tumour size. Both gray-scale and CEUS breast ultrasound examination were performed by the same experienced breast radiologist in all cases.

Surgical resection of the tumour was performed in all patients within 2 weeks. Histologic sections of the resected tumours after hematoxylin and eosin (H&E) staining were examined under a light microscope and used for measurement of histopathologic tumour size in millimeters in three dimensions. Margin status was recorded as involved or not involved. For those patients who underwent re-excision for tumour-involved margins, the extent of invasive ductal carcinoma in the re-excision specimen was recorded.

To assess the difference between the three methods of tumour size measurement, data were analyzed in a SPSS database (version 9.0). The greatest lesion diameters (mm) obtained by gray-scale breast ultrasound and CEUS of the breast were compared with the greatest lesion diameter (mm) on pathology. Tumour size measured in greatest dimension was compared between the groups by using Student t-test analysis ($P<0.05$).

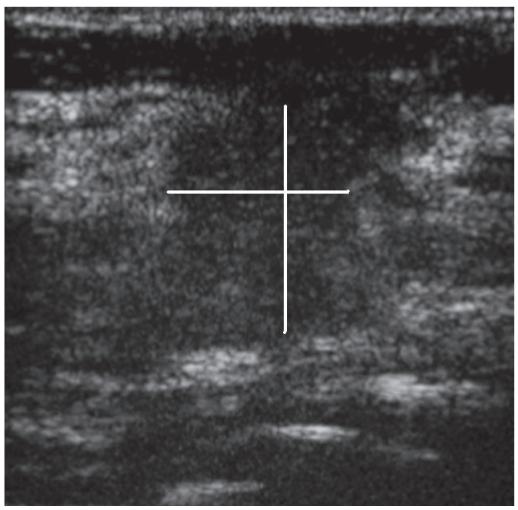

Figure 2. Image of the same lesions with CEUS of the breast, lesion has become more hyperechoic due to centripetal contrast enhancement. For measurements (see lines) the tumour edge was defined as the end of the hyperechoic mass at time of maximal contrast enhancement of the lesion.

Furthermore, the percentage greatest tumour diameter as assessed by gray-scale ultrasound and CEUS was within 2mm of pathologic tumour size, which is considered accurate[14]. The percentage of over- and underestimated tumour size for each modality was calculated using Fisher's exact test, with a P-value <0.05 considered to be significant.

Results

The mean patient age in this study was 49 years (range 42-57 years). Two patients presented with 2 breast lesions in the same quadrant (multifocal disease), and the remaining 5 patients presented with a solitary breast lesion.The sonographic characteristics of the lesions according to the sonographic BI-RADS criteria are presented in Table 1. Definitive diagnosis on pathology was invasive ductal carcinoma in all cases, with an additional ductal carcinoma *in situ* (DCIS) component in 2 cases.
Gray-scale ultrasound of the breast showed a mean greatest tumour diameter of 15.5mm (range 10.1-20.6 mm), compared to 16.5mm (range 11.5-18.5 mm) in the CEUS group. Mean greatest histopathologic tumour diameter was 15.6mm (range 9.0-25.0 mm). Table 2 shows the greatest tumour diameter as measured with each modality compared to pathologic tumour size. Mean greatest tumour diameter as assessed with both ultrasound techniques did not significantly differ (P=0.23). However, gray-scale ultrasound underestimated tumour size in 6/9 (67%) cases, whereas CEUS of the breast underestimated tumour size only in 3/9 (33%) cases. Consequently, the accuracy of both imaging techniques for tumour size assessment differed significantly. Tumour as measured with gray-scale ultrasound of the breast was within 2mm of the pathologic tumour size in only 2/9 cases (22%), whereas CEUS of the breast accurately assessed tumour size within 2mm of pathologic tumour size in 6/9 (67%) of the cases (P<0.05). No complications due to SonoVue administration were noted. Margin status was recorded as not involved in all 9 cases; none of the patients underwent re-excision.

Discussion

To our knowledge this is the first study to assess the accuracy of CEUS for pre-operative size assessment of invasive ductal carcinomas of the breast. In this
prospective feasibility study CEUS of the breast proved to be a safe and technically feasible procedure. CEUS of the breast was significantly more accurate than gray-scale ultrasound of the breast for tumour size measurement. The maximal tumour diameter as assessed by CEUS of the breast was within 2mm of pathologic tumour size in 67% of cases, compared with 22% in the gray-scale ultrasound group (P<0.05).
The ability to accurately and reliably measure breast tumour size prior to any surgical treatment or primary medical treatment is essential[3, 5, 6]. As a consequence previous research focused on different methods enabling non-invasive tumour size measurements, including clinical examination (palpation), mammography, gray-scale ultrasound, and magnetic resonance imaging (MRI) of the breast[7-14]. Of these methods palpation proved to have the lowest accuracy, because it is influenced by skin thickening, breast edema, and obesity, and is prone to overestimation of tumour size[7, 10]. Mammography proved to be more accurate than palpation, however it is taken in two standard projections (cranio-

caudal and mediolateral-oblique) not necessarily expressing the largest dimension of the tumour[7, 8, 10, 12]. As a consequence, mammography in general underestimates tumour size. Although all studies showed significant correlation between mammographic and gray-scale ultrasound measurements, the latter technique is considered the most accurate for breast tumour size measurement. Previous studies that compared maximum breast tumour size as measured with gray-scale ultrasound of the breast to tumour size on pathology, reported correlation coefficients in the range of 40-84%[7-14]. However, all concluded that gray-scale ultrasound of the breast still underestimates tumour size in more than half of the patients. MRI of the breast has been reported to be the most accurate imaging modality for non-invasive tumour size assessment. In a prospective study including 111 women with 177 breast lesions, MRI was reported to have an accuracy of 85% for evaluation of disease extent. Since, breast MRI is expensive, time-consuming and still not available in every institute, we wanted to tackle the problem of tumour size underestimation rate on greyscale ultrasound, by using contrast-enhanced ultrasound of the breast for tumour size measurement. CEUS of the breast is performed with the second generation contrast agent SonoVue, which is made of microbubbles stabilized by phospholipids and containing the inert gas, SF6[17]. The microbubbles have a high reflectivity and are not extravasated from the vessel lumen, and as a consequence act like true blood pool agents. The effective vessel diameter from which an echo can be detected is in the range of a capillary. It has been postulated that this technique reliably visualizes the neovascularization within and around the tumour, and can potentially be used for tumour boundary identification and lesion characterization[16, 20]. Several studies have proven the potential of CEUS of the breast in differentiating malignant from benign breast lesions, with varying sensitivities (67-95%) and specificities (58-82%) depending on the patient population being studied, the type of equipment, and the criteria used for interpretation of the CEUS images[16, 18, 20].

To date, no studies have been performed evaluating the accuracy of CEUS of the breast for size measurement of malignant breast tumours. Our study results showed that both gray-scale ultrasound and CEUS of the breast underestimated tumour size. Gray-scale ultrasound of the breast underestimated tumour size in 6/9 (67%) cases, which is in agreement with previous literature. However, CEUS of the breast underestimated tumour size only in 3/9 (33%) of cases. Although the numbers in this study are small, a trend towards lower tumour size underestimation rate with CEUS of the breast was found. More important, the accuracy of CEUS of the breast for determining tumour size within 2mm of pathologic tumour size was 6/9 (67%), compared with 2/9 (22%) for gray-scale ultrasound. This implies that CEUS of the breast is a more accurate technique than gray-scale ultrasound of the breast for breast tumour lesion size measurement.

A possible limitation of the study is the small number of patients included; as a consequence a well-founded statistical analysis and firm conclusions cannot be made. Furthermore, subgroup analysis reporting accuracy of tumour size assessment for different tumour subtypes could not be made. Second, it is known that ultrasound examination is operator dependent; both the quality of ultrasound and the accuracy of tumour size estimation may depend on the clinician's experience. Since, in our study all the ultrasound measurements were performed by the same breast imaging radiologist, no inter- and intra-observer bias of CEUS for lesion size measurement could be calculated. Third, whether to include the echogenic interface (halo) around the hypoechoic lesion for measurement purposes on gray-scale breast ultrasound examination is still a matter of debate in the current literature[13]. In our study the halo was not included for tumour size measurement, which is in agreement with most other previous studies. Finally, currently no standard with regard to lesion size measurement on CEUS

of the breast exists. Because it is a novel breast imaging modality, it is only rationally assumed that lesion size should be measured at the time of maximal contrast enhancement of the lesion, and that edges are defined as the end of the hyperechoic mass at that time. As a consequence, larger studies focusing on CEUS tumour size measurement will be needed in the future.

This feasibility study proves that CEUS of the breast is a feasible and safe technique for breast tumour size measurement. In this small group of patients with invasive ductal carcinoma of the breast we showed that CEUS of the breast was more accurate than gray-scale ultrasound of the breast for tumour size assessment. The maximal tumour diameter as assessed by CEUS of the breast was within 2mm of pathologic tumour size in 67% of cases, compared with 22% in the gray-scale ultrasound group.

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Part 1 Imaging

Chapter 3

Preoperative MRI and surgical management in patients with nonpalpable breast cancer: The MONET – randomized controlled trial

submitted

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Summary

Background
We evaluated whether performing contrast-enhanced breast MRI in addition to mammography and/or ultrasound in patients with nonpalpable suspicious breast lesions improves breast cancer management

Methods
The MONET - study (MR mammography Of Nonpalpable BrEast Tumours) is a randomized controlled trial in patients with a nonpalpable BIRADS 3-5 lesion. Patients were randomly assigned to receive routine medical care, including mammography, ultrasound and lesion sampling by large core needle biopsy, or additional MRI preceding biopsy. Patients with cancer were referred for surgery. Primary endpoint was the rate of additional surgical procedures (re-excisions and conversion to mastectomy) in patients with a nonpalpable breast cancer.

Findings
418 patients were randomized, 207 patients were allocated to MRI, and 211 patients to the control group. In the MRI group 74 patients had 83 malignant lesions, compared to 75 patients with 80 malignant lesions in the control group. The primary breast conserving surgery (BCS) rate was similar in both groups; 68% in the MRI group vs. 66% in the control group. The number of re-excisions performed because of positive resection margins after primary BCS was increased in the MRI group; 18/53 (34%) patients in the MRI group vs. 6/50 (12%) in the control group (p=0.008). The number of conversions to mastectomy did not differ significantly between groups.

Interpretation
Addition of MRI to routine clinical care in patients with nonpalpable breast cancer was paradoxically associated with an increased re-excision rate. Breast MRI should not be used routinely for preoperative work-up of patients with nonpalpable breast cancer.

Introduction

Since the 1970's, breast conserving therapy (BCT), i.e. local excision followed by breast irradiation, has replaced mastectomy as the treatment method of choice in women with early stage breast cancer.[1] Although BCT has excellent 5-year survival rates, a substantial number of patients (20% - 49%) have tumour positive resection margins after breast conserving surgery (BCS) and require a re-excision or a conversion to mastectomy.[2-4] When less invasive surgery is performed, accurate preoperative imaging is considered to be important in order to accurately assess tumour size in 3 dimensions and detect additional foci of disease other than the proven index cancer (multifocal and/ or multicentric disease). Many studies have shown that tumour extent is more accurately determined by means of Magnetic Resonance Imaging (MRI) compared to mammography and ultrasound [5-8]. Furthermore, the results of a meta-analysis show that MRI detects 16% (interquartile range 11-24%) additional cancers in patients with known breast cancer [9]. It has been suggested that preoperative MRI may improve surgical planning, leading to a reduction of re-excision rate and conversions towards mastectomy. This has resulted in the increasing use of preoperative Breast MRI in patients with early stage breast cancer scheduled for BCT.[5-9]

To date only one randomized controlled trial assessed the effect of preoperative Breast MRI on surgical management. The COMICE trial investigated the clinical efficacy of preoperative Breast MRI in 1623 primary breast cancer patients. Patients were randomized to triple assessment only (n=807), or combination of Breast MRI and triple assessment (n=816). In this trial, the addition of Breast MRI to conventional triple assessment was not associated with a reduction in re-operation rate (re-excisions and mastectomies), which was 19% in both groups. They concluded that pre-operative Breast MRI might be superfluous in this patient population.[10]

The impact of Breast MRI for work-up of patients with nonpalpable breast lesions has not been assessed yet. As a result of screening and technical improvements in mammography and other imaging techniques such as Breast MRI, the number of small, early stage breast carcinomas and *in situ* carcinomas has increased substantially.[11-14] The problem of nonpalpable breast cancer is that it cannot be visualized or palpated by the surgeon during excision. As a consequence, in approximately 30% - 40% of the patients a breast amputation is planned as initial surgical procedure.[14] In 25% to 50% of all patients initially treated with BCS more than one surgical intervention (re-excision or amputation) is required to remove all tumourous tissue.[12]

We conducted a randomized controlled trial to assess the clinical efficacy of dynamic contrast-enhanced Breast MRI in women diagnosed with a nonpalpable breast lesion, with the effect of breast MRI on the number of additional surgical procedures (re-excisions and conversions to mastectomy) in these patients as its primary endpoint.

Materials and Methods

Design

The MONET (*M*R mammography *O*f *N*onpalpable Br*E*ast Tumours) study is a randomized controlled trial (NCT00302120) in which patients with nonpalpable suspicious breast lesions (BIRADS category 3,4 or 5) detected on mammography or breast ultrasound, who are referred for histological analysis of the lesion, are eligible for the study. Patients were recruited from three large community teaching

hospitals and one university hospital. Exclusion criteria were palpable lesions, age below 18 years, breast surgery or radiation therapy less than nine months prior to inclusion, pregnancy or lactation, obesity (> 130 kg), claustrophobia, inability to maintain prone position for one hour, or other general contra-indications for MRI (e.g. pacemaker, other metal implants). Written informed consent was obtained from all patients and the study was approved by the ethical boards of the participating hospitals. After informed consent was obtained, patients were randomized to the control group who received care as usual, or to the MRI group who underwent an MRI scan of the breast in addition to the usual care. Randomization was performed by an independent trial centre and stratified by hospital. The design of the study has been described in detail elsewhere. Trial registration number: NCT00302120.[15]

Control group

Patients in the control group received routine medical care, including mammography, ultrasound and lesion sampling by ultrasound-guided or stereotactic large core needle biopsy (LCNB). A minimum of four 14-16 Gauge biopsy specimens per lesion were taken and histopathological analysis of the lesion was performed. Patients with a benign biopsy result were discharged from clinical follow-up. Patients with cancer (*in situ* carcinoma or invasive carcinoma) were referred for surgery. Depending on the size of the tumour, the size of the breast and patient's preference, breast conserving surgery (BCS) followed by whole breast irradiation or a mastectomy was scheduled. According to our national guidelines needle-wire localization was performed of the non-palpable breast cancer prior to BCS. In patients with invasive breast carcinoma, a sentinel node biopsy was performed during surgical excision of the tumour.

MRI group

All MR imaging was performed at the university hospital. Bilateral dynamic contrast enhanced (DCE) Breast MRI was performed on a 3 Tesla clinical MRI scanner (Achieva, Phillips Healthcare, Best, the Netherlands) prior to LCNB of the suspicious nonpalpable breast lesion. Patients were placed prone on a dedicated phased-array bilateral breast coil (MRI devices, Würzburg, Germany). The scan protocol included a transverse high-resolution T1-weighted fast gradient echo series, a transverse T2- weighted fat suppressed spin echo series. A transverse diffusion weighted fat-suppressed series was acquired to assess the cellularity of the lesion. Dynamic contrast-enhanced (Gadolinium DTPA) fat-suppressed T1-weighted gradient echo images were acquired with a temporal resolution of 59 seconds (6 dynamics), followed by a post-contrast T1-weighted fat suppressed series. The scan protocol is described in more detail elsewhere.[15] The images were interpreted by breast radiologists with five or more years of experience in breast MRI, using a Picture Achieving and Communications System (Phillips Healthcare, Best, the Netherlands). Classification of the lesions was based on lesion morphology, enhancement pattern, and enhancement kinetics (persistent, plateau, or washout) according to the BI-RADS MRI classification system as proposed by the American college of Radiology.[16] Additionally, the suspicious non-palpable lesion detected with conventional imaging (mammography, and/or ultrasound) at inclusion was coded as 'detectable' or 'non-detectable' on MRI. Lesions visible on MRI only were reported as well. All patients underwent stereotactic or ultrasound-guided LCNB of the suspicious nonpalpable breast lesion. In case additional lesions were detected on MRI, a second-look ultrasound was performed and the lesion was sampled by ultrasound or by MRI guidance. MR images were discussed with the surgeon preoperatively in a multidisciplinary meeting.

Study endpoints en statistics

Patient baseline characteristics on age, height, weight, parity, history of breast cancer were retrieved from questionnaires. Data on mammographical findings, MRI findings, large core needle biopsy (LCNB), surgical interventions and histopathological results were prospectively collected during 1 year of follow-up after the LCNB. The primary outcome was the proportion of patients undergoing repeat operation (re-excision or mastectomy) due to positive margins after the first surgical procedure. The number and type of surgical procedures in patients in the MRI group was compared to the number of procedures in the control group.

The statistical power of the study was calculated for a potential reduction of the number of surgical procedures as primary endpoint. Based on data of previous studies on nonpalpable breast cancers, we expect that 23% of the patients would require more than one surgical procedure to remove all tumourous tissue. We expected that DCE Breast MRI would reduce this rate to 11% due to the detection of multifocal and multicentric disease and better 3D depiction of the tumour. The MONET trial was powered at 90% to detect this 12% reduction as significant ($p<0.05$, two-sided), which required 250 women in the control group and 250 in the MRI group. For each patient the number of days between inclusion and LCNB, the number of days between inclusion and the first surgical procedure and the number of days between inclusion and complete tumour removal was assessed and compared between the MRI group and control group (Mann-Whitney test). The number of primary mastectomies, the number of re-excisions and conversions to mastectomy after primary breast conserving surgery (BCS) were compared between both groups (Chi-square). To compare the diagnostic performance of MRI (in combination with mammography and ultrasound) and LCNB, a two-by-two table was constructed. The positive predictive value was calculated by dividing the number of correctly identified positives by the total number of positive Breast MRI's. The negative predictive value was calculated by dividing the number of correctly identified negatives by the total number of negative MRI's. In all analyses, a p-value < 0.05 was considered statistically significant. The data were analyzed using SPSS version 15.0.

Results

Of the 626 patients that were eligible for inclusion, 463 patients were included in the study (participation rate 74%). After randomization 45 patients were excluded (24 in the MRI group; 21 in the control group). Reasons for non-participation and exclusion after randomization are listed in table 1. The mean duration between randomization and completion of follow-up for all patients was 41 months (range 27 – 61 months) Upon completion, the results of 418 patients were available for analysis. A total of 207 patients (n=225 mammographic lesions) was randomly allocated to the MRI group and 211 patients (n=231 mammographic lesions) to the control group. Baseline characteristics of the patients was comparable between both groups and is presented in table 2.

Of all lesions detected by mammography in the MRI group (n=225), 105 lesions were detected on MR images as well (47%). %). The 120 lesions that were not detected on MRI included 96 benign lesions (6 fibroadenoma, 57 fibrocystic change, 1 papiloma, 16 hyperplasia/adenosis, 1 LCIS, 3 metaplasia, 3 inflammatory changes, 9 other benign lesions), 21 *in situ* carcinomas (8 well-differentiated DCIS, 13 non well-differentiated DCIS), 2 DCIS lesions with micro-invasive disease and 1 invasive lobular carcinoma.

MRI detected 11 additional suspicious breast lesions that were occult on mammography, 2/11 of the suspicious MRI-only breast lesions were proven to be malignant (DCIS in the contralateral breast in both cases). On overview of the included patients and corresponding histopathological lesion diagnosis is presented in figure 1.
In the MRI group, 74 patients had 83 malignant lesions (41 DCIS, 42 invasive carcinomas) compared to 75 patients with 80 malignant lesions in the control group (41 DCIS, 39 invasive carcinomas). In the MRI group a total of 78 surgical procedures were initially performed; 51 BCS and 23 mastectomies for ipsilateral cancer. Additionally, 2 BCS and 2 mastectomies were performed for treatment of contralateral cancer. This resulted in a primary BCS rate of 53/78 (68%), and a primary mastectomy rate of 25/78 (32%) in the MRI group. In the control group 76 surgical procedures were initially performed; 49 BCS and 26 mastectomies for ipsilateral cancer, and 1 BCS performed for treatment of contralateral disease. This resulted in a primary BCS rate of 50/76 (66%), and a primary mastectomy rate of 26/76 (34%) in the control group. The number and type of initial surgical procedures was comparable between both groups (p=0.776) (figure 2).
The number re-excisions performed because of tumour positive resection margins after primary breast conserving surgery was higher in the MRI group; 18/53 (34%) re-excisions in the MRI group, compared with 6/50 (12%) re-excisions in the control group (p=0.008). The number of conversions to mastectomy after primary BCS was lower in the MRI group than in the control group, 6/53 (11%) vs. 8/50 (14%) respectively, but did not reach statistical significance (p=0.489). Overall, the rate of an additional surgical intervention (BCS and mastectomy combined) after initial breast conserving surgery was 24/53 (45%) in the MRI group vs. 14/50 (28%) in the control group (p=0.069). The median number of days between inclusion and complete tumour removal was 42.5 days in the MRI group and 40 days in the control group (p=0.11). The surgical procedures performed in both groups are described in more detail in figure 2, specified for DCIS and invasive carcinomas.

Table 1. Reasons for non-participation and exclusion

Reasons for non-participation	**Number of patients**
Contra-indication for MRI	63
Personal / logistical reasons / fear of delay in diagnosis	100
Reasons for exclusion	
MRI required for clinical reasons	4
Technical problems with MRI	3
Contra-indication for MRI	7
Personal / logistical reasons	8
No histological analysis of the lesion	20
Unknown	3

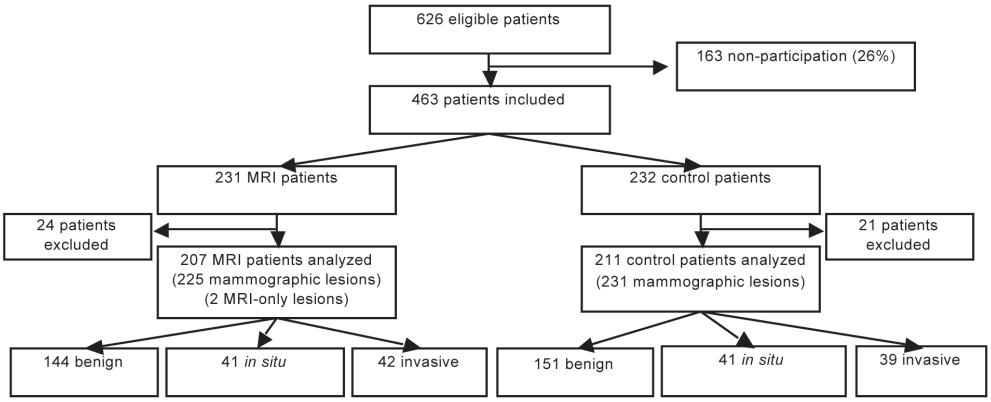

Figure 1. flow chart of eligible and included patients

Table 2. Patients baseline characteristics

Characteristic	**MRI group n=207 (225 mammographical lesions)**		**Control group n=211 (231 mammographical lesions)**	
Age (yrs)	Mean: 55.1	[sd: 9.5]	Mean: 56.1	[sd: 9.6]
Body Mass Index (kg/m^2)	Mean: 25.5	[sd: 3.8]	Mean: 25.6	[sd: 4.6]
Nulliparity	35	(17%)	36	(17%)
Breast cancer history (yes)	13	(6%)	21	(10%)
BI-RADS classification				
BIRADS 3	91	(40%)	87	(38%)
BIRADS 4	118	(53%)	120	(52%)
BIRADS 5	14	(6%)	22	(9%)
Unclear	2	(1%)	2	(1%)
Lesion characterization				
Microcalcifications only	136	(60%)	134	(58%)
Microcalcifications & density	14	(6%)	14	(6%)
Density	67	(30%)	80	(35%)
Other	8	(4%)	3	(1%)
Number of days between inclusion and LCNB	Median: 7.0 [Interquartile range: 4-9]		Median: 3.0 [Interquartile range: 1-7]	
Number of days between inclusion and first surgical procedure	Median: 36.0 [Interquartile range: 28-47]		Median: 31.5 [Interquartile range: 24-48]	

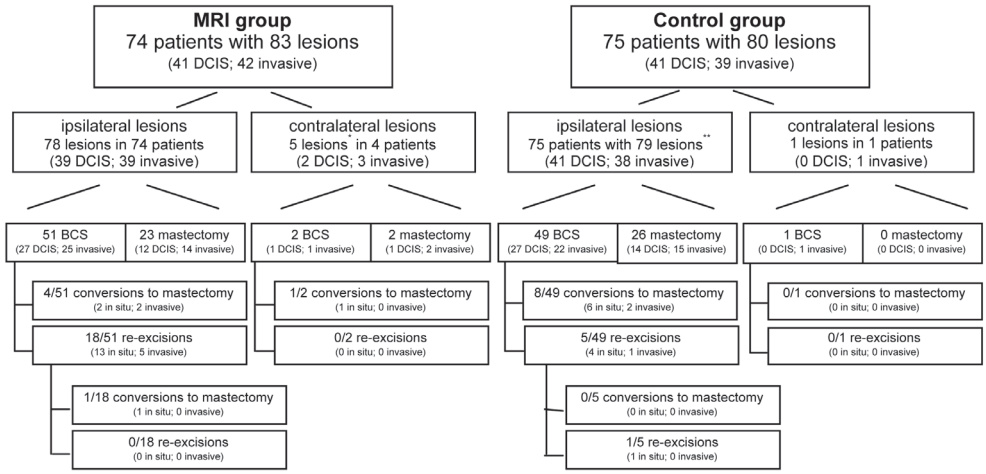

Figure 2. Summary of surgical procedures in MRI group and control group specified for *in situ* carcinomas and invasive carcinomas
* two lesions were MRI-only lesions
** one patient (with 1 invasive lesion) did not undergo surgery due to metastasized renal cancer

Discussion

Our results showed that breast MRI in addition to routine medical care (mammography, ultrasound and lesion sampling by large-core needle biopsy) in patients with nonpalpable breast tumours did not reduce the number of surgical procedures in cancer patients. In fact, the number of re-excisions due to positive tumour margins after initial breast conserving surgery was increased in the MRI-group, i.e. 34% vs. 12% in the control group. The number of conversions to mastectomy after BCS did not significantly differ between both groups. The increased re-excision rate in the MRI-group contradicts the theory that the use of breast MRI in clinical practice may improve surgical planning, leading to a reduction of re-excision rate and conversions towards mastectomy.
The past decades several nonrandomized retrospective studies have demonstrated that MRI increases the detection of tumour foci around the primary index lesion (multifocal or multicentric disease), not identified on conventional imaging.[18-27] A recent meta-analysis of these studies has shown that preoperative MRI detects MRI-only foci that turned out to be cancer in up to 16% (range 1%-28%) within the affected breast.[28] The variability in the prevalence of MRI-only foci is likely to be the result of differences in used MRI technology. The impact of increased detection rate of additional disease foci with MRI on clinical outcome was not studied. So far, only one study prospectively assessed the value of MRI in clinical practice (The COMICE trial). In this study 1623 breast cancer patients (proven after triple assessment) were randomized for MRI (yes/no) prior to surgery. They reported that addition of MRI to conventional triple assessment was not significantly associated with reduced operation rate. In the MRI group 153/816 (19%) needed reoperation, compared to 156/807 (19%) in the control group. They concluded that MRI might be unnecessary in this population of patients.[10] Additionally, two large observational studies reported that MRI was not associated with a significant

reduction in positive margins after local excision. Pengel, et al. found positive margins in 22/159 (14%) of the MRI patients vs. 35/180 (19%) in the control group.[29] Whereas, Bleicher, et al. reported positive margins in 11/51 (22%) of the MRI patients vs. 33/239 (14%) in the control group. Furthermore, for women with a pre-operative MRI mastectomy was the initial surgery in 28% of the women compared with 20% for women who did not underwent MRI.[30] These findings are further supported by a recent meta-analysis of non-randomized studies assessing the clinical value of pre-operative breast MRI. Pooled estimates of the impact of MRI on surgical management, defined as change in surgery due to MRI-detection, showed that 11.3% (95% CI 6.8-18.3) had more extensive surgery (mastectomy or increased lumpectomy size) than initially planned. The meta-analysis concluded that preoperative MRI in breast cancer patients may increase the number of unnecessary surgical procedures.[28]

The study population of the COMICE trial differed from ours due to the fact that mainly patients with palpable breast tumours are suitable for triple assessment. For the present study, we decided to focus solely on patients with nonpalpable breast tumours because these may be considered the most challenging to remove in one attempt since these lesions cannot be seen or palpated during surgery. Moreover, the number of nonpalpable lesions is increasing due to the widespread introduction of screening programs. Our results indicate that MRI does not reduce the number of reoperations in these patients. The increased re-excision rate in the MRI group is difficult to explain, taking into account that the baseline characteristics (tumour size, type, location and surgical institute) were comparable between both groups.

In an attempt to clarify this controversy, we analyzed the volumes of the excision specimens of the initial breast conserving procedure and found that the median excision volume in the MRI group was 69.1cm^3 versus 90.2cm^3 in the control group. When the MRI group was divided in those patients with a MRI positive finding (suspicious lesion was detected on MRI and conventional imaging) the median excision volume was 84.8cm^3, whereas when no lesion was detected on MRI (suspicious lesion only visible on conventional imaging) the median excision volume was 40.3cm^3. This implies that patients with a suspicious nonpalpable breast lesion which could not be reproduced on MRI were treated with smaller lumpectomy specimens during the initial BCS procedure, resulting in an increased rate of tumour positive resection margins. We propose that additional routine breast MRI in patients with nonpalpable breast cancers may be counter-productive: non-visualization of a lesion on the MRI paradoxically mislead the surgeon into removing a smaller lump than indicated.

A potential limitation of our study is the fact that, although patients included in this study are a representative sample of the national screening population, we had a relative high percentage of lesions consisting of microcalcifications only, i.e. 60% vs. the 25% described in the literature. This could perhaps be explained by the fact that patients who were diagnosed with a suspicious solid mass which was visible on ultrasound were less willing to participate in the study for logistical reasons, since randomization for MRI would imply a small delay in time to biopsy for these patients. Another important issue is the difficulty to effectively incorporate the MR images during surgery. In our study MR images were presented and discussed with the surgeon preoperatively in a multidisciplinary meeting, but perhaps they should have been made digitally available during surgery in the operation room.

In conclusion, our results indicate that the addition of MRI to the usual care in patients with nonpalpable breast cancer does not reduce the number of surgical procedures. Paradoxically, MRI appears to be associated with a significantly increased re-excision rate. Hence, breast MRI, should not be considered during work-up of these patients.

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Part 2 Tumour localization

Chapter 4

Surgical outcome of patients with core biopsy proven nonpalpable breast carcinoma A large cohort follow up study

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Abstract

Background
Breast conserving surgery is the preferred treatment of the nonpalpable breast carcinoma. The outcome, however, may be disappointing. In this study the surgical outcome in a large cohort of patients diagnosed with nonpalpable breast carcinoma is evaluated.

Methods
In 833 patients with 841 nonpalpable breast carcinomas the number of re-excisions and type of surgical procedures was calculated and summed per patient. Subsequently, the number of conversions to mastectomy and the number of days until complete tumour removal were analyzed. In a subgroup analysis the patients with an *in situ* carcinoma were compared to the patients with an invasive carcinoma.

Results
The initial surgery consisted of breast conserving surgery (BCS) for 589 tumours (70%) and of mastectomy for 242 tumours (29%). For 10 tumours (1%) the initial surgery was unknown. After BCS 158/589 tumours (27%) required a re-excision, 116/337 (34%) for the *in situ* carcinomas and 63/504 (13%) for the invasive carcinomas, p=0.0001. The number of conversions from BCS to mastectomy was 106/589 (18%), 66/241 (28%) in patients diagnosed with an *in situ* carcinoma versus 40/348 (11%) in patients with an invasive carcinoma, p=0.0001.
The median number of days until complete tumour removal was 28, this was 38 days for the *in situ* carcinomas and 25 days for the invasive carcinomas (p=0.0001).

Conclusions
There is room for improvement in the surgical treatment of nonpalpable breast carcinoma, especially in the relatively favorable *in situ* carcinoma as it requires significantly more excisions, mastectomies, conversions to mastectomy and days for complete removal.

Introduction

The most radical change in breast surgery has been the transition from modified radical mastectomy to breast conserving surgery (BCS) first described in 1969 [1]. Following several large randomized clinical trials that showed no difference in long term survival after BCS compared to radical mastectomy, BCS in combination with radiotherapy became the new standard of care for women with early stage breast carcinomas [2-4]. Another example of the development towards a less invasive approach of breast cancer diagnosis and treatment was the replacement of open breast biopsy by large core needle biopsy (LCNB). The COBRA study (COre needle Biopsy after RAdiological localization) was conducted in 973 patients with radiologically suspicious nonpalpable breast lesions to assess whether the sensitivity and specificity of large core needle biopsy were comparable to the diagnostic performance of open breast biopsy [5]. The results of this study showed a comparable diagnostic performance for large core needle biopsy and open breast biopsy [5, 6]. A second study (COBRA2000) was performed to assess the diagnostic performance of the COBRA guidelines outside a controlled study setting, i.e. in clinical practice [7]. In clinical practice the sensitivity of LCNB of nonpalpable breast lesions approached the high sensitivity of the surgical excision biopsy [8].
The introduction of large breast cancer screening programs in most western countries resulted in the detection of larger numbers of early-stage invasive and *in situ* breast carcinomas [9]. The increasing number of small, early-stage breast cancer stimulated the development of less-invasive diagnostic and treatment modalities. Early-stage, small nonpalpable tumours are difficult to discern at surgery. Therefore a guide-wire is usually placed preoperatively to allow localization of the tumour. However, placement of the hooked guide-wire may be difficult in patients with dense breast tissue. The likelihood of wire displacement is increased in these patients and repositioning of the wire in dense fibroglandular tissue is often problematic. Furthermore, surgical excision with tumour-free resection margins is technically challenging even with a perfectly placed wire [10-12]. The literature on surgical outcome purely focusing on nonpalpable breast cancer is scarce and often includes diagnostics excisions [13]. Overall, in patients with a nonpalpable breast tumour, a re-excision is reported to be necessary in 40 to 56% [14-17].
The purpose of this study was to evaluate the number of re-excisions and the number of conversions from BCS to mastectomy in patients with a nonpalpable malignancy on LCNB. Furthermore, the time interval between LCNB diagnosis and complete removal of all tumourous tissue was assessed.

Materials and Methods

Patients

Patients were retrieved from the COBRA / COBRA 2000 study which was conducted from 1997 - 2003. This cohort was described in detail by Hoorntje et al and Verkooijen et al [5, 18]. A total of 1700 consecutive patients underwent LCNB. Inclusion criteria for this study included a nonpalpable malignancy (*in situ* or invasive) on LCNB and available histhopathological data on both LCNB and surgical specimens. Exclusion criteria were missing pathology data until 1 year after biopsy and a benign LCNB diagnosis. Ultimately eight hundred and fifty-six patients diagnosed with an invasive or non-invasive carcinoma on LCNB were eligible for inclusion.
Large core needle biopsy

LCNB was performed following a standard protocol in four medical centers [5]. Lesions were localized with digital mammography. A minimum of 5 biopsy specimens was taken. In case of microcalcifications, at least 8 specimens were obtained and specimen radiography was carried out to identify the calcifications in the biopsy specimen. After the LCNB, patients returned to the hospital that they were referred from. There, all further diagnostic (including histological analysis of the LCNB tissue samples) and therapeutic procedures were performed in a routine clinical setting. All patients with an *in situ* carcinoma or an invasive carcinoma underwent a hooked wire localized surgical excision.

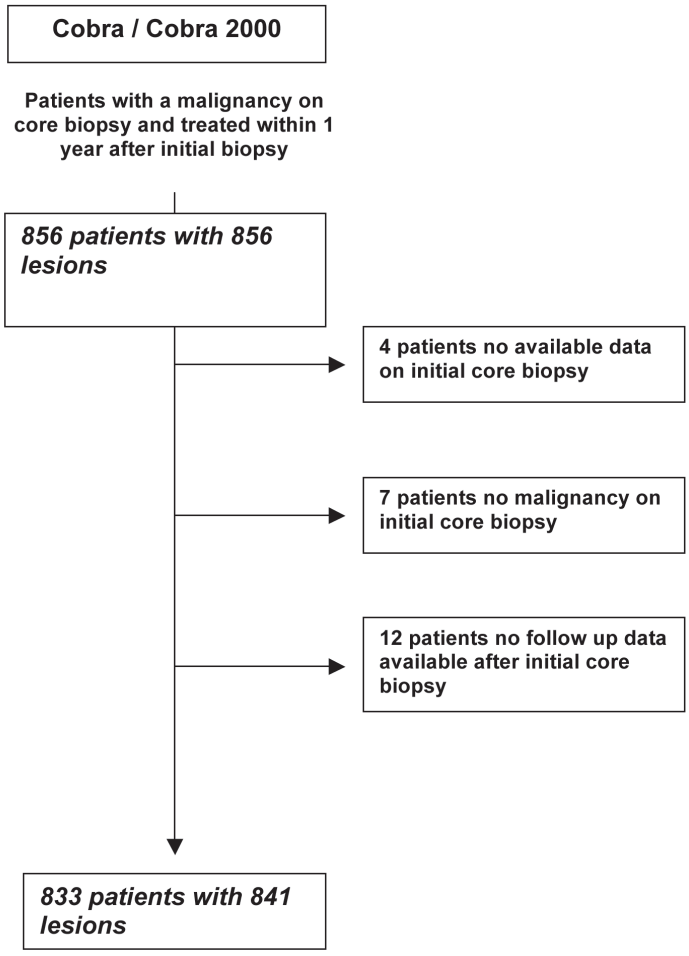


Figure 1: flowchart patient inclusion

Histopathological analysis
Histopathological samples were taken from the macroscopically closest margin. Tumour free margins of >1mm were considered adequate. Tumour tissue in ≤ 2 low power fields (LPF) was considered focal irradicality and treated with local radiotherapy. Irradicality is defined as tumour tissue in > 2 LPF and was treated with a re-excision or mastectomy.

Data collection and analysis
To avoid missing surgical procedures the number and type of surgical procedures, histopathological diagnosis and time between the LCNB diagnosis and final surgery up to a maximum of 1 year after initial LCNB were extracted from the Dutch National Pathology Database (PALGA = Pathologisch Anatomisch Landelijk Geautomatiseerd Archief).
The first surgical procedure after LCNB was assessed, the number of initial planned mastectomies and the number of surgical procedures for complete tumour removal was calculated and summed per patient and the number of conversions from BCS to mastectomy was documented. All LCNB (excluding the first one), lumpectomy, re-excisions, mastectomies, sentinel node biopsies and axillary lymph node dissections were included in the analysis. Furthermore the total number of days between first LCNB and final removal of all tumourous tissue was calculated for each patient. To assess whether the number of surgical procedures differed between patients with *in situ* carcinoma and invasive carcinoma, a subgroup analysis was performed. Patients with pure invasive carcinoma were compared with patients with invasive and *in situ* carcinoma on final histhopathology. Patients younger than the median age were compared with patients older than the median age. The number of surgical procedures and total number of days until all tumourous tissue was removed for both groups were compared using the t-test for the non normal distribution (Mann-Whitney-U test). The number of conversions to mastectomy for both groups was compared using the chi-square test. The number of surgical procedures after final histopathology was compared using the ANOVA and Bonferroni test. Differences in number of surgical interventions between younger or older than the median age were compared using the chi-square test. P-value <0.05 was considered to be statistically significant. Data were analyzed using SPSS version 12.0.

Results

After evaluation of the 856 eligible patients, 833 patients with 841 tumours were included in this study (mean age ± SD, 60.0, ± 9.9). In 4 patients no data on the initial core biopsy were available, in 7 patients core biopsy revealed no malignancy and in 12 patients no data on follow-up after the core biopsy were available (figure 1). Pathology revealed 337 *in situ* carcinomas and 504 invasive carcinomas. The left breast was affected in 416 patients (49%), the right breast in 408 patients (49%), 8 patients had breast cancer in both breasts (1%) and in 17 patients (2%) the affected side was unknown (table 1). The histological biopsy results are summarized in table 1. The median histological tumour size was 12 mm (range 1 - 82 mm).
The number of surgical procedures after LCNB ranged from 1 to 4 procedures, with a median of 1. The initial surgery consisted of BCS for 589 tumours (70%) and of mastectomy for 242 tumours (29%). For 10 tumours (1%) the initial surgery was unknown. After BCS 158/589 tumours (27%) required a re-excision, consisting in 67/158 tumours (42%) of BCS and 91/158 tumours (58%)

of mastectomy. Twenty-one of these 158 tumours (13%) required more than one re-excision (see figure 2 and table 2). Finally 106/589 (18%) re-excisions after initial BCS were converted to a mastectomy. The median number of days from the time of the LCNB until all tumourous tissue was removed was 28.
Subgroup analysis showed that the median number of interventions after LCNB in both groups was 1 and the range was 1 to 4 interventions for the patients diagnosed with an *in situ* carcinoma and 1 to 3 for the patients diagnosed with an invasive carcinoma. Patients with an *in situ* carcinoma on LCNB initially underwent significantly more breast amputations (figure 2 and table 2) than patients with an invasive carcinoma, 157/337 (47%) versus 193/504 (38%), p=0.01.The total number of re-excisions was 116/337 (34%) for patients diagnosed with an *in situ* carcinoma and 63/504 (13%) for patients diagnosed with an invasive carcinoma, p=0.0001. The number of conversions from BCS to mastectomy differed significantly between both groups: 66/241 (28%) in patients with an *in situ* carcinoma versus 40/348 (11%) in patients with an invasive carcinoma, p=0.0001. The difference in median number of days until all tumourous tissue was removed significantly differed as well i.e. 25 days for patients with an invasive carcinoma and 38 for patients with an *in situ* carcinoma (p= 0.0001).

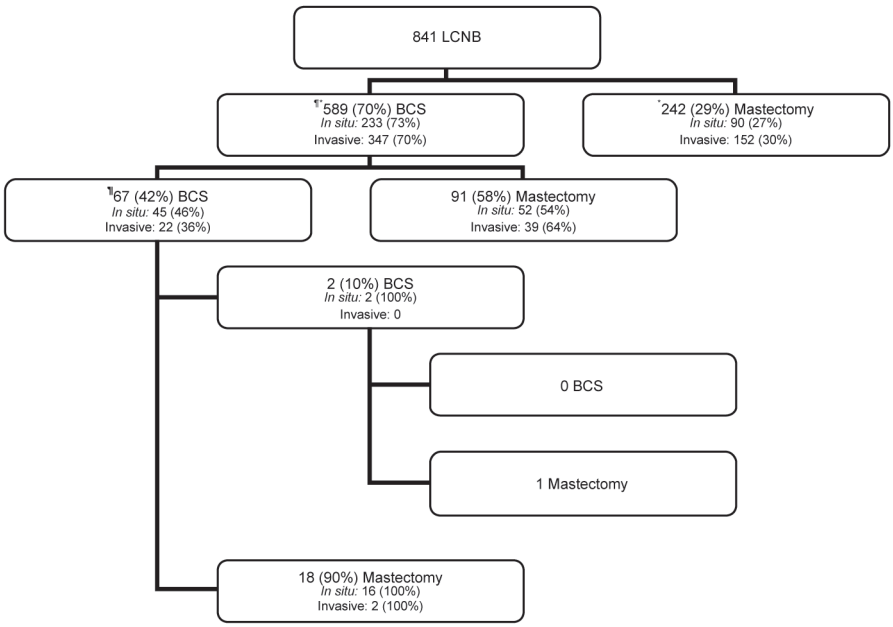
Table 1: Baseline characteristics

Baseline characteristics	Frequency
Number of patients	833
Number of tumours	841
Median age (years)	60
Affected side	
- Left	416
- Right	408
- Unknown	17
Median tumour size (mm)	12
Median tumour size *In situ* on LCNB (range)	12 (1-80mm)
Median tumour size invasive on LCNB (range)	12 (2-82mm)
Histology (on LCNB)	
• *In situ*	
- DCIS	307
- LCIS	3
- Both	2
• Invasive	
- Ductal	420
- Lobular	69
- Both	4
• Other breast malignancy	29
• Unclear	7

Patients who showed invasive ductal carcinoma and ductal carcinoma *in situ* on histopathological evaluation after surgery had significantly more surgical interventions than patients with pure ductal carcinoma *in situ* (p=0.048) and patients with pure invasive ductal carcinoma (p=0.001). Next patients who showed an invasive lobular carcinoma and an *in situ* lobular carcinoma on final histhopathological evaluation had significantly more surgical interventions than patients with pure invasive lobular carcinoma (p=0.01) and patients with an invasive ductal carcinoma (p=0.03), see table 3

Patients who were younger than the median age (60) had significantly more surgical interventions than the patients older or equal to the median age (p= 0.021).

Finally in this study we found a 5 year survival of 93% for the patients with an invasive carcinoma and 98% for patients with an *in situ* carcinoma, the overall 5 year survival was 95%.



¶ Patients undergoing a second LCNB or FNAB are included
*10 unknown surgery

Figure 2: Flowchart surgical procedures (BCS= breast conserving surgery)

Table 2: Surgical procedures in both groups

	Invasive carcinoma n (%)	In situ carcinoma n (%)	Total n (%)
First procedure			
- Breast conserving	*348 (70)	**241 (72)	589 (70)
- Mastectomy	152 (30)	90 (27)	242 (29)
Second procedure			
- Breast conserving	22 (36)	45 (47)	67 (42)
- Mastectomy	39 (64)	52 (54)	91 (58)
Third procedure			
- Breast conserving	0	2 (11)	2 (10)
- Mastectomy	2	16 (89)	18 (90)
Fourth procedure			
- Breast conserving	0	0	0
- Mastectomy	0	1	1 (100)
Total number of:			
- Breast conserving	370 (73)	288 (85)	658 (65)
- Mastectomy	193 (38)	159 (47)	352 (35)
Total number of conversions from breast conserving to mastectomy	40*** (11)	66**** (28)	106 (18)

* 4 missings, ** 6 missings, *** 1 missing, **** 3 missings

Table 3: histopathological results after surgery

Diagnose	Median Histopathological tumour size (range)	Frequency (%)	Mean number of surgical interventions
Pure DCIS	20.00 (2-80mm)	206 (24.5)	2.29
Pure invasive ductal carcinoma	12.00 (2-60mm)	388 (46.1)	2.10
Invasive ductal carcinoma and DCIS	10.00 (1-40mm)	121 (14.4)	2.45
Pure invasive lobular carcinoma	15.00 (3-82mm)	50 (5.9)	2.14
Invasive lobular carcinoma and LCIS	6.00 (5-8mm)	3 (0.4)	3.00
Invasive ductal carcinoma and invasive lobular carcinoma	11.00 (5-50mm)	43 (5.1)	2.19
LCIS and DCIS	13.00 (5-20mm)	8 (1)	2.25
Other	12.00 (3-50mm)	22 (2.6)	2.00

Discussion

To the best of our knowledge this is the first large study that solely describes the surgical performance of patients diagnosed with nonpalpable breast carcinoma. Our results show a total of 179 tumours of the 841 (22%) needed re-excisions to completely remove all tumourous tissue. The number of re-excisions was significantly higher in patients with an *in situ* carcinoma then in patients with an invasive carcinoma: 34% vs. 13%, p=0.0001. The number of conversions from BCS to mastectomy was 18%, this number was significantly higher in patients diagnosed with an situ carcinoma 28% vs. 11% in patients with an invasive carcinoma, p=0.0001. Patients with both an *in situ* ductal carcinoma and an invasive ductal carcinoma on final histopathology and patients with both an *in situ* lobular carcinoma and an invasive lobular carcinoma had significantly more re-excisions than patients with pure invasive or *in situ* carcinomas. Patients younger than 60 years had significantly more re-excisions than patients of 60 or older.

Kurniawan et al described the surgical outcome of patients with both palpable and nonpalpable breast carcinoma. All patients were included by way of the mammography screening program. The patients undergoing an initial mastectomy were excluded from this study. The number of initial mastectomies in this study was 9% this is lower than the number of initial mastectomies in our study. The number of irradical re-excisions in patients with both DCIS and invasive ductal carcinoma was higher than in the patients with pure DCIS or pure invasive ductal carcinoma, corresponding with our findings.

Next, they describe 23% conversions from initial BCS to mastectomy [19]. This number is higher than our overall number of conversions. This can be explained by the fact that all tumours were included in this study: palpable, non palpable and T1-T4 tumours and the lower number of initial mastectomies. Our number of conversions to mastectomy is higher in patients diagnosed with an *in situ* carcinoma. Kurniawan et al did not perform a subgroup analysis on the number of conversions for patients diagnosed with an *in situ* carcinoma.

There are several factors influencing the decision of performing a re-excision and the kind of surgery in (nonpalpable) breast cancer. Firstly, the definition of tumour-free margins is subject to discussion. The definition of tumour-free resection margins ranges from 1mm to 5mm [13, 20]. In literature we found tumour positive resection margins in 35-42% in patients with T1-4 tumours [13, 21]. Again the tumours described in these studies were both palpable and nonpalpable and larger (T1-4) than the tumours we analyzed. In these studies a tumour free margin was defined as >5mm from the inked resection plain. The number of re-excisions we describe in this study is lower than described in the literature, possibly the fact that in our study a tumour free margin of >1mm was considered adequate contributed to the lower number of re-excisions. Furthermore, in this study focal irradicallity of the excised tumour was treated with radiotherapy as is described in literature [22].

Secondly, the hooked wire placement is an important part of the surgical accuracy and is probably influenced by the experience of the radiologist. The hooked wire was placed in a routine clinical setting by both experienced and inexperienced radiologists. The wire guided localization has several known disadvantages, like wire displacement and the chance of a pneumothorax[11]. Currently other localization techniques, including the promising ROLL technique, are subjected to intensive research[23-26].

Thirdly the experience of the surgeon performing the BCS is an important factor influencing the number of tumour-free margins. Dedicated breast surgeons obtain more tumour-free margins and

perform less initial mastectomies than surgical residents or general surgeons [27, 28]. As in this study both general and dedicated breast surgeons performed the BCS and mastectomies, possibly the number of tumour-free margins was lower and the number of initial mastectomies was higher than when only dedicated breast surgeons participated [28]. The overall number of days until all tumourous tissue was removed was 28 and differed significantly between *in situ* carcinomas and invasive carcinomas 25 versus 38 days (p=0.0001). In a study assessing differences in dedicated versus general surgeons the median duration from diagnosis to operation was found to be 5 weeks, which is similar to our data [28].

Finally, the kind of treatment is influenced by the patient's desire. Although it is well known and overall accepted that the survival rates after breast conserving procedures and breast amputations are the same in patients with small localized breast carcinomas [29] around 35% of the patients when offered the choice still choose to undergo a mastectomy [30]. This could be an explanation for the high number of primary mastectomies.

Reliable pre-operative imaging is important for excision with tumour-free margins of the tumour, especially in nonpalpable cancer that has to be radiologically localized prior to surgery. Mammography and ultrasound are the most widespread imaging modalities for imaging of breast tumours. Unfortunately these imaging modalities have limitations. Although not recorded in this study, overall mammography and ultrasound tend to underestimate the true tumour size as assessed on histopathology. The correlation improves in larger tumours [31]. The patients with an *in situ* carcinoma scheduled for a BCS in this study underwent significantly more breast amputations than the patients with an invasive carcinoma. Limited possibilities to delineate the extent of *in situ* carcinoma with mammography and ultrasound could have contributed to the number of irradical excisions. Although current data on magnetic resonance imaging (MRI) are mixed, it could be more accurate in pre-operative tumour size and distribution assessment and possibly reduce the number of re-excisions[32-34].

The difference in the number of days between patients with an *in situ* carcinoma and patients with an invasive carcinoma could also be explained by the fact that determining the extent of *in situ* carcinoma is difficult. The survival found in this study is comparable to current literature [35].

In conclusion in this study we showed that it is difficult to completely remove all tumourous tissue in 1 procedure. A total of 42% of patients diagnosed with early stage, nonpalpable breast cancer had a mastectomy. The treatment of *in situ* carcinoma is significantly more frequently converted from BCS to mastectomy than of invasive carcinoma. Improvements in pre-operative imaging and surgical technique for nonpalpable breast carcinoma are needed to decreases the number of mastectomies.

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Part 2 Tumour localization

Chapter 5

Radio guided occult lesion localization (ROLL) for non palpable invasive breast cancer

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Abstract

Background
Wire guided localization (WGL) for non palpable breast cancer is technically difficult and patient unfriendly. Radio guided occult lesion localization (ROLL) takes advantage of the possibility to detect the tumour through the nuclear tracer that is injected directly into the tumour for the sentinel node procedure.

Methods
Fourty patients with 41 invasive breast carcinomas were treated using ROLL. Patients received a dose of 120Mbq 99mTc Nanocolloid intra-tumourally on the day of surgery or a dose of 370Mbq 99mTc Nanocolloïd intra-tumourally the prior day.
The sentinel node (SN) was located using patent blue and a gamma ray detection probe that was also employed to guide the tumour excision.

Results
In 31 patients (78%) the invasive tumour was adequately excised. In 2 cases (5%) a re-excision was required due to inadequately excised carcinoma *in situ* and in 3 patients (7.5%) both the invasive and the *in situ* tumour were inadequately excised. In 35 patients (88%) the SN was found and removed.

Conclusions
The ROLL procedure seems to be an alternative to WGL in patients with non palpable breast carcinoma. To determine the place of ROLL versus WGL in the treatment of non-palpable breast cancer, a randomized clinical trial is needed.

Introduction

The early detection of breast malignancies decreases the mortality and morbidity of breast cancer patients[1, 2]. Early detected tumours are generally small and non-palpable. We performed a short survey by telephone among 25 selected large hospitals in the Netherlands, showing that 80% of the hospitals use wire guided localization (WGL) for the detection of non palpable breast cancer. Therefore, WGL can be considered standard of care in the Netherlands. This holds for other European countries as well [3-5]. The wire can be inserted under stereotactic or ultrasonographic guidance. WGL has several known disadvantages: the radiological guided wire placement is a technically difficult procedure[3, 4, 6], particularly in dense breast tissue; the wire can displace and repositioning is often restricted because of the hook fixed in the tissue; surgical excision of a wire located lesion with clear histological margins is technically difficult; patients experience the insertion of the wire as unpleasant; and there is a small risk of pneumothorax[4].
Other localization methods described include iodine seed localization, ultrasound localization and the Radio guided occult lesion localization (ROLL) method introduced in 1998[7-9]. The ROLL technique utilizes the intratumourally injected radiotracer that is generally used for lymphatic mapping and sentinel node biopsy (SNB). In the same surgical procedure, this tracer can be used to localize the primary tumour guided by the gamma probe as well (figure 1).

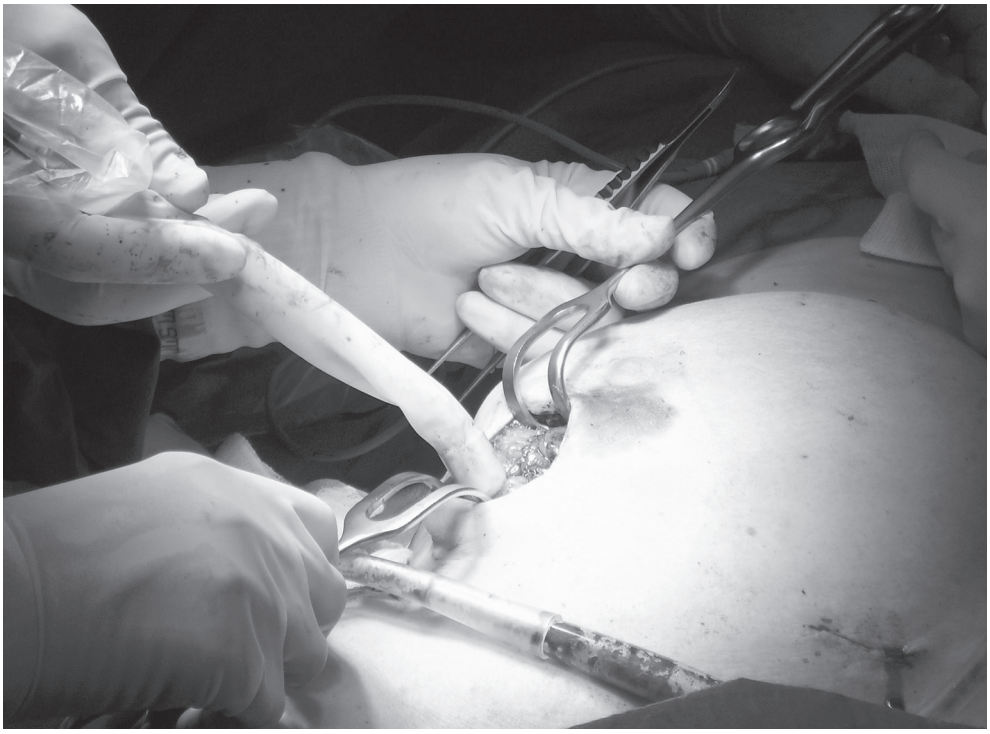

Figure 1: Radio guided occult lesion localization intra operatively

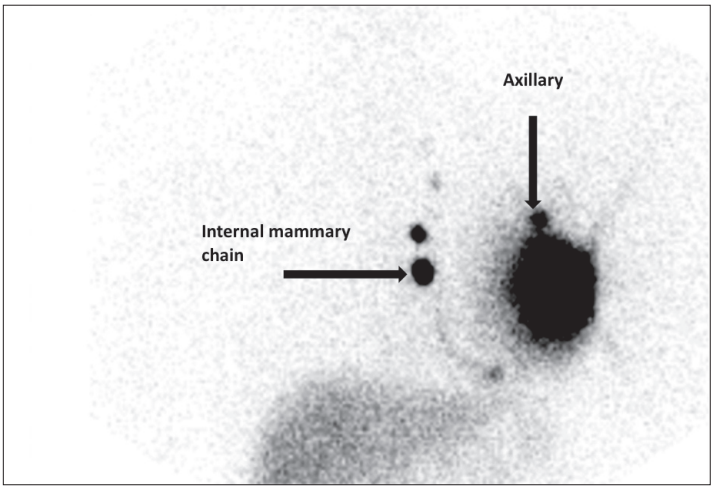

Figure 2: Static imaging, arrows indicating sentinel node

With the ROLL procedure, patients with invasive breast cancer can undergo 1 procedure less as no wire has to be inserted. Possibly, the oncologic outcome is better and the lump size smaller, resulting in a better cosmetic outcome.
If ROLL is proven to be superior to WGL, the current standard surgical treatment of non-palpable breast cancer could be changed substantially by the introduction of a technique that is possibly more convenient for patient and physician, less time consuming and more effective (higher percentage of adequate resections).
As the number of non palpable breast carcinomas will increase due to the early detection, this new procedure could benefit thousands of women each year and possibly improve cost effectiveness.
Especially patients requiring SNB could benefit from the ROLL procedure. Most studies performed so far included a wide range of patients with benign, *in situ* carcinomas and invasive carcinomas[3-5, 10-15], not always in combination with SNB procedure. We therefore performed a study in a homogeneous patient population consisting of patients with only non-palpable invasive breast cancer undergoing SNB to optimally evaluate the feasibility of the ROLL procedure. Furthermore the results of the ROLL procedure are compared to the results of WGL.

Materials and Methods

Between February 2005 and December 2007, 40 patients with non-palpable breast cancer presenting in the University Medical Center Utrecht were included. All patients had core biopsy confirmed non-palpable invasive breast carcinoma. The first 23 patients were treated according to a 2-day protocol. These patients received 370Mbq of 99mTechnetium nanocolloïd intratumourally on the day before surgery. The remaining 18 patients received 120 Mbq 99m Technetium nanocolloïd intra-tumourally on the day of surgery. Image guidance was done either by ultrasound or stereotaxis. The nanocolloïd

consisted of at least 95% human albumine colloïd particles of ≤ 80 nm. After 10, 60 and 120 min, lymphoscintigraphic imaging was done to asses the migration of the radiotracer (figure 2). After finding the SN on the static images the skin was marked. Intra-operatively, patients received an intra-parenchymatous injection of 2ml patent blue (Bleu patenté V 'Guerbet') on the site of the maximum counts found with the gamma probe (Europrobe Strassbourg, France). First, the SNB was performed and subsequently, the primary tumour was excised using the gamma probe to detect the location. The handheld gamma probe was used with a high threshold setting to detect only the site of maximal activitiy. A small incision was made in the skin above the site of maximum counts, followed by resection guided by the gamma probe. Counts were recorded in different angles in order to optimally localize the tumour.
The resected specimen and SNs were histopathologically evaluated using standard protocols22. Specimens were lamellated and blocks were taken at the macroscopically most threatened margins. Microscopically, the distance from the tumour to the closest margin was measured with a ruler. Excision was considered inadequate if a margin less than 1 mm was achieved.

Results

A total of 40 patients with 41 lesions were treated with the ROLL protocol. Their mean age was 63 years (range 48 - 77 years). In 4 (10%) cases the nanocolloïd was placed stereotactically and in the remaining 37 (90%) this was done ultrasonographically. Median tumour size was 12mm. Histopathology revealed a total of 36 invasive ductal carcinomas, 3 invasive lobular carcinomas and 2 invasive ductolobular carcinomas. Patient and tumour characteristics are listed in table 1. In 23 cases (56%) ductal carcinoma *in situ* (DCIS) surrounded the invasive tumour and in 5 cases (13%) lobular carcinoma *in situ* (LCIS).
In 31 cases (78%) the invasive tumour was adequately excised in 1 procedure, and 2 cases (5%) required re-excision due to inadequate excision of the DCIS component. In 3 patients (7.5%) both the invasive and the *in situ* tumour were not adequately excised. In 2 of these cases histopathology showed inadequately excised invasive ductal carcinoma and DCIS and in 1 case invasive ductolobular carcinoma and LCIS were inadequately excised. Thus, in 3/5 cases the LCIS component was adequately excised (60%), while 18/ 23 cases of DCIS were adequately excised (78%) this difference was not significant (p=0.39). In 28 cases (70%) no re-excision was required.
In 1 patient histopathology revealed a secondary tumour distant from the adequately excised primary tumour. This tumour was not seen on pre-operative imaging and thus not localized. One case showed no tumour tissue in the excision specimen caused by misplacement of the 99mTc-nanocolloïd. In this case a wire guided re-excision was performed in a second operation were the tumour was adequately excised.
The mean lump volume was 238 (18ml – 1215) ml. Lymphoscintigraphy revealed on average 2 SN's (range 0-4). In 35 patients (88%) the SN was identified and removed. In 5 (12%) cases the SN could not be found and an axillary dissection was performed. In 1 patient pre-operative visualization was very difficult due to the close relation between the radiofarmacon depot and the SN. Also the count rate was very low pre-operative (<25 counts). Another case showed a very extensive visualization of the liver and possibly there was an accidental intravenous deposition of the nanocolloïd,

Table 1: Patient and tumour characteristics

Parameter	Value
Number of patients	40
Number of tumours	41
Age, mean (range)	63 (48 – 77)
Tumour type	
- Ductal	36
- Lobular	3
- Ductolobular	2
Grade	
- 1	14
- 2	18
- 3	9
T stage	
- 1	39
- 2	2
- 3	0
- 4	0

Table 2: Sentinel node procedure results

Parameter	Value
Nr SN's on static imaging, mean (range)	2 (0 – 4)
Location:	
- Axillary	34
- IMC	4
- IM	2
Nr SN's removed, mean (range)	2 (0 - 3)
Patients with metastasis	
- None	32
- ITC	3
- Micro	2
- Macro	3

IMC= internal mammary chain, IM= intra mammary,
ITC= isolated tumour cells

resulting in an 80% count rate for the liver. The failure of the SLN procedure in the third and the forth patient is unclear. Again the LN was visualized very close to the radiofarmacon depot. The fifth patient also had a non invasive tumour in the same quadrant of the breast. In this patient a guide wire was placed in the non-invasive tumour prior to the intra tumoural injection of the radiofarmacon. There was no pre-operative visualization. The differences in mean age in the success group and the failure group was not significant (p=0.14) and the difference in tumour size in both groups was not significant either (p=0.7). In 34 cases an SN was found in the axilla, in 2 cases both an internal mammary chain (IMC) and an axillary SN was found, 1 case both an intra-mammary (IM) and an IMC SN was found and in 1 case both an axillary, an IMC and an IM SN were found (see table 2). The SNB was successful in 35 cases (88%). In 33 cases (83%) the SN was free of tumour. All patients with macro-metastases (3 patients) or micro-metastasis (2 patients) underwent a subsequent axillary lymph node dissection (ALND). Two patients with isolated tumour cells refused ALND. In 1 patient an additional positive lymph node was found in the ALND specimen, in the remaining patients no additional lymph nodes were found. All patients received post operative radiotherapy; 4 patients underwent adjuvant chemotherapy. Apart from the misplacement of the 99mTechnetium nanocolloïd in 1 patient no serious complications occurred.

Discussion

As the number of detected non palpable breast carcinomas is increasing due to widely applied and well conducted screening programs, good, safe and patient friendly treatment modalities are needed. Since there are known disadvantages to the current standard of care, WGL, we performed this study in order to investigate the applicability of the ROLL procedure in a homogeneous patient population consisting of non-palpable invasive breast cancer patients.

Our results show a complete resection of the invasive tumour in 78%, which is comparable to other published ROLL studies, showing a range of 69 to 89% adequate excisions[5, 16-19]. Residual disease after surgery is more likely in patients with tumours surrounded by *in situ* carcinoma. Lobular carcinoma is known to have a diffuse growing pattern and extensive *in situ* carcinoma. *In situ* carcinoma is a difficult problem; current literature shows that up to 50% of the patients with DCIS require a re-excision[20, 21]. Patients with lobular carcinoma and/or LCIS are more likely to require re-excision than patients with ductal carcinoma and/or DCIS. The explanation could be the incomplete imaging of the lobular carcinomas, due to lack of calcifications and solid lesion on mammography and ultrasound[22]. In our study there were only three patients with a lobular differentiation, although this is a low number it seemed not to have lead to a clearly higher inadequate excision rate. Our results are as good as the results found for the WGL lumpectomies found in current literature. A range of 57 – 69% of complete excision for WGL procedures is described[16, 19, 23].

Compared to literature the specimen volume in our study is high with 238ml (range 47 – 1215ml) versus 83ml (range 63 – 300ml)[4]. Possibly this is due to a patient bias. The latter group also included diagnostic excisions which could have resulted in lower excision volumes. Furthermore 8 patients received neo-adjuvant chemotherapy and had a coil placed on biopsy, which may have influenced specimen volume as well. A study done on WGL found a higher specimen volume 143ml (range 54-229ml)[24]. Possibly the specimen volume in patients treated with WGL is larger then in patients treated with the ROLL procedure.

In our study, the injection of the radiotracer was done stereotactically in 10% of patients. This is in agreement with the reported percentages of 7-26% in current literature[4, 5, 14].
As has been described in previous studies, there are several factors influencing the success of the SNB. Significant influencing factors are particle size of the radiotracer, body mass index and the age of the patient. Age < 50 years, a low body mass index and a small particle size are considered to be beneficial in the finding of the SNB25. In our study we show a success rate of the SNB of 88%. In literature we found this number to be 90% in patients with a non-palpable breast carcinoma treated with the ROLL method14. All patients were injected with nanocolloïd of at least 95% human albumine colloïd particles of ≤ 80 nm.
In case of SN's located close to the tumour we advise to start with the ROLL guided lumpectomy followed by the SNB to reduce the interference of the radioactive tumour site. In some cases both the tumour and the SN may perhaps be removed in one specimen. No data on these cases are available in current literature. Also it is advisable not to treat patients with the ROLL guided lumpectomy after neoadjuvant chemotherapy. It is unclear what the best timing of the SNB is: pre- or post chemotherapy[26-28].
Complications described for the WGL procedure are serious. Wire migration and displacement and interference with the SN procedure are well known[4, 6, 29]. Unlike the wire guided procedures, there are no serious complications described so far in the ROLL procedure apart from misplacement of the radiotracer which occurred in 1 patient (2.4%) in the present study where no tumour was found on histopathology. On post-operative mammography and ultrasound the tumour was located 2cm distant from the excision cavity. Re-excision guided by a wire placed stereotactically followed and resection margins were clear. A 1-5% incorrect placement rate of the radiotracer has been described in literature[3, 30, 31].
Unlike other studies on the ROLL technique, we only included patients with a core biopsy proven non-palpable breast carcinoma. These patients benefit from undergoing 1 procedure less compared to the WGL, in which an additional wire has to be placed. Patients treated according to the WGL protocol will have 2 injections. While patients with an *in situ* carcinoma or a benign lesion will only have a wire and no second injection for the radiotracer, the patient discomfort may therefore not differ from the ROLL treatment. Therefore patients with an invasive breast carcinoma could benefit the most from the ROLL procedure.
In conclusion the ROLL approach appears to be safe and associated with high tumour free margin rates. In order to implement this procedure nationwide as the desired standard, a clinical trial randomizing between ROLL and WGL should be the next step. Our group has recently started such a large multicenter clinical trial.

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Part 2 Tumour localization

Chapter 6

The efficacy of 'Radio guided Occult Lesion Localization' (ROLL) versus 'Wire-guided Localization' (WGL) in breast conserving surgery for non-palpable breast cancer: a randomized clinical trial - ROLL study

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Abstract

Background
With the increasing number of non palpable breast carcinomas, the need of a good and reliable localization method increases. Currently the wire guided localization (WGL) is the standard of care in most countries. Radio guided occult lesion localization (ROLL) is a new technique that may improve the oncological outcome, cost effectiveness, patient comfort and cosmetic outcome. However, the studies published hitherto are of poor quality providing less than convincing evidence to change the current standard of care.
The aim of this study is to compare the ROLL technique with the standard of care (WGL) regarding the percentage of tumour free margins, cost effectiveness, patient comfort and cosmetic outcome.

Methods/design
The ROLL trial is a multi center randomized clinical trial. Over a period of 2-3 years 316 patients will be randomized between the ROLL and the WGL technique. With this number, the expected 15% difference in tumour free margins can be detected with a power of 80%. Other endpoints include cosmetic outcome, cost effectiveness, patient (dis)comfort, degree of difficulty of the procedures and the success rate of the sentinel node procedure. The rationale, study design and planned analyses are described. (www.clinicaltrials.gov, study protocol number NCT00539474)

Background

The early detection of breast malignancies decreases the mortality and morbidity of breast cancer patients. These early-detected tumours are generally small and non-palpable.
Wire Guided Localization (WGL), is currently the most commonly used localization method for non-palpable breast lesions. This technique uses a wire to localize the lesion to be excised. The wire can be inserted under stereotactic or ultrasonographic guidance. WGL has several known disadvantages: the radiologically guided wire placement is technically difficult, particularly in dense breast tissue (the wire can displace and reposition is often restricted because of the hook fixed in the tissue). Surgical excision of a lesion with clear histological margins following wire localization is demanding as well. Finally, patients experience the inserted wire as painful and uncomfortable and there is a small risk of a pneumothorax.[1-3]
The Radio Occult Lesion Localization (ROLL) introduced in 1998, is a new technique to localize the non-palpable breast tumour[4]. The ROLL technique utilizes the intratumourally injected radiofarmaceutical that is used for lymphatic mapping and sentinel node biopsy (SNB). In the same surgical procedure, this tracer can be used to localize the primary tumour guided by the gamma probe.
Previous small non randomized trials, comparing WGL and ROLL have found the ROLL technique to be simpler and faster to perform, potentially resulting in fewer costs associated with the use of ultrasound, operation rooms and hospital stay[5].

Methods/Design

Design
A multicenter, prospective randomized clinical trial. Eligible patients will be randomized for either radio guided occult lesion localization (ROLL) or wire guided localization (WGL).

Subjects
Three hundred and sixteen patients will be recruited in 2 years in a University Medical Center and medium sized to large hospitals in the Netherlands. All patients will have confirmed occult breast cancer (core needle biopsy proven) and need to be treated with a lumpectomy and sentinel node biopsy. Written informed consent will be obtained from all patients. This study has been approved by the ethical board of the university medical center Utrecht.

Patient selection
All patients will be selected based on the in- and exclusion-criteria. The inclusion of patients will take place at the outpatient clinic in the participating hospitals. Patients will be informed about this trial by both written and oral explanation. Given the number of regular treatments of occult breast tumours in the collaborating hospitals (250-300 patients per year), the aim to finish the inclusion in 2 years is considered realistic.
Women ≥18 years with a non palpable breast carcinoma (cT1) that need to be treated with breast conserving surgery are asked to participate. Exclusion criteria are pregnancy, multifocal tumour growth, *in situ* ductal carcinoma only, lobular *in situ* carcinoma only and patients requiring breast amputation.

Randomization
Randomization is stratified for hospital. In each hospital, randomization within strata is blocked with a fixed block size. Randomization is performed by an independent trial center. If a patient meets the inclusion criteria and has provided informed consent, the physician contacts the trial center by phone. The trial center will perform the randomization of the patients.

Time schedule
Patient recruitment will take place between 2008 and 2010.

ROLL procedure
Patients in the ROLL group will undergo intratumoural injection of the radiofarmaceutical under stereotactic or ultrasound guidance. After scintigraphic imaging, 1, 2 or if necessary 3 hours post injection, the excision of the primary tumour and the sentinel node procedure are both guided by a gamma probe. At the site of maximum counts with the gamma probe (Europrobe, Strassbourg, France) patent blue (Bleu patenté V 'Guerbet')is injected intratumourally (see figure 1).
As with all localization techniques, care is required in the initial placement of the lesion marker. A few studies have described failures in placement of the radioactive marker. However, the tracer was positioned correctly in 95-99% of patients.[6, 7]. After localization, the surgical excision is guided by the probe at its lowest sensitivity setting. The exact site of the lesion can be checked constantly during the procedure by using the probe. In this way centering of the lesion within the specimen can be achieved, potentially resulting in a smaller quantity of removed tissue and a higher chance of achieving tumour free margins.

WGL procedure
Patients in the WGL group will receive a guide wire, positioned intratumourally under ultrasonigraphic or stereotactic guidance after the scintigrafic imaging 1, 2 or 3 hours post injection. The excision of the tumour is guided by the inserted wire and the sentinel node procedure is performed using per operatively injected patent blue and a gamma probe. This is the current golden standard.

Outcome parameters
The outcome parameters are tumour free margins (and number of re-excisions), resection specimen volume, cosmetic outcome, quality of life, cost effectiveness also participating physicians will score the difficulty of the procedures. Patients will be asked to fill in questionnaires on pain during the procedure, quality of life and the cosmetic outcome. A specific burden questionnaire, aimed at evaluating the burden of the cosmetic result, is developed. Such an instrument is currently not available. To further assess the net impact in terms of Health Related Quality of Life (HRQoL) also the EQ5D and the EQVAS will be obtained at T = 0, 6, 12 and 26 weeks after the initial diagnostic work-up.
The outcome of the study can be divided in 3 groups of outcome; negative outcomes, outcomes open to discussion and positive outcomes. Less tumour free margins in the ROLL group are considered negative outcomes, also more tumour free margins in combination with a larger resection volume is a negative outcome and equal tumour free resection margins combined with larger resection specimens are considered negative. Secondly outcomes open to discussion are more tumour free margins in combination with an equal resection volume and equal resection margins in combination

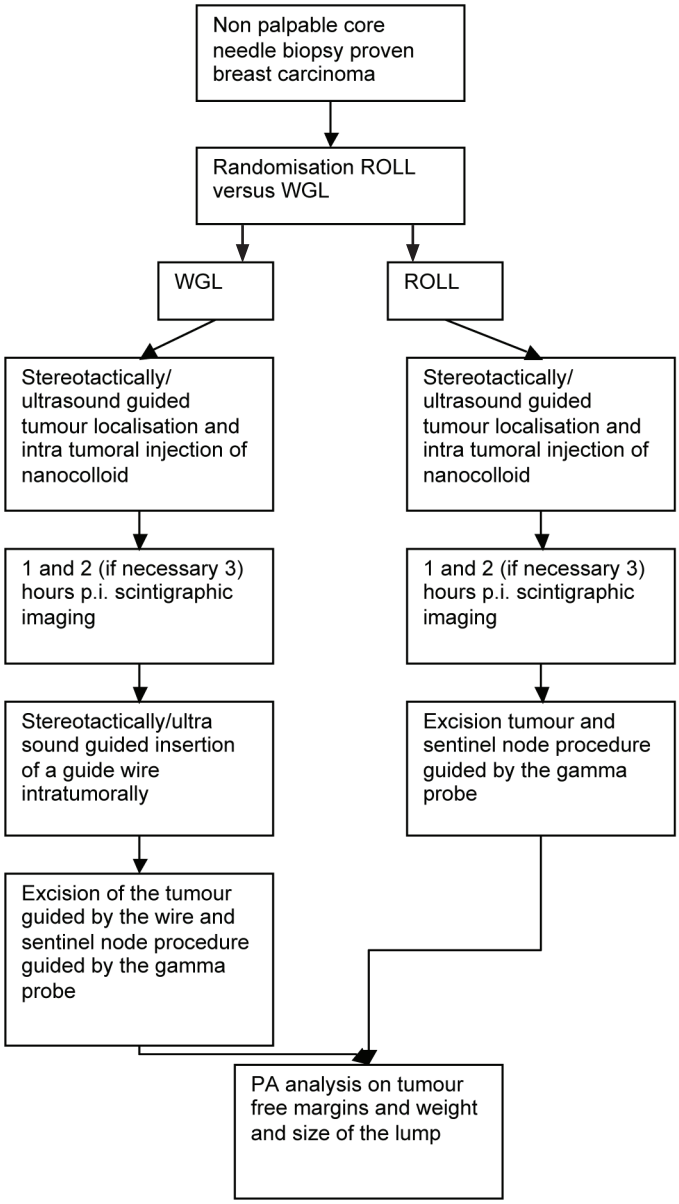

Figure 1: Flowchart

with smaller resection specimens in the ROLL group. Finally positive outcomes are more tumour free resection margins in combination with smaller resection specimens and equal tumour free margins in combination with smaller resection specimens. These data will be based on pathology reports. All surgical specimens will be analysed by one dedicated reference pathologist (PvD).
The overall outcome will be cost-effectiveness in terms of incremental costs per quality adjusted life years gained with a 6 month time horizon. We hypothesize that the short-term burden will result in an overall superior result after ROLL.
When indeed our expectations are evidenced, than a situation of dominance may occur, i.e., costs may be saved while at the same time clinical effects are optimal after ROLL.
Should the results indicate that overall the WGL procedure leads to better clinical outcome a cost-effectiveness analysis is foreseen using bootstrapping to assess the uncertainty with regard to the balance between costs and effects. All analyses will be limited to a half year time horizon. Accordingly, discounting of costs or effects is not applicable.

Sample size
Sample size is calculated based on the primary endpoint: tumour free margins. Based on currently available literature we assume a difference in tumour free margins of 15% in favor of the ROLL procedure[2, 8-13]. With a statistical power of 80% to detect this 15% improvement as significant ($p<0.05$), we will require 158 patients in the control (WGL) group and 158 in the ROLL group.
Assuming a weight of 50 gr in the WGL group and a difference of 10 gr in the ROLL group[14] and a standard deviation of 3gr, $\alpha=0.05$ and $\beta=0.80$, the groups are sufficient to show a significant reduction in weight.

Economic evaluation
The goal of the economic evaluation is to assess the balance between costs and effects of ROLL versus WGL. The principal underlying assumption is that once tumour free margins are obtained the prognosis will be similar.
Therefore, long term analyses will not be necessary. In fact ignoring the possible difference in burden
associated with WGL as compared to ROLL a cost-minimization would suffice. This is the initial approach, i.e., comparing actual costs incurred with both strategies up until 6 months after the first operation. Costs estimates will be based on the actual costs of both procedures. This includes the costs of operation rooms, hospital stay, ultrasound/ stereotactic imaging, wire placement, gamma probe use and if necessary, costs associated with complications and re-operations.
To assess the impact of the psychological burden of prolonged uncertainty regarding curative excision and the psychological burden associated with re-operation, dedicated questionnaires are developed.
Finally, there is a possibility that after ROLL, on average, a larger part of the breast is excised leading to less satisfactory cosmetic results. This is evaluated by interviewing the patients on their appreciation of the shape and appearance of their breast.

Statistical analysis

The difference in radicality of the resected specimen in both groups will be calculated in a confidence interval (CI) of 95%.

The volume of the specimens is presented in mm^3 and the maximum diameter in mm. The approach for the cost-analysis is comparing actual costs incurred with both strategies up until 6 months after the first operation. Costs estimates will be based on the actual costs of both procedures. This includes the costs of operation rooms, hospital stay, ultrasound/ stereotactic imaging, wire placement, gamma probe use and if necessary, costs associated with complications and re-operations. The degree of difficulty of radiological and surgical procedure will be expressed on a 1-10 scale (1 being extremely easy and 10 extremely difficult). The average score for both procedures will be calculated. Patient discomfort of the radiological procedure is expressed on 1-10 scale to (1 being not painful and 10 being very painful). The success rate of the sentinel node procedure is presented in a percentage of successfully detected and found sentinel nodes. The weight and size of the surgical specimens as well as the degree of difficulty of the surgical and radiological procedures and patients discomfort in both groups will be analyzed using the students T test.

The cost-effectiveness analysis will be done using the multivariate analysis. If the baseline characteristics differ after randomization, i.e. there is a lack of balance in the confounding factors, this will be corrected using the multivariate analysis.

Discussion

The purpose of the ROLL trial is to compare the standard of care (WGL) with the ROLL procedure on oncological outcome, cost effectiveness, cosmetic outcome, patient comfort and learning curve for the participating physicians.

As published previously by our group, the published studies so far indicate a benefit of the ROLL procedure, but are not conclusive[15]. So far only 1 randomized clinical trial is available, but this trial lacks essential information on tumour free margins and tumour size[16].

A large trial on ROLL published recently including 368 patients showed tumour free margins in 89% of the cases and a 97% identification rate of the sentinel node[17]. These figures are encouraging, but the patients in this study were not randomized, and a hook wire was always inserted at the primary tumour site. In our opinion this will not improve patient comfort and the technique is not easier to perform.

In some studies, patients with non palpable invasive carcinoma, carcinoma *in situ* and benign lesions were included[18, 19]. However, patients with an invasive carcinoma are likely to benefit the most from the ROLL technique. As these patients have to undergo a SNB, they will have to undergo one procedure less, i.e. the placement of a wire.

To the best of our knowledge none of the studies published have evaluated cost-effectiveness. In order to implement the new procedure nationwide, besides oncological outcome the cost-effectiveness should be balanced to make this the new standard of care. Approximately 4.000 out of 13.000 women diagnosed with breast cancer need wire guided localization and a sentinel node procedure. Our hypothesis, based on the current literature, is that 15% (600 patients) less re-operations are necessary after treatment with the ROLL technique. A re-operation costs about €7000, so eventually €4.200.000 a year might be saved by this method. Furthermore, abandoning the

radiological wire insertion procedure and the shorter surgical operating times could provide an additional cost reduction. In conclusion, the ROLL trial aims to prove oncological, patient satisfaction and cost effective superiority of the ROLL technique versus the WGL technique in the treatment of patients with a non palpable breast carcinoma.

Abbreviations

ROLL: Radio guided occult lesion localization, WGL: Wire guided localization, SNB: Sentinel node biopsy, Gr: Grams, HRQOL: Health related quality of life, EQ5D: EuroQuol 5d, EQVAS: EuroQuol visual analogue scale

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Part 3 Sentinel node biopsy

Chapter 7

Comparison of the 1- versus 2-day protocol for lymphatic mapping and sentinel lymph node biopsy in patients with nonpalpable breast cancer

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Abstract

Purpose
To compare the identification rate of the sentinel node in a 1-day protocol versus a 2-day protocol in patients with a nonpalpable breast carcinoma.

Methods
In the 1-day protocol an average dose of 120 Mbq ^{99m}Tc nanocolloid was injected intra-tumourally on the day of surgery, in the 2-day protocol an average dose of 370 Mbq ^{99m}Tc nanocolloid was injected intra-tumourally the day before surgery.
Both a gamma ray detection probe and patent blue were used to locate the sentinel node.

Results
In 57/67 (85%) patients treated in the 1-day protocol and in 51/56 (91%) patients treated in the 2-day protocol the SLNB was successfully detected (p=0.311). Eighteen (27%) patients in the 1-day protocol showed metastasis and 13 (23%) patients in the 2-day protocol (p=0.975)

Conclusion
There is no significant difference in the identification rate of the SLNB between the 1-day protocol and the 2-day protocol in patients diagnosed with a nonpalpable breast carcinoma.

Introduction

Lymphatic mapping and sentinel lymph node biopsy (SLNB) are reliable staging tools in the management of breast carcinoma patients. Especially patients with small, often nonpalpable breast carcinomas benefit from the SLNB instead of axillary dissection (AD) as only 7.8 – 28.5% of the patients with T1a-c breast carcinomas have tumour positive lymph nodes[1]. Therefore, without SLNB 70-90% of axillary dissections would be redundant in this particular group. In order to avoid invalidating AD-associated morbidity like lymph edema, a successful SLNB is of great importance.
Nonpalpable breast carcinomas are often difficult to discern at surgery. Therefore a guide wire is usually placed pre-operatively in order to localize the tumour. It is suggested that a guide wire placed intra- or peritumourally could disturb the lymph drainage pattern and thereby decrease the successrate of the SLNB[2].
Currently wide differences exist in SLNB protocols used. Radiocolloid, vital dye or both are used as localizing pharmaceuticals, while injection routes include intra-tumoural, peritumoural, intradermal and/or subareolar injection. Injection of the localizing pharmaceutical can be done either pre- or intra-operatively, the same day or the previous day[3, 4]. Lymphoscintigraphy can be performed using either the dynamic and/or the static technique[5]. In our hospital, both nanocolloid and blue dye are injected intra-tumourally in patients diagnosed with a nonpalpable breast carcinoma. Therefore, in nonpalpable breast cancer, the injection of a radiotracer needs to be performed guided by ultrasound or stereotaxia.
Initially patients diagnosed with a nonpalpable breast carcinoma were treated according to a 2-day protocol. This protocol was chosen to increase the number of successful SLNB due to the possibility to perform late nuclear imaging[6]. The 1-day protocol was introduced to allow all patients to be treated in daycare and to lower the radiation burden. It is unclear if there is a difference in the visualization and successful surgical removal of the SLNB between the 1-day and the 2-day protocol and if guide wire placement influenced the SLNB.
The aim of this study was to compare the 1 and 2-day protocols with regard to the identification rate and removal of the sentinel node in patients diagnosed with nonpalpable breast cancer.

Materials and methods

In this retrospective, nonrandomized, cohort study 123 patients with a nonpalpable breast carcinoma treated between July 2002 and July 2008 were included. Women with newly diagnosed primary, nonpalpable invasive breast cancer undergoing tumour resection and SLNB were eligible for the study. Exclusion criteria were previous breast cancer in the same breast, pregnancy and palpable breast cancer.
Fifty-six patients underwent SLNB according to a 2-day protocol. Patients in the 2-day protocol received a median dose of 370 Mbq ^{99m}Tc-nanocolloïd in 0,5 cc of water (range 80–550 Mbq). A 1-day protocol was introduced to allow patients to be treated in daycare and to lower the radiation burden. From then on, 67 patients were included in the 1-day protocol. The first 23 patients in the 1-day protocol received a dose of 80 Mbq ^{99m}Tc-nanocolloid. Due to low visualization rates the latter 44 patients received a median dose of 120 Mbq ^{99m}Tc-nanocolloid (80–220 Mbq) in 0,5 cc of water.

The nanocolloïd consisted of at least 95% human albumine colloid particles of ≤ 80 nm. In both groups we injected the radiofarmacon intra-tumourally guided by either ultrasound or stereotaxis depending on the visibility of the tumour. Patients were asked to massage their breast after injection of the tracer. Patients in the 1-day protocol underwent lymphoscintigraphic imaging after 10 minutes, 1 and 2 hours and patients in the 2-day protocol underwent lymphoscintigraphic imaging directly after injection and the next morning before surgery to asses the migration of the radiotracer. After finding the sentinel node on the static images the skin was marked. Intraoperatively patients received a peritumoural injection of patent blue on the site of the maximum counts found with the gammaprobe (Europrobe Strassbourg, France). First, the sentinel node biopsy was performed and subsequently the primary tumour was excised, followed by histopathological analysis using regular haematoxyline & eosine (H&E) and immunohistochemical staining. In case of failure of the SLNB a regular AD was carried out.
The number of lymph nodes (LN) seen on static imaging was compared to the number of LN found during surgery. The hot and/or blue sentinel nodes were removed and when the exact localization of the sentinel node was unclear intraoperatively the second echelon nodes were removed as well. The nodes both inside and outside the axilla were removed. The SLNB was considered successful if the tissue removed during surgery was hot and/or blue and proved to be LN tissue on histopathologic assessment. The lymphoscintigraphic visualization rate and the surgical success rate were compared between the 1-day protocol and the 2-day protocol.
Furthermore the success rate of the SNB with patients having a guide wire placed intra-tumourally before injection of the radiofarmacon in the 1-day protocol versus the 2-day protocol was compared to patients without a guide wire *in situ* during administration of the radiofarmacon.

Statistics
Identification and removal of one or more SN's was considered a successful SLNB. The successful removal of the SN, the proportion of patients with lymph nodes on scintigraphy and the difference in success rate of the SLNB in patients having a guide wire *in situ* during the injection of the radiotracer between both protocols were compared using the chi square test, $p<0.05$ is considered significant.
The number of sentinel nodes seen on the pre-operative images and number of LN removed during surgery were compared using the independent sample T-test, $p<0.05$ is considered significant.

Results

The baseline characteristics in both groups were comparable, except for tumour morphology, see table 1. The visualization rate of the 1-day protocol was 61/67 (91%) and the visualization rate of the 2-day protocol was 55/56 (98%), p=0.087. In the 1-day protocol a mean number of 1.48 (range 0-5) nodes was seen pre-operatively versus 1.88 nodes in the 2-day protocol (p=.0.007). The rate of visualized nodes outside the axilla was similar in both protocols (see table 2).
The surgical success rate of the SLNB was 57/67 (85%) in the 1-day protocol, versus 51/56 (91%) in the 2-day protocol (p=0.311). A mean number of 1.64 (range 0-6) nodes was removed in the 1-day protocol, this was 1.61 (range 0- 4) for the 2-day protocol, p=.209.

Table 1: Baseline characteristics

Baseline characteristics	1-day protocol (%)	2-day protocol (%)	P
Number of patients	67	56	
Number of tumours	68	59	
Median age (years)	59	59.5	**.955**
Median size of primary (mm)	13	12	**.188**
Histology			**.006**
Ductal	53 (77%)	56 (95%)	
Lobular	5 (7.1%)	1 (1.7%)	
Ductolobular	8 (11,4%)	1 (1.7%)	
Mucinous	1 (1,4%)	1 (1.7%)	
Papillary	1 (1,4%)	0	
Quadrant tumours			**.119**
Retro areolar	5 (7.4)	10 (18)	
Lateral upper quadrant	35 (52.2)	26 (44)	
Medial upper quadrant	7 (10.2)	10 (18)	
Lateral lower quadrant	10 (14.7)	6 (11)	
Medial lower quadrant	12 (18.0)	5 (9)	

After finding LN's on pre-operative static imaging in the 1-day protocol a mean of 0.28 LN was not found during surgery (range 0-3), and in the 2-day protocol a mean of 0.41 LN (range 0-4) was not found (p=0.664). In the 1-day protocol 4 nodes and in the 2-day protocol 5 nodes were found assisted by patent blue only, this difference was not significant (p=0.73). The number of SN's found assisted by the radiofarmacon and/or patent blue in the 1-day protocol versus the 2-day protocol did not differ significantly (see table 2). In 1/6 (17%) of the non-visualized SN's in the 1-day protocol and 1/1 (100%) non-visualized SN's in the 2-day protocol the SN was found using the patent blue.

Forty-nine (73%) patients in the 1-day protocol showed no metastasis in the SN, 3 patients had isolated tumour cells (4.5%), 3 patients (4.5%) had micro metastases (i.e. <2 mm) and 12 patients (18%) showed macro metastases (i.e. > 2 mm). In the 2-day protocol 42 patients (76.4%) showed no metastases, 1 (1.8%) patient had isolated tumour cells, 3 patients (6%) had micro metastases and 9 patients (16.4%) showed macro metastases. The number of metastases in both protocols did not differ significantly (p=.975).

In the 1-day protocol the first 23 patients had a median dose of 80Mbq radiofarmacon. After excluding these patients, we found a successrate of the SLNB of 88%.

Furthermore in 29 of 67 patients (43%) treated according to the 1-day protocol a guide wire was *in situ* when injecting the nanocolloïd. In 15 of the 56 patients (26%) treated according to the 2-day protocol a guide wire was *in situ* when injecting the nanocolloïd. As is shown in table 3 the presence of a guide wire during injection of the radiofarmacon did not influence the success rate of the SLNB.

Table 2: Characteristics of the sentinel lymph node procedure

Sentinel node	1-day protocol (%)	2-day protocol (%)	p
Static lymphoscintigraphy:			**0.530**
- Axillary	59 (88)	53 (95)	
- Intra mammary	2 (3)	2 (5)	
- Internal mammary chain	9 (13)	4 (7)	
Mean number of nodes visualized	1.48	1.88	**0.007**
Visualization rate	61 (91)	55 (98)	**0.087**
Surgery:			**0.524**
- Hot not blue	23	18	
- Blue not hot	4	5	
- Blue and hot	31	29	
Mean number of nodes retrieved	1.64	1.61	**0.209**

Table 3 : Influence of the guide wire on the success rate of SLNB

Protocol	Guide wire (%)	No guide wire (%)	Total	p
1-day protocol	23/29 (80)	34/38 (89)	67	**0.247**
2-day protocol	14/15 (93)	37/41 (90)	56	**0.720**
Total	41	75		
p	**0.228**	**0.910**		

Discussion

In this retrospective comparison of two historical cohorts of patients who underwent lymphoscintigraphy using a 1- or a 2-day protocol we did not observe statistically significant differences in the identification and removal of the sentinel nodes. No significant difference in location of the SN was found between both protocols. Moreover the presence of a guide wire when injecting the radiofarmacon did not influence the success rate of the SLNB.

There are some weaknesses in this study. A relatively small number of patients were retrospectively included. Therefore some possible confounders could have influenced the results. In both protocols patients had a guidewire *in situ* during injection of the radiofarmacon. It has been suggested that the presence of a guide wire can disturb the regular draining pattern and cause leakage of the radiofarmacon past the guide wire[7]. In both groups described in our study the number of guide wires that were *in situ* during injection of the radiofarmacon was comparable. We could not demonstrate a negative influence of a guide wire placed intra-tumourally before injection of the radiofarmacon.

Next, the dosage of Tc nanocolloid injected in the 1 day protocol differed. It is suggested that a mean dose of at least 90 Mbq ^{99m}Tc nanocolloid is needed for adequate lymphoscintigraphy[8, 9]. Possibly the higher dose of radiofarmacon, after excluding the first 23 patients in the 1-day protocol, resulted

in the observed higher success rate of the SLNB as is suggested in literature[10]. Nevertheless, this study was nonrandomized and firm conclusions on this subject are not justified.
In order to facilitate an adequate injection volume in both groups the total injected volume was 0.5cc. Therefore, the dilution of the radiofarmacon was different in both protocols. Although there is no consensus on the volume and dilution in current literature, the difference in dilution could have influenced the drainage patterns and speed[11].
The patients treated according to the 1-day protocol underwent lymphoscintigraphic imaging up to 2 hours post injection. In literature imaging up to 4 hours post-injection is described. Possibly, the late imaging could increase the number of visualized nodes and thereby improve the success rate of the SLNB.
Finally, the success rates found in this study are lower than found literature, where 90-99% success is reported [12-15].
The strength of this study is that, to our knowledge, this is the first study on the comparison of success rates in the 1- and 2-day protocols in nonpalpable breast cancer. Furthermore, this study provides a concise answer to a practical question.
Studies performed so far included both patients with palpable and nonpalpable breast cancer. Although the protocols in these studies differed (i.e. particle size and injection region) they show no differences between the 1-day and 2-day protocols either[16-19].
As was proven in the past, the combination technique of both radiofarmacon pre-operatively and dye injection per-operatively is superior to the use of radiofarmacon or dye only[20, 21]. In our study, in the 1-day protocol in 4 cases (6%) and in the 2-day protocol in 5 cases (9%), the SN was found with the patent blue only. This stresses the importance of the combination technique. In cases of non-visualization pre-operatively, surgeons can still rely on the patent blue[22].
The site of injection of the radiofarmacon is open for discussion. In our protocol we injected the nanocolloid intra-tumourally, using either ultrasound or stereotaxis. As reported by others, injecting the radiofarmacon and the patent blue intra/peritumourally is as reliable as injecting subareaolarly23.
After intra-tumoural injection, the internal mammary chain LN's can be found more often and thereby alter the adjuvant therapeutic plan and possibly the long term survival[24, 25]. In addition, injecting intra-tumourally allows for lumpectomy with the radio-guided occult lesion localization (ROLL) technique in the same procedure[26-28].
The use of a 1-day protocol or a 2-day protocol is often a choice based on local preferences driven by logistic considerations. In a 2-day protocol multiple patients can be scheduled for lymphoscintigraphic imaging and sentinel node procedures in the operating room. The advantage of the 1-day protocol is that patients only require 1 hospital visit and the radiation dose is minimized. Lowering the dose of Tc nanocolloïd from 370 Mbq in the 2-day protocol to 120Mbq in the 1-day protocol is a threefold reduction of the radiation burden for both patients and physicians.
In conclusion, there is no significant difference in the success rate of the SLNB between patients diagnosed with a nonpalpable breast carcinoma treated in a 1-day protocol versus a 2-day protocol. In our hospital currently all patients diagnosed with a nonpalpable breast carcinoma are treated in day care using the 1-day protocol.

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Part 3 Sentinel node biopsy

Chapter 8

Axillary staging in breast cancer patients with exclusive lymphoscintigraphic drainage to the internal mammary chain

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Abstract

Purpose
To evaluate the need of axillary staging in breast cancer patients showing exclusive lymphatic drainage to the internal mammary chain (IMC)

Materials and methods
A total of 2203 patients treated for breast carcinoma in 3 participating hospitals between July 2001 and July 2008 were analyzed. Patients showing only drainage to the IMC on pre-operative lymphoscintigraphy were included. The number of harvested IMC-SN's, axillary SN's and metastases were recorded. Finally the follow up of this group of patients was analyzed.

Results
In 25/426 patients drainage was exclusively to the IMC. Exploration of the axilla resulted in the harvesting of blue SLN's in 9 patients (36%), and the retrieval of an enlarged lymph node in 1 patient. In 4 of the remaining 15 patients, an axillary lymph node dissection (ALND) was done. Lymph node metastases were found in 3 patients who had blue axillary SLN's and in 1 patient who underwent ALND. In the 11 patients who had no blue SLN and no ALND, no axillary recurrences were observed during follow-up (median 26 months).

Conclusion.
Proper staging of the axilla remains crucial, in patients showing exclusive drainage to the IMC. When no axillary node can be retrieved, ALND remains subject to discussion.

Introduction

The introduction of the sentinel lymph node (SLN) biopsy has renewed the interest in regional lymph nodes outside the axilla as a potential site of regional lymph node metastases. SLN's in the internal mammary chain are observed on preoperative lymphoscintigraphy in up to 30 percent of the patients[1-3].

Although harvesting these internal mammary chain SNL's is discussed by some authors, retrieval of them is advocated by others[4, 5]. Not only as a proof of principle but also because non-surgical treatment may be influenced by the presence or absence of metastases in these nodes, especially when no axillary SNL's are found[6, 7].

In most patients internal mammary SLN's are visualised together with axillary SLN's, while in 2.6 – 4% of these patients isolated lymphatic drainage to the internal mammary chain is seen, with no transport to axillary lymph nodes[7, 8]. While axillary lymph node dissection is commonly advised in patients when there are no axillary SLN's on the preoperative lymphoscintigraphy, there is no agreement on what to do when there is lymphatic drainage to the internal mammary chain without drainage to the axilla9. The question is whether solitary IMC-SN's are sufficient for staging, or if axillary dissection, SLN biopsy following patent blue injection, or a wait and see policy are required for adequate staging.

In the present study we analysed the case histories of patients who showing isolated lymphatic drainage to internal mammary SLN's on the preoperative lymphoscintigraphy. The aim of the present study was to address the question whether axillary staging should be done in these patients.

Material and methods

In this retrospective study, a cohort of 2203 consecutive patients diagnosed with cT1-2N0 breast cancer in three hospitals in the Middle Netherlands between July 2001 and July 2008 underwent surgery that included SLN biopsy as a staging procedure.

Lymphoscintigraphy protocols were different for the three hospitals (figure 1). In hospital A and B patients received a combination of peritumoural, intratumoural and subcutaneous injection of ^{99m}Tc nanocolloïd with an average dose of 70 MBq in a total volume of 0.6cc of physiologic saline. In case of a nonpalpable breast tumour the injection of the radiofarmacon was guided by ultrasound or stereotaxia. Surgery was done on the same day. In hospital C patients were injected with ^{99m}Tc nanocolloïd (80 – 550 MBq) in 0.5cc of physiologic saline intra and peritumourally guided by ultrasound or stereotaxia using a 1 or a 2 day protocol[10]. In all hospitals the nuclear physician used both static images and a gamma ray detection probe (Europrobe, PI Medical Diagnostics) to detect and mark the SLN. At the start of the operation 1-2cc of patent blue (Bleu patente´ V 'Guerbet') was injected peritumourally in all patients. In addition, in hospital A and B 1cc of patent blue was injected subcutaneously.

Sentinel lymph node retrieval

When preoperative lymphoscintigraphy showed axillary SLN's, these lymph nodes were retrieved using a gamma ray detection probe intraoperatively. A parasternal intercostal exploration was done to retrieve apparent SLN's in the IMC[2]. If no axillary SLN was visualised on the preoperative

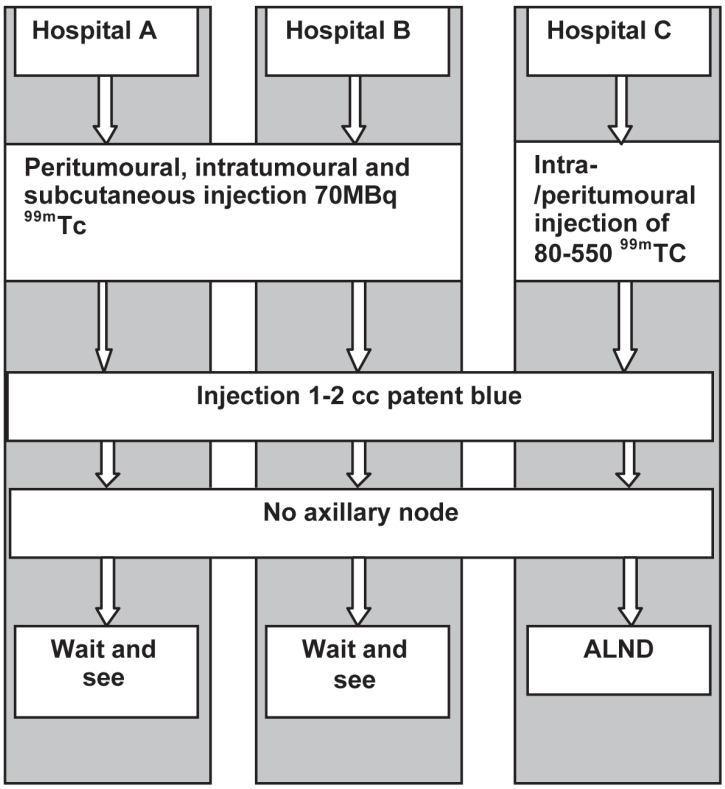

Figure 1: Sentinel node protocol for each participating hospital

lymphoscintigraphy, the axilla was still explored using the gamma ray detection probe and patent blue irrespective of the presence of internal mammary SLN's. Axillary exploration and subsequent retrieval of a blue and/or hot SLN was considered a reliable staging procedure. In case no blue node was retrieved from the axilla, surgical strategies were different in the three hospitals: in hospital C these patients underwent ALND, in hospital A and B a "wait and see" policy was common.
All SLN's were formalin fixed and 5 µm thick step sections were cut at 250 µm intervals for staining with haematoxylin and eosin (H&E) and immunohistochemical cytokeratin-8 staining. The size of the metastases found in the lymph nodes were defined as follows: macrometastases are metastases of 2.0mm or larger, micrometastases are larger than 0.2mm and smaller than 2.0mm and isolated tumour cells are smaller than 0.2mm in diameter[11].
The proportion of patients with isolated lymphatic drainage to the internal mammary chain was assessed. In the selection of patients with isolated lymphatic drainage tot the internal mammary chain the yield of the patent-blue guided axillary exploration was evaluated by describing the proportion of patients with blue sentinel nodes, the frequency of lymph node metastases when ALND was done and the occurrence of axillary relapses when no ALND was done.

Results

Lymphatic drainage to the IMC was observed in 426/2203 patients (19%), while exclusive IMC drainage was seen in 25/2203 (1.1%) patients (figure 2). Baseline characteristics of the 25 patients with exclusive drainage to the IMC are shown in table 1. In 16/25 (64%) patients the tumour was located in the upper inner quadrant.

In the patients with exclusive lymphoscintigraphic visualisation of SLN's to the IMC, these lymph nodes could be extirpated successfully in 16/25 patients (64%). In 12 of these 16 patients the node was hot and in 4 patients the node was hot and blue. Metastases were detected in the IMC-SLN's in 4 of the 16 patients (see figure 3): isolated tumour cells in 2 patients, micro metastasis in 1 patient and macro metastasis in 1 patient.

Table 1: baseline characteristics

Baseline characteristics	
Median age (years)	60 (48 – 78)
Tumour quadrant	
Upper outer	6 (24%)
Upper inner	16 (64%)
Lower inner	2 (8%)
Central	1 (4%)
Tumour histology	
Ductal	19 (76%)
Lobular	3 (12%)
Ductolobular	2 (8%)
Papillary	1 (4%)
Median tumour size (mm)	15 (5 – 80)
Oestrogen receptor expression	21 (84%)
Progesterone receptor expression	17 (68%)
Her2Neu over expression	5 (20%)
B&R:	
1	9 (36%)
2	8 (32%)
3	7 (28%)
Unknown	1 (4%)
MAI	5 (0-45)

MAI: Mitose Activity Index
B&R: Bloom and Richardson grade

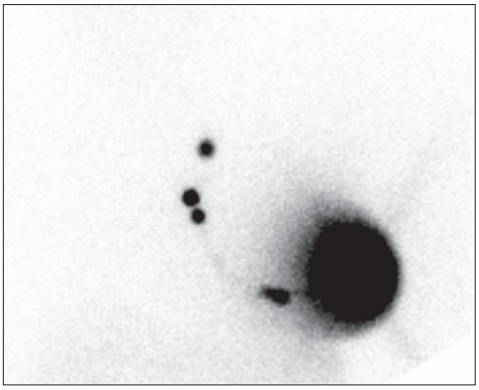

Figure 2: pre-operative imaging of IMC-SLN's

In addition to the exploration of the IMC, the axilla was explored for hot and/or patent blue containing SLN's. In 14/25 patients an additional nodes were retrieved from the axilla. A total of 10 patients underwent a successful SLN of the axilla: in 9 patients a blue lymph node was retrieved from the axilla, and in another patient an enlarged node was removed. The remaining 4 patients underwent ALND. Four of the 14 patients who underwent axillary staging had axillary lymph node metastases: in 3 patients who had SLN staging of the axilla and in 1 of the patients who had an ALND following a failed exploration for a blue SLN. Axillary lymph node involvement was categorized as: macrometastases (n=1), micrometastases (n=2) and isolated tumour cells (n=1) (table 2). Additional axillary staging by SLN biopsy or ALND in patients with exclusive drainage to the IMC on the preoperative lymphoscintigraphy resulted in an increase of the frequency of regional lymph node metastases from 16 to 28 % (4/25 versus 7/25 patients). One patient had axillary metastases concomitant with IMC metastases. In 2 patients with axillary metastases, postsurgical treatment was adjusted: adjuvant chemotherapeutic treatment and 1 patient chose not to receive additional chemotherapy (table 2).

Table 2: sentinel node and tumour characteristics

Patient	Age (y)	Tumour size (mm)	Location metastasis	Grade metastasis	Recurrence	Additional treatment
1	60	70	Axillary	Micro	No	Chemotherapy
2	59	9	Axillary	ITC	Yes	No
3	57	10	Axillary	Micro	No	No
4	73	19	IMC	Micro	No	No
5	62	16	IMC	ITC	No	No
6	60	25	IMC	ITC	No	No
7	58	16	Axillary and IMC	Macro	No	Chemotherapy

The overall median follow up was 26 months (4 – 82). A total of 3/25 (12%) patients died after a median of 53 months (21 – 72). One of these patients had undergone removal of an axillary node containing isolated tumour cells ITC. This patient received loco regional radiotherapy on the IMC, no axillary dissection was performed. In another patient only an IMC-SN was harvested, without tumour cells and no axillary nodes were removed. These 2 patients died due to progression of the breast carcinoma; one suffered bone metastases and the other suffered skin recurrence and distant metastases to liver and lungs. The third patient showed micro metastases in the IMC, no axillary dissection was performed and loco regional radiotherapy was given on the IMC. This patient was diagnosed with a simultaneous oesophageal carcinoma and died due to progression of this carcinoma. In none of these patients axillary recurrence was observed.

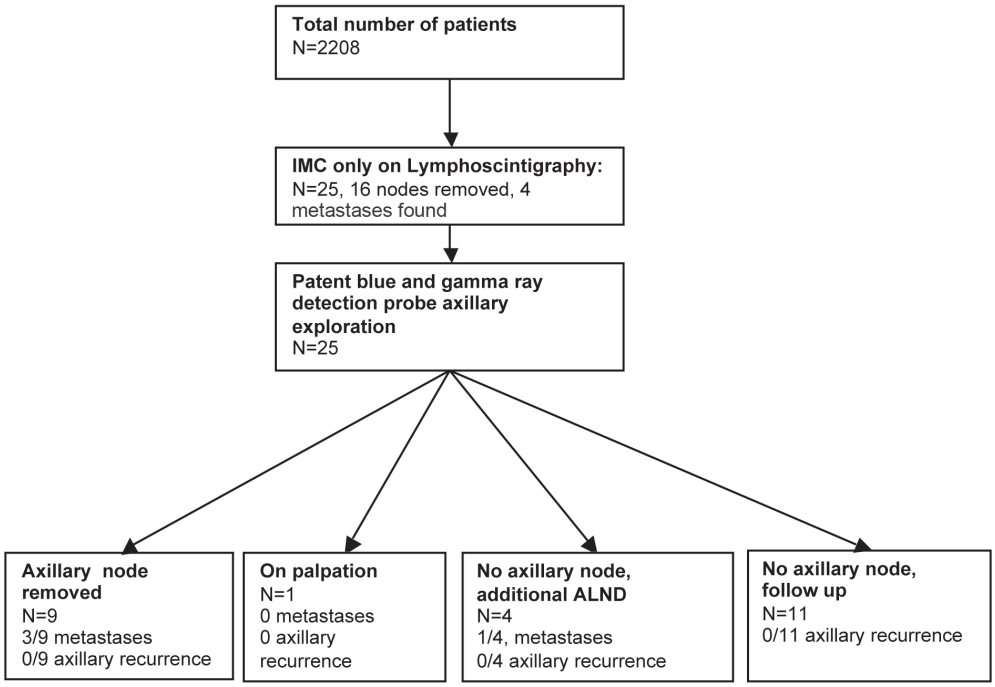

Figure 3: flowchart

Discussion

Although the utility of harvesting internal mammary chain SNL's is discussed by some authors, we strongly believe that there is a rationale for retrieving these nodes. Tumour staging will be more accurate after histological judgement of all sentinel lymph nodes, especially in the absence of axillary SNL's, which might influence adjuvant treatment[2, 6, 7]. However, we realize that this debate will continue as long as there are no reliable results of randomized trials regarding the treatment principle of intramammary chain metastases.

In this large retrospective cohort of patients who underwent SLNB as part of breast cancer surgery, 1% had exclusive lymphoscintigraphic drainage to the IMC. Axillary staging revealed metastases in a clinically relevant and additional proportion of patients.
We realize that the retrospective design of the study has its drawbacks. Despite this, it is this one of the largest studies evaluating this important clinical dilemma[6, 7].
The type of nuclear protocol is of influence on the number of nodes found in the IMC. After intra- or peritumoural injection of the radiofarmacon, the number of nodes found in the IMC is higher than after subcutaneous injection. This can be explained by the differences in drainage patterns of the breast. Tumours lying deeper in the breast tend to drain more often to the IMC than tumours lying superficially. The deep and the superficial drainage system in the breast are not connected. So when injecting only subcutaneous, the deep drainage system is missed and the SLN's connected to the deep drainage system are missed as well[12]. In this study all patients had an intra- or peritumoural injection, in hospital A and B in combination with a subcutaneous injection, and all patients underwent axillary exploration, although in not all of the cases a SLN could be harvested. Furthermore, it is known that tumours in the upper inner quadrant of the breast tend to drain more often to the IMC[13, 14]. Indeed, most of the patients described in this study had tumours located in the upper inner quadrant of the breast.
Despite lymphoscintigraphic absence of axillary drainage, axillary staging detected lymph node metastases with an at least similar frequency as SLN biopsy revealed in the IMC node. The observed absence of lymphoscintigraphic drainage to the axilla could not be attributed to blockage of this path by massive axillary lymph node involvement as is suggested by others[7]. Instead, the extent of metastatic lymph node involvement was comparable and limited both in the axilla and the IMC, as is described by others[15, 16]. Furthermore the presence of lymph node metastases in the axilla and IMC was not interdependent. Hence, additional axillary staging led to an increased overall frequency of regional lymph node metastases.
As described earlier, younger age could be of influence on the occurrence of the detection of SN in the IMC, in this study we could not confirm this[2]. Tumour stage (I-II) is also described as being a factor in identifying IMC-SLN's and tumour positivity in these nodes. Indeed the majority of the patients described in this study had stage I-II breast cancer. One of the patients had a tumour of 8 cm and another of 7 cm on histopathology. According to the Dutch guidelines patients with tumours clinically smaller than 5 cm (T2 tumours) undergo SNB and tumours larger than 5 cm undergo primary ALND[17]. Both these patients had a secondary ALND in both cases showing no additional metastases.
In this study in nine patients the IMC-SLN could not be harvested, others described a conservative approach to harvesting IMC-SLN's as a limited number of patient would benefit from it and the possible morbidity of harvesting IMC-SLN's should weigh against the benefit. We demonstrated that performing the IMC-SLN did not change the adjuvant treatment in most cases, so indeed a critical approach and selection of patients in who the IMC-SLN can be performed is justified[5].
The retrieval of blue SLN's from the axilla that contain metastases demonstrates the complementary aspect of patent blue and radioactive tracer injection when performing SLNB in breast cancer patients. In that respect, our findings are in line with the observation of others[6, 7, 18]. Van der Ploeg et al performed patent blue guided axillary exploration in a group of 82 patients with exclusive lymphoscintigraphic drainage to the IMC and blue SLN's were identified in 62 of these patients.

We confirm the need for additional axillary staging in patients with exclusive lymphoscintigraphic drainage to the IMC[7, 19].

Optimal staging of breast cancer patients becomes ever more important. Even ITC's and micrometastases in regional lymph nodes may have a prognostic effect and the indications for adjuvant chemotherapy will be expanded to these categories of patients[20]. In the present study population of patients with no axillary drainage on lymphoscintigraphy 3 patients were proposed to receive adjuvant chemotherapy because of additional metastases in the axilla.

Whether or not to perform an axillary dissection when exploration for a blue SLN is unsuccessful is more complex to answer. Some authors argue that in case of successful retrieval of IMC-SLN's, axillary exploration for blue SLN's is a sufficient means of staging. In their view, when exploration of the axilla does not reveal a blue SLN, there is no lymphatic drainage to the axilla and an ALND may be omitted safely[7]. In line with their results, we observed no axillary recurrences in the patients in the "wait and see" group. However, our data can be used to support the "ALND" policy too, since axillary lymph node metastases were found in one of the patients in whom an ALND was performed when no axillary SN could be indentified. Furthermore, the survival and recurrence rate of the patients in this study are comparable to literature[3, 7, 16].

In order to reach consensus on whether an additional ALND is needed when no other than IMC-SLN's are found, more data are needed. As a prospective randomized trial on this subject probably will not be feasible we encourage other authors to present their data likewise.

In conclusion, when preoperative lymphoscintigraphy shows exclusive lymphatic drainage to the internal mammary chain, proper staging should include exploration of the axilla for blue SLN's too. Metastases can be found in a relevant additional proportion of patients and postsurgical treatment could be adjusted accordingly. Performing an ALND when no axillary node can be retrieved remains subject to debate.

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Part 4 Minimally invasive treatment

Chapter 9

Minimally invasive ablative therapies for invasive breast carcinoma: An overview of current literature

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Abstract

Background
Minimally invasive treatment may be an alternative to breast conserving surgery.

Methods
A structured pubmed, embase, Cochrane and web of science search was performed. Endpoints studied were feasibility, completeness of ablation, timing of the sentinel node (SNB), imaging modalities and treatment related complications.

Results
A total of 24 articles were retrieved, the level of evidence varied (2B-4). Mainly fase II studies with a treat and resect protocol were analyzed. Up to 100% completeness of ablation was reported for Radiofrequency ablation (RFA), cryosurgery and Focused ultrasound (FUS). The oncologic results need further evaluation. Dynamic enhanced MRI seems to be the best method for monitoring treatment response (77% sensitivity, 100% specificity). Ultrasound is suitable for guiding probes into the tumour. There is no consensus on the timing of sentinel node biopsy (SNB).

Conclusions
All studies on minimally invasive ablative modalities published so far show that these techniques are feasible and safe. At this stage only T1 tumours should be ablated in a clinical trial setting; it is unclear which of the modalities is most suitable.

Introduction

Breast cancer is the most frequently occurring malignant disease in Western women with a lifetime risk of 1/9 women[1]. Due to the nationwide implementation of screening for breast cancer, the proportion of small carcinomas found at the time of treatment has increased[2]. In the management of small breast carcinomas, breast conserving therapy (BCT; i.e. local excision with adjuvant radiation therapy) is the standard of care[3]. However, the cosmetic outcome of BCT is often disappointing, caused by the resection of the tumour with a margin of 1 cm normal breast tissue and post operative radiation[4]. Furthermore, BCT carries a relatively high morbidity rate mainly due to bleeding (up to 11%), infections (3.63%) and only 81% is satisfied with the cosmetic result[5-7]. In case of surgical complications, adjuvant treatment is often delayed which may unfavourably affect the outcome of the patient[8]. Therefore, it would be desirable to have a minimally invasive treatment that is equally effective but offers fewer complications and a better cosmetic outcome.

Such a treatment should efficiently and completely destroy the tumour locally and requires exact visual localization of the tumour within the breast. Cryosurgery, Radiofrequency ablation (RFA), Laser Induced Thermal Therapy (LITT), microwave ablation and Focused Ultrasound (FUS) are the currently most widely used minimally invasive procedures[9-13]. All but one[14] of the studies published so far are based on a treat and resect protocol: ablation, followed by surgery.

Tissue injury by cryosurgery is described in the "two-step" theory of Mazur[15]. First, ice forms in the extracellular fluid, whereas the intracellular fluid remains unfrozen. As the ice forms, the osmolarity of the extra cellular fluid increases. Water flows out of the cell to equilibrate this osmolarity, in turn increasing the osmolarity of the intracellular fluid and causing chemical damage to the cell. The degree of chemical damage can be related to the amount of time the cell is exposed to this damaging condition. Eventually, as the cooling rates increase, the intracellular super cooling results in intracellular ice crystals. This is the second factor of damage because intracellular ice is extremely lethal to cells. Complete cell destruction can be achieved with two freeze/thaw cycles at 1ºC/min resulting in end-temperatures lower than -40ºC.

With RFA, a high frequency alternating current flows from uninsulated tips into the surrounding tissue. The tissue ions attempt to follow the change in direction of the alternating current and as a result of ionic agitation, frictional heating results. This causes thermal coagulation and protein denaturation, destroying the tissue[9]. LITT requires a laser fibre to guide the light energy directly into the tissue to be treated. Upon absorption in the tissue, heat is produced inducing lethal thermal injury comparable to RFA. Prolonged heating of tumour cells to 45–55°C leads to cell death, whereas short exposure of cells to temperatures that exceed 60°C causes irreversible cell damage and death from protein denaturation, inhibition of protein synthesis, breaking of chemical bonds in DNA and RNA molecules, and loss of integrity in lipid bilayers[16-18]. Microwave ablation refers to an oscillating electrical charge that due to interaction with water molecules causes the electrical charge of the molecules to flip back and forth. Because of the movement of the water molecules the temperature rises and causes thermal damage to the cells[19]. Focused ultrasound (FUS) is another method of thermal tissue destruction, based on an extra-corporal source of ultrasound to target specific tissue without damaging the overlying tissue. The ultrasound beams (1.5 MHz) are generated by the ultrasound transducer and penetrate soft tissue up to 20 cm inside the body. The beams can be focused on tissue volumes with dimensions of 1 to 2 cubic millimeters. Due to rapid energy deposition a rapid rise in temperature is achieved[20].

A review of the literature was performed to assess the current status regarding feasibility and accuracy of these different methods in ablating breast cancer.

Methods

A literature search on breast cancer and minimally invasive treatment was done using the electronic search engines Pubmed, embase, cohrane and web of science. All available synonyms on breast cancer, cryosurgery, RFA, LITT and FUS were identified and combined using AND and OR. All available original, clinical (i.e. phase I-IV) articles were included. Animal studies were excluded. Articles were screened on title and abstract. Full text copies of all identified articles were obtained. Studies in languages other than English were excluded.
The following data were extracted from the selected studies: completeness of ablation, TNM classification of the included patients, application and type of image guidance, timing and technique of the sentinel node biopsy (SNB), and complications of the procedure. Over a 170 articles were found. After exclusion based on type of article or differences in therapy or patients criteria a total of 24 articles were consistent with the search criteria. The results were analysed and compared.

Results

Cryosurgery
Four cryosurgery studies were found involving both pilot studies and feasibility studies (table 1,2)[12,21-23]. Complete ablation of the tumour ranged from 52%-100% confirmed by histopathology. The size of the invasive breast carcinomas treated with cryosurgery varied from T1–T3. Cryosurgery was followed by surgical excision 5 days - 4 weeks later.
The SNB was done mostly after the cryosurgery, except for 1 study that used complete axillary dissection after cryosurgery[21].
US guidance was used in three studies with a success rate of 100%[23], 83%[12] and 78%[22], respectively. It was reported that during ablation, US only shows the surface of the ice ball and that the area behind the surface is not made clearly visible, making accurate monitoring of that area difficult[12]. No figures concerning sensitivity or specificity of US have been reported thus far. Near real time MRI guidance in an open configuration was used in one of the studies. In 96% of cases, MRI predicted the cryosurgery results correctly, but again no figures concerning sensitivity or specificity were noted[21]. No serious complications were seen. One of the studies mentioned occasional skin burn and a sensation of heaviness after the cryosurgery, but no figures were noted[21].

Radiofrequency Ablation (RFA)
The eight RFA studies were pilot and feasibility studies performed under US guidance (table 3, 4). The percentage of histologically confirmed complete ablation using nicotinamide adenine dinucleotide (NADH)–diaphorase staining, varied from 64-100%[9,14,18,24-28].
All studies included T1-2 invasive breast carcinomas except for one study that included only T3 tumours. In that study, tumours were only partially ablated[26]. In five studies after the RFA treatment the lesions were surgically removed[9,18,24-26]. In two studies, surgery was performed 1-3 weeks after

the RFA9,25 and in 3 studies the surgery was performed immediately after the ablation[18,24,26]. In the remaining three studies no post ablation surgery was planned. In two of these studies 3 and 4 inoperable elderly patients were included with T1-T2 core biopsy proven invasive breast cancer[27,28]. Ultrasound was used to guide the probe and monitor the ablation. Post ablation, ultrasound and MRI images were acquired and percutaneous biopsies were taken to evaluate completeness of ablation. In this study after 18-36 months follow up, local recurrence occurred in 1 patient. The third study included 52 patients with T1 tumours and did not perform surgery after ablation; cytology was acquired three to four weeks post ablation. One to three months after ablation MRI assessment was done. The average follow up time was 15 months, patients were examined with palpation and US was performed[14].
SNB was performed both pre- and post RFA, positive axillary nodes were found in 23% and 20%, one study did not mention the status of the SNs. Two studies did not describe the SNB, and in two

Table 1: Overview of studies on the value of cryosurgery for ablation of breast cancer

Ref.	No. patients	Tumour characteristics	Sentinel node	Image guidance	Complete ablation (%)	Complications
23	29	Ultrasound-visible primary invasive breast cancer ≤2.0 cm	Sentinel node biopsy after cryosurgery	Ultrasound	100 in patients with a tumour <1.0 cm, or 1.0-1.5 cm without a DCIS component	None mentioned
21	25	Invasive breast carcinomas <7.0 cm	Complete axillary dissection after cryosurgery	MRI	52	Minimal skin burn at probe entry site, sensation of heaviness in treated breast
22	9	Invasive ductal carcinoma, invasive colloid carcinoma <1.8 cm	Sentinel node biopsy after cryosurgery	Ultrasound	78	None mentioned
12	29	Invasive carcinomas <4.0 cm	Sentinel node biopsy after cryosurgery	Ultrasound	83	Pain

Table 2: Quality of evidence of the studies on cryosurgery

Ref.	Level of evidence	Study design	End points
23	2B	Individual cohort study	Completeness of ablation, treatment-related complications
21	3B	Individual case control study	Feasibility, safety, effectivity, and predictability
22	3B	Individual case control study	Correlation of mammography and ultrasonic findings with histopathology
12	2B	Individual cohort study	Feasibility, efficacy, and safety

further studies axillary dissection was performed routinely. In two studies pre- and post ablation MRI scans were performed. No figures concerning sensitivity and specificity were provided. Apart from an abcess requiring surgery[27] only minimal complications due to the RFA treatment were observed: skin burn (4.2%), breast ecchymosis (no figures mentioned) and mild discomfort (all patients). In one study Doppler US and contrast medium injection (DUPC) was used. DUPC showed 70% specificity and 20% sensitivity for detecting residual tumour tissue after ablation compared to histology.

Laser induced thermal therapy (LITT)

The studies on Laser induced thermal therapy (LITT) were all feasibility and pilot studies (table 5, 6)[10,29-32]. Each of these studies included more patients (up to 54) than the studies applying other minimally invasive treatment modalities for breast carcinoma. T1-T3 tumours were included in these

Table 3: Overview of studies on the value of radiofrequency ablation for ablation of breast cancer

No. patients	Tumour characteristics	Sentinel node	Image guidance	Complete ablation (%)	Complications	Complications
5	Proven T3-T4 breast cancer or tumours >5.0 cm	Axillary dissection after RFA	Ultrasound	80	None mentioned	None mentioned
26	T1-T2 tumours <3.0 cm	Axillary dissection after RFA	Ultrasound	96	1 patient: full-thickness skin burn	Minimal skin burn at probe entry site, sensation of heaviness in treated breast
22	Proven T1 carcinomas	Depending on patient's wish, SNB or axillary dissection after RFA	Ultrasound	64	Skin burn, mild discomfort	None mentioned
10	Proven T1 carcinoma <2.0 cm	Not mentioned	Ultrasound, pre- and post- ablation MRI	89	Minimal breast ecchymosis	Pain
20	Invasive breast cancer ≤2.0 cm	Injection technetium-labeled sulfur colloid before RFA, SNB after RFA	Ultrasound	100	None mentioned	
3	Proven T1 ductal carcinomas	Not assessed	Ultrasound	Unclear	None mentioned	
4	Proven invasive carcinoma T1	Not mentioned	Ultrasound	75	Abcess[a]	
52	Both proven T1 and localized breast carcinomas	Preablation SNB	Ultrasound	Unclear[b]	Skin burn	

SNB = sentinel node biopsy; RFA = radiofrequency ablation
[a]After 9 months
[b]Only cytologic biopsy was performed after the procedure

studies. Complete ablation of the breast carcinomas was achieved in 0-98% of the patients and in two studies completeness of ablation was not mentioned[29,30]. All except one of the studies used H&E staining to determine the extent of coagulation[10,29,30,32], one study also used NADH staining[32](fig 2). Surgery followed 0-70 days after LITT.
In two studies, axillary dissection was mentioned with a 5% axillary lymph node involvement in one study, the remaining three studies did not mention SNB or axillary dissection. In four of the studies a diode 805 nm laser was used for ablating the tumours and one of the studies a 1064 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) pulsed wave laser (figure 1)[29]. In two of the studies the laser fibre tip was pre-charred in order to establish larger necrosis diameters[31,32]. In two of the five studies, the needle was placed in the tumour under stereotactic guidance and during the procedure monitoring images were taken[10,30]. No figures however were presented concerning sensitivity and specificity. In two studies real time US guidance was used and MRI images were made before and after LITT. One study showed correlation of MRI vs. histopathology (correlation for laser burn diameter was 0.80 and for residual tumour 0.86) but no correlation between US and histopathology was assessed[32]. The other study was performed under US guidance, but no correlation between US and histology[31] was found and too few data were available to draw any conclusions on the value of MRI or CT monitoring[31]. Apart from small skin burns (3.7%) a gaseous rupture of the tumour has been noted as a serious complication of LITT.

Focused Ultrasound (FUS)

So far four clinical studies have been performed on FUS (table 7, 8)[13,33-35]. A randomised clinical trail included 48 women with biopsy proven breast cancer (T1-2)[13]. In 23 women, FUS was performed before modified radical mastectomy, and in 25 patients modified radical mastectomy was performed without FUS (control group). A 100% completeness of ablation including a 1.5-2.0cm margin of normal breast tissue histopathologically confirmed by H&E and immunohistochemistry (proliferating

Table 4: Quality of evidence of the studies on radiofrequency ablation

Level of evidence	Study design	End points
3B	Individual case control study	Lesion size, tumour vitality, and margin between ablated and nonablated tissue
2B	Individual cohort study	Completeness of ablation, safety, and treatment-related complications
2B	Individual cohort study	Completeness of ablation, technical success, marginal clearance, skin damage, patient reports of pain, and procedural acceptability
2B	Individual cohort study	Patient tolerability, size of coagulation zone, and correlation of MRI with histopathology
3B	Individual case control study	Feasibility and safety
4	Case series	Feasibility and efficacy
4	Case-series	Feasibility and efficacy
4	Case series	Safety, local control, and cosmesis

cell nuclear antigen, cell adhesion molecule CD44v6 and matrix metalloproteinase -9) was found. Severe damage to the vessels and nuclei was seen. 92% of all patients included had one or more positive axillary nodes. Apart from skin burn in one patient (4.3%) no serious complications were reported.
The second (phase II) study found a completeness of ablation of 24% confirmed by H&E staining. The aim of this study was to assess the value of DCE-MRI to detect residual tumour after ablation[34]. Tumours <3.5 cm were included. DCE MRI showed 77% sensitivity and 100% specificity for detecting residual tumour. The difference in grey scale was consistent and conformed to the extent of coagulative necrosis induced by FUS. The third study included 30 patients with a core biopsy proven invasive ductal tumour ≤ 2.5cm; no lobular tumours were included[33]. The procedure was guided using contrast enhanced MRI. Patients received breast conserving surgery or mastectomy and axillary dissection 5

Table 5: Overview of studies on the value of laser-induced thermal therapy for ablation of breast cancer

No. patients	Tumour characteristics	Sentinel node	Image guidance	Complete ablation (%)	Complications
44	Unknown	Not mentioned	Ultrasound//CT/ MRI	98	None mentioned
20	Proven T1–T4 tumours (median diameter = 2.2 cm)	Axillary dissection after LITT	MRI	0	None mentioned
35	Proven T1-T3 invasive carcinoma (1-6 cm)	Not mentioned	Ultrasound	71% local tumour control	Gaseous rupture of tumour
40	Proven T1 tumours. (0.5-2.3 cm)	Not mentioned	Stereotactically guided	Not mentioned	None mentioned
54	Proven T1-T2 invasive and *in situ* (0.5-2.3 cm)	Axillary dissection after LITT	Stereotactically guided	70	small (4 × 3 mm) skin burns

LITT = laser-induced thermal therapy

Table 6: Quality of evidence of the studies on laser-induced thermal therapy

Level of evidence	Study design	End points
3B	Individual case control study	Treatment-related complications, thermal laser effect, method of treatment monitoring
3B	Individual case control study	MRI correlation with histopathology after treatment (i.e., extent of necrosis and residual tumour)
3B	Individual case control study	Tolerability and effectiveness
2B	Individual cohort study	Pathologic changes after LITT, tumour tissue vitality
2B	Individual cohort study	Completeness of ablation

to 23 days after the procedure. In 53.7% the ablation was histologically complete (confirmed by H&E staining). DCE MRI was used for pre treatment planning and treatment guidance using closed loop feedback and temperature monitoring. No figures are given concerning the accuracy of the monitoring.

The fourth (phase I) study included 10 patients with biopsy proven infiltrating breast cancer <3cm in diameter[35]. The procedure was MRI guided, no figures concerning the accuracy were presented. Seven to ten days after the procedure all patients underwent lumpectomy and axillary sampling. After histopathological evaluation (method unclear) 20% of the treated tumours were completely ablated. In one case skin burn occurred.

Table 7: Overview of studies on the value of focused ultrasound for ablation of breast cancer

No. patients	Tumour characteristics	Sentinel node	Image guidance	Complete ablation (%)	Complications
17	Small invasive carcinomas <3.5 cm	Not mentioned	DCE MRI	24	None mentioned
23	Proven breast cancer (T1–T2) ≤6 cm	Axillary dissection after FUS	Ultrasound	100	Mild local pain, warmth and sensation of heaviness, and minimal skin burn
10	Proven invasive breast cancer (T1–T2) <3 cm	SNB after FUS	DCE MRI	20%	Local pain and skin burn
30	Proven invasive breast cancer (T1–T2) ≤2.5cm	Axillary dissection	DCE MRI	53.5	Pain, hyperemia, skin burn

LITT = laser-induced thermal therapy; SNB = sentinal node biopsy; FUS = focused ultrasound

Table 8: Quality of evidence of the studies on focused ultrasound ablation

Level of evidence	Study design	End points
3B	Individual case control study	DCE-MRI correlation with histopathology after treatment
2B	Individual cohort study (low-quality randomized controlled trial)	Efficacy, safety, and feasibility
2B	Individual cohort study	Feasibility and efficacy
2B	Individual cohort study	Efficiency, safety, and reproducibility

Microwave ablation

So far 3 studies on this subject were published[11,36,37](table 9, 10). A pilot safety (phase 1) study included 10 patients with a core needle biopsy proven invasive breast carcinoma (T1-T3 tumours)[11]. Of the 8 patients responding 82-97% tumour cell kill was found, confirmed by M30 immunohistochemistry. Image guidance was performed using US. 5-27 days after treatment patients underwent mastectomy. No figures concerning SNB are mentioned. Both skin flap necrosis (3 patients) and skin burn (1 patient) were seen. The same group also published another article, 21 patients with a T1-T2 invasive breast carcinoma underwent microwave ablation[36]. In 68% of the patients histologic evidence of tumour necrosis was present. The focus of this study was to find the SN after ablation. In 91%, the SN was found, and in 42% axillary metastases were detected. No figures concerning procedural complications were given.

Finally, this group published a dose escalation study[37]. 25 patients with a core needle biopsy proven invasive breast carcinoma (T1-T2 tumours) were included. US provided image guidance; there was no correlation between clinical/ultrasonographic size changes and pathologic tumour response. In 68% of the cases there was evidence of pathological response using H&E staining. In 2 cases complete ablation was reached; these patients received the highest temperature dose. Complications mentioned were mild pain during treatment, skin burn and short lived erythema of the skin

Table 9: Overview of studies on the value of microwave ablation for ablation of breast cancer

No. patients	Tumour characteristics	Sentinel node	Image guidance	Complete ablation (%)	Complications
10	Proven invasive breast cancer T1-T3	Not mentioned	Ultrasound	0	Skin burn
21	Proven T1-T2 invasive breast cancer	SNB after microwave ablation	Not mentioned	68% histologic evidence of tumour necrosis	Not mentioned
25	Proven T1-T2 invasive breast cancer	Not mentioned	Ultrasound	8	Mild pain, short-lived erythema, and 1 case of skin burn

Table 10: Level of evidence of the studies on microwave ablation

Level of evidence	Study design	End points
3B	Individual case control study	Tumour size reduction correlated with thermal dose and safety
2B	Individual cohort study	Succes rate of sentinel node biopsy after treatment
3B	Individual case control study	Safety and needed thermal dose for complete tumour ablation

Discussion

Minimally invasive ablative therapy for small invasive breast carcinoma could be a successful next step in breast conserving therapy. This emerging treatment modality may come with great benefits regarding patient comfort and cosmetic results. Currently, the major issues to be solved with all of the described techniques are real time imaging, determining the completeness of ablation without definitive histology, the place of the SNB, and the cosmetic outcome.

The importance of real time imaging during the ablation procedure lies in the fact that for complete tumour destruction, good images of the tumour area are required before, during and after therapy. Although in some select cases (i.e. elderly, inoperable patients) RFA ablation could be considered as sole therapy, there is at this stage no significant evidence that surgery can be safely omitted in a curative setting, where surgery remains essential to evaluate the ablated tissue histopathologically for margin status with regard to invasive cancer and ductal carcinoma *in situ* (DCIS) to set the indication for further local treatment. Patients with extensive DCIS often require re-excision or mastectomy. After breast conserving surgery patients will have radiotherapy. If surgery is omitted after ablation, it is unclear if the margins are free of invasive carcinoma and DCIS and whether patients require re-ablation, re-excision or a boost of radiotherapy on the ablated tissue. At least, radiotherapy should be given in this situation, and a local boost may be an option in all these patients to prevent recurrence.

Alternatively, it may be advisable to exclude patients with signs of extensive DCIS (i.e. extensive DCIS on the core biopsy or extensive micro calcifications on the mammography) from ablation therapy, as well as patients with invasive lobular cancer that are more difficult to radically remove due to their diffuse growth pattern. The improvement of imaging techniques to detect the extent of ductal *in situ* and lobular carcinomas would be an important step in the feasibility of local ablative therapies. US is useful to guide needle and fibre-tip placement within the tumour in the different studies that have been performed so far. Although monitoring the occurrence of gas bubbles in the treated area can give an indication of the progress of the procedure, US is not accurate enough to measure the volume of the induced tumour necrosis[30-32]. In thermal treatment of breast carcinomas, significant ultrasonographic shadowing from this hyper echoic thermal lesion makes it difficult to measure the size of the area of coagulative necrosis[18,24,26]. Furthermore, no correlation could be found between US and histology. Real time monitoring therefore seems to be difficult using US. Contrast enhanced US can visualise blood flow in the tumour and therefore may give a better indication of tumour destruction[38].

MRI could be a more reliable modality in monitoring tumour destruction with minimally invasive treatment than US[9,21,32,34]. With MRI, a correlation for the coagulated diameter of 0.80 and a correlation for residual tumour of 0.86 was found[32]. DCE-MRI showed good image guidance for FUS treatment of breast carcinomas. Data acquired with the DCE-MRI correlated excellently with the histopathologic findings. A sensitivity of 77% and a specificity of 100% was found for finding residual tumour[32]. DCE-MRI with real time thermal mapping may well become the best modality to guide and monitor ablation of early breast cancer. MR thermal mapping is mostly based on proton resonance frequency of tissue water. An excellent linearity, near tissue independency and good temperature sensitivity is found[39].

As one of the aims of minimally invasive treatment of T1 breast tumours would be to avoid breast surgery. To this end, it is essential that tumours are completely ablated to avoid recurrence due to

outgrowth of residual vital tumour cells. The four studies regarding FUS all included T1-T2 tumours and yet provided contra dictionary results: 20%, 24%, 53.5% and 100% completeness of ablation[13,33,34].

In one of the studies treatment length of 120 minutes is mentioned[35]. One of the main issues to be solved for FUS is the long treatment length needed to completely ablate tumours. In order to apply FUS in clinical practice it is essential that treatment length is reduced.

In liver metastasis in 80% of the treated patients surface cracking of the iceball causing heamorrage is mentioned as a serious complication of cryosurgery[40]. None of the studies on cryosurgery in breast cancer mentioned these complications. To our opinion this could be a potential hazard in the future.

In all studies, the best results seem to be obtained in T1 tumours (see tables 1-5). Clearly, minimally invasive treatment should be confined to patients with small unifocal breast tumours (T1). It has to be noted that when minimally invasive treatment is performed, all essential prognostic and predictive primary tumour characteristics (including mitotic index, histologic grade and ER/PR/HER-2 receptor status) should be performed on the pre-operative core biopsy which must therefore be large enough (preferably at least 14 gauge) to allow this[41].

Not all studies performed so far accurately assessed vitality of tumour cells. H&E staining is not reliable enough to this end, as are most other immunohistochemical stains including proliferation markers which remain positive after successful ablation. According to our experience, NADH staining is most accurate. This requires however frozen material, which must be taken before fixation.

Determination of the status of the SN in breast cancer is important for further treatment. Possibly lymph drainage is disturbed after local tumour ablation, so it is important to assess the optimal timing of the SNB. In the studies reviewed the SNB was done both pre and post ablation. Some studies performed axillary dissection on all patients included. In 1 study the success rate of finding the SN after ablation was determined. In 91% of the cases the SN was found. Whilst the authors claim this is within the normal range, the range found in current literature is 95-100%[42,43]. In our vision performing the SNB before the ablation is most reliable, because the lymph drainage is not disrupted by local treatment of the tumour.

At this stage the different techniques have shown to be feasible, but there is no long term follow up. Before including minimally invasive therapy as standard care, larger patient series with a long term follow up are required. A multi disciplinary approach is essential for the success of the treatment. Radiologists, surgeons and pathologists should work closely together in order to get the best results.

In conclusion, all except one study on minimally invasive treatment modalities published so far are phase I - II studies that show that these techniques are comparably feasible and safe. It appears to be advisable to designate only unifocal T1 tumours to be ablated without signs of extensive DCIS. The data reported presently do not allow any firm conclusions regarding efficacy of either technique. At this stage only in select cases surgery can be omitted. These modalities should be further assessed in the context of large clinical trials.

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Part 4 Minimally invasive treatment

Chapter 10

Ultrasound guided laser induced thermal therapy for small palpable invasive breast carcinomas A feasibility study

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Abstract

Background and purpose
The next step in breast conserving surgery (BCS) for small breast carcinomas could be local ablation. In this study the feasibility of ultrasound guided laser induced thermal therapy (LITT) is evaluated.

Methods
Patients with large core needle biopsy proven invasive, palpable breast carcinoma (clinically ≤2cm) underwent ultrasound guided LITT, followed by surgical excision. Completeness of ablation was determined using both haematoxylin&eosin (H&E) and nicotinamide adenosine diaphorase (NADH) staining.

Results
Fourteen patients completed the treatment. The mean histological tumour size was 17 mm (range 8-37 mm); 6/14 tumours were histologically larger than clinical entry threshold of 2 cm. The power applied in all patients was 7 Watts and the mean treatment time was 21.4 minutes (range 15-30 min). In one patient a skin burn occurred and one patient had a localized pneumothorax that could be treated conservatively. In 7/14 patients (50%) the tumour was completely ablated confirmed by NADH staining. In 11 cases extensive *in situ* carcinoma was present, in 1 case the *in situ* carcinoma was completely ablated as well. A total of 7/8 tumours (88%) <2cm were completely ablated versus 1/6 (17%) tumours that were ≥2cm, p=0.026.

Conclusions
Successful LITT of invasive breast cancer seems to be feasible when confined to small (< 2 cm) non-lobular carcinomas without surrounding extensive *in situ* component and angioinvasion. However, in order to implement LITT in a curative setting, improvements in imaging to more reliably pre-operatively assess tumour size and monitoring of fibre tip placement and treatment effect are essential.

Introduction

Over the past decades there has been a transition from extensive oncological surgery to minimally invasive oncological surgery. In the treatment of breast carcinomas, clearly the transition from the radical Halsted operation to breast conserving surgery (BCS) and adjuvant radiotherapy for the small carcinomas was a great improvement[1-3]. The introduction of the sentinel node procedure is in line with the aim at minimally invasive surgery[4]. Due to the extensive screening programs for breast cancer, the proportion of small breast carcinomas has increased[5]. Especially for this group of patients with early breast cancer, there is still room for improvement of the treatment. The cosmetic outcome of BCS is often disappointing and BCS carries a relatively high morbidity rate mainly due to postoperative bleeding (up to 11%) and infections (3-4%)[6-8]. As a result of surgical complications, adjuvant treatment may be delayed, affecting the outcome unfavourably[9].

The next step in BCS could be local ablation of small breast carcinomas provided it is equally effective but results in fewer complications and a better cosmetic outcome than a lumpectomy. Local ablation should efficiently and completely destroy the invasive breast carcinoma and surrounding *in situ* carcinoma. Currently, cryosurgery, radiofrequency ablation (RFA), laser induced thermal therapy (LITT), microwave ablation and high intensity focused ultrasound (HIFU) ablation are clinically available local ablation modalities[10-15]. In all of these modalities a change in temperature is used to lethally damage the intracellular DNA binding structures and thereby causing cell death[16, 17]. LITT requires a laser fibre to guide the light energy directly into the tissue to be treated. Upon absorption in the tissue, heat is produced inducing lethal thermal injury. At present LITT and RFA are mostly used to treat unresectable colorectal liver metastases as an alternative to surgery[18, 19]. The results are promising and possibly in the future these modalities could be used for the local ablation of breast carcinoma in curative setting as well.

In order to implement this minimally invasive approach there are several steps to be taken. First, the exact tumour size should be reliably assessed. Second, the treatment should be safe and able to completely destroy all tumour tissue (including *in situ* cancer) locally. Finally, a reliable real-time possibility to monitor the treatment results should be available.

In this feasibility study we evaluated the second prerequisite using ultrasound guided LITT for local treatment of patients with clinically small palpable breast carcinomas.

Materials and Methods

The study was approved by the medical ethical committee of our hospital. All patients had a palpable invasive breast carcinoma diagnosed by an ultrasound guided large core needle biopsy (LCNB). The tumour characteristics (i.e. grade, oestrogen receptor status, progesterone receptor status, HER-2/*neu* status and mitotic activity index) were pre-operatively determined on the LCNB.

Inclusion criteria were age >18 years, palpable cT1 (as measured by pre-operative ultrasound and mammography), unifocal invasive breast carcinoma, visible on ultrasound, pre-operative available tumour characteristics and distance ≥ 1cm from the thoracic wall and the overlying skin.

The sentinel lymph node biopsy (SLNB) was done prior to the LITT procedure. For the SLNB 4 depots of a total of 120 MBq ^{99m}Tc nanocolloïd were injected peritumourally and up to 4 hours after post injection static images were acquired. Per-operatively, 1cc of patent blue (Bleu patenté V 'Guerbet')

was injected peritumourally. The exact tumour size was measured in 2 dimensions after the SLNB using ultrasound (Philips, iU22 scanner, equipped with an 8 MHz linear array transducer).
Next, a 17 gauge guidance needle (Bard Truguide, Covington, United Kingdom) was placed into the centre of the tumour. The position of the needle was checked ultrasonographically in 3 dimensions. Both the tumour size assessment and the placement of the guidance needle were performed by a dedicated breast radiologist.
Then, an uncooled Microdom LITT laser fibre with an active length of 2.5cm was inserted into the tumour and attached to an Nd: YAG continuous laser of 1045 nm (KLS Martin, Umkirch, Germany). After confirming the exact position, the guidance needle was retracted to avoid heath conduction to the skin and the procedure commenced. The amount of energy needed to fully ablate the tumour was determined in an experimental *ex vivo* setting in bovine udder tissue. The maximum tumour size determined the amount of energy that was used.
After the ablation a wide local excision or mastectomy was performed according to local practice.
At pathology, the margins of the specimen were inked and the specimen was sliced in 5-mm slices. The macroscopic lesion size was recorded and samples were taken from the centre of the coagulated area and the transition zone between tumour and tumour free margin (see figure 1).The samples were snap frozen and embedded in paraffin. Both haematoxylin&eosin (H&E) of paraffin sections and nicotinamide dinucleotide adenosine diaphorase (NADH) staining of the frozen sections were used to determine tumour vitality after ablation. Participating patients underwent routine outpatient follow up and standard breast radiation therapy as a part of breast conserving surgery. Based on the status of the sentinel node and primary tumour characteristics, patients had an additional axillary dissection and/or adjuvant chemotherapy.

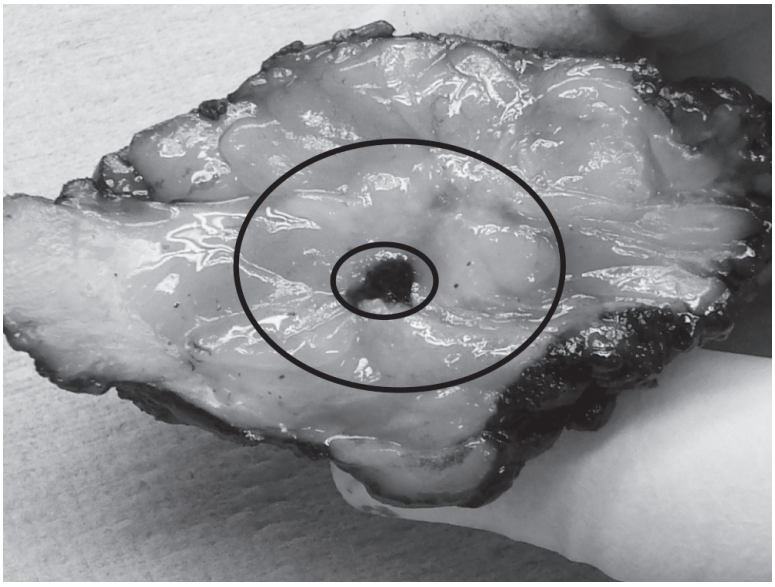

Figure 1: Macroscopic view of ablated tumour tissue. Outer circle reflecting the ablation zone, inner circle showing the fibre track

Table 1: Baseline characteristics

Median age (years)	54.5 (range: 35 – 85)
Median US tumour size (mm)	14.5 (range: 9-20)
Median histological tumour size (mm)	17 (range: 8-37)
Tumour location (%)	
Upper lateral	7 (50)
Lower lateral	3 (22)
Lower medial	2 (14)
Retro aureolar	2 (14)
Tumour histology (%)	
Ductal carcinoma	12 (86)
Lobular carcinoma	1 (7)
Ductolobularcarcinoma	1 (7)
SLNB found (%)	13 (93)
SLNB free of tumour (%)	7 (50)
Breast conserving surgery (%)	13 (93)
Mastectomy (%)	1 (7)

Results

Fourteen patients completed the LITT procedure. Baseline characteristics are summarized in table 1. The majority (50%) of the tumours were located in the upper lateral quadrant of the breast and 12/14 tumours were invasive ductal carcinomas. All patients underwent a SLNB prior to ablation; in 13/14 (93%) the SN was found. Six patients showed axillary metastases, containing isolated tumour cells (ITC) in 3 and macro metastases in the other 3. Two of the patients with axillary ITC chose not to undergo an additional axillary dissection. The 3 patients with macro metastases all had an additional axillary dissection.

LITT time ranged from 15 to 30 minutes (mean 21.4 minutes). The power applied was 7 Watts (2.8W/cm diffuser length) in all cases. The mean US measured tumour size was 15.3 mm and the median US measured lesion size (see figures 1 and 2) after ablation was 18 mm (9-22 mm). In all patients extensive air bubble formation around the fibre tip was seen ultrasonographically. The maximum diameter of the largest histological lesion size was 30mm. The median histological tumour diameter was 17 mm (range 8 – 37mm) and the median histological ablated tumour diameter was 23 mm (2-35 mm). In total 7/14 (50%) of the invasive tumours were completely ablated confirmed by the NADH staining. In 11 cases an extensive *in situ* component surrounded the tumour and in 1 case this *in situ* component was completely ablated as well. In 2/14 (14%) cases only a very small component of the tumour appeared to be ablated due to misplacement of the guidance needle.

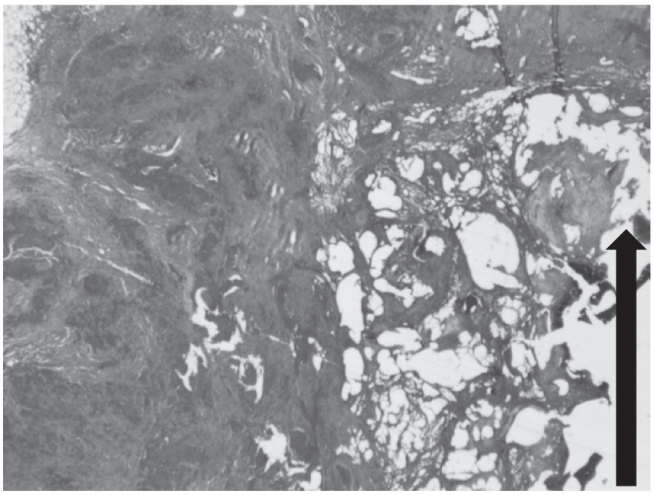

Figure 2: Microscopic (25x) (H&E staining) view of ablation zone; arrow indicating the position of the LITT probe

Two tumours had an extensive angio-invasive growth pattern resulting in pre-operative underestimation of tumour size.
The invasive carcinomas that were histological smaller than 2cm were significantly more frequent completely ablated (7/8, 88%) than the invasive carcinomas that were larger than 2cm (1/6, 17%) (p=0.026).
In 1 patient a superficial skin burn occurred during the procedure. This was treated with a partial skin resection as a part of the lumpectomy. In another patient the guidance needle was placed close to the pectoral muscle resulting in a localized pneumothorax that could be treated conservatively.
All but one patient had subsequent breast conserving surgery. One patient preferred breast amputation to avoid radiation therapy, this patient suffered post-operative bleeding that could be treated conservatively. A post-operative wound infection occurred in 2 patients.

Discussion

The aim of this study was to assess the feasibility of ultrasound guided LITT in invasive breast cancers clinically up to 2 cm in size. Overall, the invasive breast cancer was completely ablated in 7/14 (50%) patients. There was a clear association between the success rate of LITT and tumour size, as cancers were completely ablated in 7/8 (88%) and 1/6 (17%) of patients with a carcinoma <2 cm and >2cm, respectively. Our results thereby show that LITT can completely ablate small invasive breast carcinomas.
Previous studies have confirmed the importance of tumour size in completely ablating breast carcinomas[15, 20]. The reasons for the discrepancies between the clinically/radiologically estimated tumour size and the histological tumour size were threefold. First, two tumours showed a lobular growth pattern. It is well known that tumour size for these type tumours is more difficult to assess,

and often these type of tumours are histological more extensive than estimated due to their diffuse growth pattern[21]. To our opinion, tumours showing lobular differentiation should therefore be excluded from local ablation treatment in a curative setting. Second, in 10/14 cases extensive DCIS was present outside the ablation zone. Incompletely ablated DCIS may later well give rise to an invasive recurrence, although radiotherapy helps to control this. Invasive carcinomas showing extensive DCIS on LCNB should be excluded from local ablation in a curative setting as well. Third, in 2 patients there was a very extensive angio-invasive growth, which was not seen on the LCNB in 1 patient. These growth patterns cannot be detected using mammography and/or ultrasound[21-24]. Therefore, to arrive at successful LITT, pre-operative tumour size assessment needs to be improved. To this end, magnetic resonance imaging (MRI) is likely to be the first option[25], although optical imaging may prove to be important in the future[26].

In order to implement LITT as the breast conserving treatment for small breast carcinomas, reliable intraoperative imaging is also needed during the LITT procedure to monitor placement of the laser fibre and the effect of treatment. The importance of monitoring of the placement fibre is apparent from the fact that in 1 patient, a localized pneumothorax occurred due to misplacement of the guidance needle. Pneumothorax is a known complication after large core needle biopsy, so far it is has not been described as a complication of minimally invasive treatment of breast carcinoma[27].

Finally, adequate imaging is vital to the treatment monitoring. In most of the studies done on LITT of breast carcinomas, the treatment parameters were pre determined[11, 28]. When treatment parameters are pre determined, possible cooling effects of blood flow and differences in density of breast and tumour tissue cannot be taken into account, possibly leading to under treatment of the tumour tissue. Real time monitoring and adjusting of the treatment parameters would be ideal. In this study the progress of the ablation was monitored using ultrasound. Temperatures close to the fibre tip reach 100°C, causing evaporation of the tumour tissue[28, 29] (see figure 2). This evaporation causes hyperechoic air bubbles, making the ultrasound monitoring difficult[30]. Nevertheless, the temperature in the fatty tissue surrounding the tumour rises slowly and is lower, possibly resulting in less fatty necrosis and therefore a better cosmetic outcome and less re-interventions[31]. Although not clinically available yet, real time MR guided thermal mapping is a promising new technique that could become a good alternative to ultrasound[32]. As LITT causes ablation through the absorption of light energy it can be monitored using MRI. On the contrary, radiofrequency ablation (RFA) is based on radio frequent waves, causing significant artefacts in MRI, making MRI monitoring a challange[33].

Determination of the SNB is important for adequate staging and further treatment. Possibly local ablation of the tumour tissue disturbs the lymph drainage pattern. Therefore, in this study the SNB was performed directly before the LITT procedure. In 13/14 (93%) patients the SNB was detected and harvested, which is comparable to current literature[34]. In available studies on LITT so far no clear data were given on the timing of the SNB.

Besides the pneumothorax in 1 patient, another patient had a skin burn that could well be treated. Other complications described in literature such as gaseous rupture of tumour tissue and hyperemia[11, 29, 15] were not seen in this feasibility study.

The NADH staining confirmed the HE stained results in all cases. As is shown in other studies NADH is a reliable staining to confirm tissue vitality. NADH staining requires tissue to be snap frozen, which can be impractical in a routine clinical setting. As posed by others Cytokeratin 8/18 could be a good and practical alternative since it does not requires tissue to be snap frozen[10].

In conclusion, successful LITT of invasive breast cancer seems to be feasible when confined to small (< 2 cm) non-lobular carcinomas without surrounding extensive *in situ* component and angio-invasion. However, in order to implement LITT in a curative setting, improvements in imaging to more reliably pre-operatively assess tumour size and monitoring of fibre tip placement and treatment affect are essential.

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Chapter 11

General discussion and future perspectives

The number of newly diagnosed, early stage breast carcinomas is increasing from 13.000 women in 2003 to an expected 17.000 in the 2015. It is also one of the most important causes of death in women. In 2003, 3.600 Dutch women died as a consequence of breast cancer; in 2015 this number is expected to be 3700[1, 2]. Overall the survival of breast cancer patients is increasing due to improved screening programs and the introduction of adjuvant radiotherapy and hormonal therapy[3-6].
This dissertation focuses on the imaging and surgical treatment of early stage breast carcinoma. What kind of pre operative imaging modality is the most reliable in an accurate tumour size assessment? Does pre operative magnetic resonance imaging (MRI) lead to an improved surgical treatment? Is there room for improvement in breast conserving surgery and sentinel node biopsy?

Imaging

One of the improvements in pre treatment imaging could be contrast enhanced ultrasound (CEUS). It is a known modality in characterizing liver lesions and determining the extent of these lesions[7, 8]. In chapter 2 the value of contrast CEUS versus gray scale ultrasound in the preoperative tumour size assessment of breast carcinomas is described. Although only a small group was analyzed in this study and both CEUS and gray scale US underestimated the histhopathogical tumour size, CEUS was significantly more accurate in predicting tumour size than gray scale US. In Gray scale ultrasound 22% of the estimated tumour sizes were within 2mm of the histopathological tumour size, versus 67% in CEUS. These numbers show that both US and CEUS underestimate the histopathological tumour size. Although the size estimation improved using CEUS, the number of tumours that were estimated correctly is still low. The number of correctly estimated tumour sizes for MRI is higher: 85%[9]. Still, the exact demarcation of tumours especially surrounded by *in situ* carcinoma, is challenging in MRI as well[10]. As was shown in chapter 3 the number of re-excisions in patients with nonpalpable breast cancer is not reduced by adding a pre-operative breast MRI scan to the diagnostic work up. In fact the number of re-excisions was higher in the MRI group (34% vs 12%). This is an unexpected finding as a reduction in number of re-excisions, mastectomies and conversions to mastectomy was predicted due to possible improvement in tumour demarcation, the finding of invasive components in areas of microcalcification and possible detection of contralateral breast cancer. This study was performed in patients presenting with nonpalpable breast lesions and 60% of these patients presented with microcalcifications without a density on mammography and subsequently 50% of the patients with a malignancy had ductal carcinoma *in situ*. In the MONET study, solely patients with nonpalpabel breast lesions were included, as the nonpalpbable breast carcinoma is considered to be the most challenging to remove completely. Since these tumours can not be seen or palpated during surgery, these tumours need to be radiologically localized pre-operatively. As stated earlier, another large randomized trial (COMICE trial) did not describe an improvement in number of re-excisions in the MRI group either[11]. On the one hand MRI does not improve surgery and on the other hand pre-operative MRI is more expensive than regular triple assessment. Therefore adding MRI to triple assessment of patients with a BI-RADS 3-5 lesion does not seem to be of additional value in reducing the number of re-excisions or mastectomies in these patients.
Although MRI did not seem to improve surgical removal of breast carcinoma there are still potential benefits of MRI in diagnosing and treating breast carcinoma. First, possibly MRI will prove to be usefull in screening of young patients with dense breasts and with BRCA 1 or 2 gene deficitis[12]. Secondly, MRI could be of use in localizing tumours for local ablation with RFA, laser or FUS and

monitoring of these treatments using real time thermal mapping could be established using (open) MRI[13]. Thirdly, MRI could be usefull in the monitoring of neoadjuvant chemotherapy of large breast carcinomas[14].

Tumour localization

In chapter 4 the surgical outcome in a large cohort of patients diagnosed with a nonpalpable breast carcinoma is analyzed. Clearly the number of conversions from breast conserving surgery (BCS) to mastectomy is high (18%). Next, patients initially diagnosed with an *in situ* carcinoma on large core needle biopsy undergo significantly more excisions, mastectomies and conversions to mastectomy than patients diagnosed with an invasive carcinoma. The number of re-excisions for patients diagnosed with an *in situ* carcinoma was 34% versus 13% in patients diagnosed with an invasive carcinoma, the number of initially planned mastectomies was 47% for patients with an *in situ* carcinoma versus 38% for patients with an invasive carcinoma and the of conversions from BCS to mastectomy was 28% versus 11%. Therefore, apart from this the total number of days until all tumourous tissue was removed was significantly higher in the group of patients diagnosed with an *in situ* carcinoma (25 versus 38 days). All of these differences were statistically significant ($p<0.001$).

Fortunately, due to the early detection of breast malignancies, the number of *in situ* carcinomas is increasing and the number of invasive carcinomas decreasing[15]. Nevertheless, the number of mastectomies and conversions to mastectomy is higher in *in situ* carcinomas than in invasive carcinomas, while the overall survival of patients with an *in situ* carcinoma is better than in patients with an invasive carcinoma[16]. The exact determination of the extent of *in situ* carcinoma using mammography and ultrasound could be an explanation for this difference. On the one hand preoperative imaging of nonpalpable (*in situ*) carcinomas and on the other hand the surgical treatment of nonpalpable breast carcinomas should be improved. The patients included in this study all had a wire guided localization of their carcinoma. Wire guide localization (WGL) is known to be a difficult procedure for surgeons, as the wire can luxate and the path from the skin to the tumour chosen by the radiologist can differ from the path preferred by the surgeon. This can complicate the procedure and possibly result in less completely excised tumours[17-19].

Due to the increasing number of early stage breast carcinomas the number of nonpalpable breast carcinomas needing preoperative localization increases as well[20]. A possible improvement in BCS of nonpalpable breast carcinomas is described in chapter 5. The radioguided occult lesion localization (ROLL) utilizes the intratumourally injected ^{99m}Tc nanocolloïd for the sentinel node biopsy (SNB) to localize nonpalpable breast carcinomas[17]. A total of 40 patients with 41 tumours underwent ROLL. In 78% of the patients the invasive tumour was adequately excised and overall 30% required a re-excision. Furthermore, this study showed that only unifocal tumours are suitable for this technique and in case the tumour lies very close to the sentinel node (SN), it is advisable to primarily excise the tumour and than the SN in order to be able to distinguish the tumour from the SN. The ROLL procedure seems to be a good and patient friendly alternative to wire guided localization (WGL). On the one hand patients undergo one localization procedure instead of two, therefore only one localization procedure has to be planned, on the other hand the ROLL procedure offers the surgeon a visible template possibly resulting in a faster and easier to execute procedure. This result in an increase in the number of completely excised tumours. Another localization method is the injection of an radioactive Iodium seed in or near the tumour. The benefit of this procedure

is that there is a clear and very localized hotspot, representing the tumour. The downside of this procedure is that patients will still have an additional injection of ^{99m}Tc nanocolloïd in their breast for the sentinel node procedure[21].
The study described in chapter 5 was a feasibility study in which the results were comparable to the results found on WGL. The results of the this study were used for the design of the dutch ROLL trial, randomizing WGL to ROLL. Possibly the results of this trial will lead to the implementation of ROLL in the surgical treatment of patients with a nonpalpable breast carcinoma. In chapter 6 the protocol of this trial is described.

Sentinel node biopsy
In chapter 7 the successrate of the 1-day protocol and the 2-day protocol for the SNB in patients with an invasive breast carcinoma is compared. There is no significant difference in the successrate of the 1-day protocol and the 2-day protocol (85% versus 91%, $p>0.05$). The 1-day protocol could be preferred because patients only have to visit the hospital once and the radiation burden is lower for both patients and physicians. The benefits of a 2-day protocol are that more patients can be planned for surgery at the same day. The subgroup analysis for patients with and without a guide wire placed before the SNB procedure showed no differences in the successrate of the SNB (84% versus 90%, $p>0.05$). Due to logistical considerations in some hospitals there is a preference for a certain protocol. As there are no significant differences in the successrate of the sentinel node procedure either protocol can be used according to local preferences. The number of patients with a guide wire was rather low (37/123 (30%)); therefore more research is needed to determine this influence on the successrate.
As a result of intra/peri-tumoural injection of ^{99m}Tc-nanocolloïd, the number of SN's found in the internal mammary chain (IMC) is relatively high[22]. In chapter 8, axillary staging in patients with lymphoscintigraphic drainage to sentinel lymph nodes in the IMC only is described. It is vital to perform axillary staging guided by patent blue, if no axillary node is found an axillary dissection could be considered for axillary staging and corresponding adjuvant treatment. In our study, the adjuvant treatment was altered in two patients due to the findings in axillary sentinel nodes. Although in only 1% of the patients undergoing an SNB as part of their breast cancer treatment, this problem is encountered, the implications can be serious. In contrast to what is stated by others[23], yet based on a very small number of patients, axillary lymph node dissection could be considered if no additional sentinel nodes are found guided by patent blue in the axilla as we did find additional tumour positive SN's in the absence of tumour positive SN's in the IMC, in 2 patients. Unfortunately, a randomized clinical trial on the subject is not feasible; therefore more authors should present their retrospective data. Possibly these collective results will lead to a consensus.

Minimally invasive treatment
The introduction of breast conserving surgery (BCS) as opposed to mastectomy was considered a great step forward in the treatment of breast carcinoma[24]. And as in other surgical area's the objective has become to treat patients as minimally invasive as possible[25-29]. The ultimate goal would be to locally ablate breast cancer percutaneously in an outpatient setting.
The current status in literature on the locally ablative modalities in the treatment of breast cancer is described in chapter 9. The available minimally ablative modalities are cryosurgery, radiofrequency ablation (RFA), laser induced therapy (LITT), focused ultrasound (FUS) and microwave ablation[30-35].

All of the studies found are small stage I-II studies showing that these techniques are able to completely ablate breast carcinomas. Although these techniques are feasible and safe, significant improvements in preoperative imaging of both the invasive carcinoma and surrounding *in situ* components are needed. Reliable treatment monitoring is essential in order to safely omit surgery after local ablation. The timing of the SNB is not clear yet, due to possible interference with the lymphdrainage patterns it seems to be advisable to perform the SNB before the ablation procedures[36].

Finally in chapter 10, the first step towards local ablation of breast carcinoma is described. LITT can safely and completely ablate small breast carcinomas. Yet, overall in 50% the carcinomas including *in situ* carcinomas were completely ablated. A total of 88% of the invasive tumours <2cm were completely ablated. Furthermore, in this small group of patients serious complications occurred, one patient suffered a small pneumothorax and in one patient the ablation caused a skin burn. The skin burn that occurred was caused by heat guidance from the guidance needle to the skin. After this complication the protocol was adjusted and the guidance needle was fully retracted before the start of the ablation and the skin was cooled using icepacks. Due to the retraction of the guidance needle the LITT fiber could not be visualized properly, therefore any movement of the fiber in the breast was difficult to detect. A probable cause of the pneumothorax was this poor visualization of the LITT fiber during ablation.

In order to implement tumour ablation in a curative setting, only patients with tumours <2cm and without surrounding *in situ* carcinoma are eligible. Next, accurate preoperative and peroperative imaging to determine tumour size and guide the ablation is vital.

Future perspectives

In the future new diagnostic methods, improved imaging techniques, and new ways to treat small breast tumours will probably further minimalize surgical interventions. In order to further minimalize the surgical treatment of breast carcinoma, there are some steps to be taken. First the preoperative delineation of *in situ* carcinomas should become more durable. Due to impaired visualization of surrounding *in situ* carcinomas often a re-excision is required to completely remove all tumourous tissue that was not seen pre-operatively.

Future research should focus on the development of an imaging modality that is capable of clearly pre-operative and possibly per-operative, visualizing *in situ* carcinoma and suspicious microcalcifications. Currently molecular imaging is being studied. Possibly molecular imaging will improve characterization and delineation of *in situ* carcinomas[37]. The next generation MRI scanners, the 7.0 Tesla MRI scanners, are being tested[38]. Maybe, in the future these stronger MRI scanners will be able to delineate and differentiate breast carcinomas more reliably, due to increased field strengths and therefore higher spatial resolutions in combination with more susceptibility artifacts the visualization of microcalcifications will be possible.

ROLL seems to be a feasible and patient friendly alternative to the wire guided localization. The main benefit of ROLL is that it combines the SNB and tumour excision in one procedure. The ROLL trial will show if the ROLL procedure is as good as the WGL in completely removing breast carcinomas in one procedure, or maybe better. On the other hand there is still a downside to the ROLL procedure. In some cases the injected nanocolloïd migrates diffusely through the interstitium

of the breast tissue, resulting in a possible localization error, or in a very large "hot" area. When localizing with an intra/peri tumourally placed iodine seed this problem could be solved[39]. The downside of the iodine seed localization is that it cannot be combined with the SNB in one procedure. The results of ROLL trial are expected in the beginning of 2011. If these results show a benefit for the ROLL procedure, possibly a randomized clinical trial comparing ROLL to iodine seed localization could be the next step.

The results of minimally invasive local ablation techniques in the curative treatment of small breast carcinomas are promising, but there is still room for improvement. Even when the challenges in pre-operative and per-operative imaging are improved and the extent of the carcinomas and surrounding *in situ* carcinomas are completely and reliably depicted there are still some challenges to overcome. The ablation of tumours lying very close to the thoracic wall or very close to the skin is difficult and complications like pneumothorax or skinburn are possible. MRI guided high intensity focused ultrasound (MRIgHIFU) is a new noninvasive modality that could be a solution[13]. The benefits of MRIgHIFU are that the localization and treatment monitoring is MRI guided, real time thermal mapping is possible and it is the only technique that is completely noninvasive. Although this technique is promising, there are still some difficulties to overcome. The treatment length should be reduced, as currently treatments can take up to 3 hours[35]. As we showed in chapter 10 noninvasive confirmation of complete tumour ablation should be available in order to completely replace surgery by these methods[40].

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Chapter 12

Summary

Nederlandse samenvatting

Dankwoord

List of publications

Curriculum vitae auctoris

In this thesis the diagnostic work up and minimally invasive surgical treatment of early stage breast carcinoma is studied. Although the surgical treatment of breast carcinoma has improved significantly over the past decades, there is still room for improvement. On the one hand the focus is on early stage (nonpalpable) breast carcinoma as it is considered a surgical challenge due to the need of preoperative localisation. On the other hand the focus is on future minimally or non-invasive treatment of early stage breast carcinoma and the improvement of adequate pre-operative determination of the extent of the disease.

Imaging

In order to completely remove or ablate breast carcinomas adequate tumour size assessment is vital. As invasive tumours develop neovascularization contrast enhanced ultrasound could improve the preoperative determination of tumour extent. In **chapter 2** the initial results of contrast enhanced ultrasound of breast carcinoma are presented. Gray-scale ultrasound (US) underestimated the histopathological tumour size in 6/9 cases (67%), whereas contrast enhanced ultrasound (CEUS) of the breast underestimated tumour size in only 3/9 (33%) cases. CEUS of the breast was significantly more accurate for tumour size assessment. The greatest tumour dimension as measured with US of the breast was within 2mm of the pathological tumour size in only 2/9 cases (22%), whereas CEUS of the breast accurately assessed tumour size within 2mm of pathological tumour size in 6/9 (67%) of the cases ($P<0.05$).

Complete excision of nonpalpable breast carcinoma is challenging. These tumour can not be palpated or seen during surgery. A possible improvement in the surgical treatment of these patients could be an additional breast MRI pre-operatively in order to determine the exact tumour extent and possibly detect invasive components in *in situ* carcinomas. In **chapter 3** the results of the MONET trial are described. In this trial 418 patients were randomised between the regular triple assessment of their BI-RADS 3-5 nonpalpable lesion and triple assessment with an additional breast MRI before biopsy.

The goal was to assess whether MRI could improve the complete surgical excision of breast carcinomas in these patients. In the MRI group, 74 patients had 83 malignant lesions (41 DCIS, 42 invasive carcinomas) compared to 75 patients with 80 malignant lesions in the control group (41 DCIS, 39 invasive carcinomas). A total of 53/78 (68%) patients had primary BCS and 25/78 (32%) a primary mastectomy. In the control group 50/76 (66%) patients underwent primary BCS, and 26/76 (34%) a primary mastectomy. The number and type of initial surgical procedures was comparable between both groups ($p=0.776$).

The number re-excisions performed because of tumour positive resection margins after primary breast conserving surgery was higher in the MRI group; 18/53 (34%) re-excisions in the MRI group, compared with 6/50 (12%) re-excisions in the control group ($p=0.008$). The number of conversions to mastectomy after primary BCS was lower in the MRI group than in the control group, 6/53 (11%) vs. 8/50 (14%) respectively, but did not reach statistical significance ($p=0.489$). Overall, the rate of an additional surgical intervention (BCS and mastectomy combined) after initial breast conserving surgery was 24/53 (45%) in the MRI group vs. 14/50 (28%) in the control group ($p=0.069$).

Tumour localization

In **chapter 4** the results of a large cohort follow up study are presented. In this study a total of 833 patients with 841 tumours were followed up. The initial surgery consisted of breast conserving surgery

(BCS) for 589 tumours (70%) and of mastectomy for 242 tumours (29%). For 10 tumours (1%) the initial surgery was unknown. After BCS 158/589 tumours (27%) required a re-excision, 116/337 (34%) for the *in situ* carcinomas and 63/504 (13%) for the invasive carcinomas, p=0.0001. The number of conversions from BCS to mastectomy was 106/589 (18%), 66/241 (28%) in patients diagnosed with an *in situ* carcinoma versus 40/348 (11%) in patients with an invasive carcinoma, p=0.0001.
The median number of days until complete tumour removal was 28, this was 38 days for the *in situ* carcinomas and 25 days for the invasive carcinomas (p=0.0001).
A possible improvement in the surgical treatment of nonpalpable breast carcinoma could be the radioguided occult lesion localisation (ROLL). In **chapter 5** the results of the first 40 patients treated with ROLL in our institute are presented. In 31 patients (78%) the invasive tumour was adequately excised. In 2 cases (5%) a re-excision was required due to inadequately excised carcinoma *in situ* and in 3 patients (7.5%) both the invasive and the *in situ* tumour were inadequately excised. In 35 patients (88%) the SN was found and removed. To determine the place of ROLL versus WGL in the treatment of non-palpable breast cancer, a randomized clinical trial is needed.
In **chapter 6** the rationale, objectives and trial design of the ROLL (Radioguided Occult Lesion Localization) trial are presented. The aim of this study is to compare the ROLL technique with the standard localization method, the Wire Guided Localization (WGL) in patients diagnosed with a nonpalpable breast carcinoma. The outcome is defined as the percentage of tumour free margins, cost effectiveness, patient comfort and cosmetic outcome. The results of the ROLL trial are expected to be available at the beginning of 2011.

Sentinel node biopsy
The sentinel node biopsy (SNB) is an important minimally invasive staging tool for breast carcinoma. Both a 1-day and a 2-day protocol can be used for the pre-operative lymphoscintigraphy. The total radiation burden for both patient and physician is lower in the 1-day protocol and patients are spared 1 hospital visit, on the other hand the 2-day protocol offers the ability to treat more patients on the same day. The successrate of the SNB in the 1- versus the 2-day protocol is described in patients diagnosed with a nonpalpable breast carcinoma in **chapter 7**. In 57/67 (85%) patients treated in the 1-day protocol and in 51/56 (91%) patients treated in the 2-day protocol the SNB was successfully detected (p=0.311). Eighteen (27%) patients in the 1-day protocol showed metastasis and 13 (23%) patients in the 2-day protocol (p=0.975). There is no significant difference in the identification rate of the SNB between the 1-day protocol and the 2-day protocol in patients diagnosed with a nonpalpable breast carcinoma.
A result of intratumoural injection of 99mTc-nanocolloïd needed for the ROLL and sentinel node procedure is an increase in the number of sentinel nodes in the internal mammary chain (IMC). In a small part of the patients showing drainage to the IMC, no drainage to the axilla is seen. This poses a problem to the surgeon because the necessity of axillary staging in these patients is unclear.
In **Chapter 8** we try to answer this question. In this study a total of 426/2203 (19%) patients showed drainage to the IMC and 25/2203 (1.1%) to the IMC only. In 16/25 patients the IMC sentinel node (SN) was successfully harvested and in 9/25 patients an additional axillary node was found using patent blue. In 1of these patients an additional axillary node was removed on palpation. The IMC-SN showed isolated tumour cells (ITC) in 3 patients, micro metastasis in 1 patient and macro metastasis in 1 patient. In 3 patients the axillary SN's showed metastases. In 1 patient this

was a macro metastasis, in 1/25 patient a micro metastasis and in 1/25 patient ITC. In 1 patient the IMC-SN was free of metastases and an additional axillary SN showed ITC. In 5 patients no axillary or IMC-SN was found, 3 of these patients underwent subsequent axillary dissection (AD). This resulted in the detection of micro metastases in 1 patient. The median follow up was 26 months and 2/25 patients died due to progression of the breast carcinoma, 1/25 patient died due to progression of a simultaneous esophagus carcinoma. No axillary recurrences were seen.

Minimally invasive treatment

In an overview of the available literature on minimally invasive treatment modalities of breast carcinoma (**chapter 9**), a total of 24 articles were retrieved, the level of evidence varied (2B-4). Mainly fase II studies with a treat and resect protocol were analyzed. Up to 100% completeness of ablation was reported for Radiofrequency ablation (RFA), cryosurgery and Focused ultrasound (FUS). The oncological results need further evaluation. Dynamic enhanced MRI seems to be the best method for monitoring treatment response (77% sensitivity, 100% specificity). Ultrasound is suitable for guiding probes into the tumour. There is no consensus on the timing of sentinel node biopsy (SNB).

Finally the ultimate goal would be to locally ablate breast carcinoma in order to improve the cosmetic outcome. Our initial experience in ultrasound guided laser induced thermal therapy is described in **chapter 10**. Fourteen patients completed the treatment. The mean histological tumour size was 17 mm (range 8-37 mm); 6/14 tumours were histologically larger than clinical entry threshold of 2 cm. The power applied in all patients was 7 Watts and the mean treatment time was 21.4 minutes (range 15-30 min). In one patient a skin burn occurred and one patient had a localized pneumothorax that could be treated conservatively. In 7/14 patients (50%) the tumour was completely ablated confirmed by NADH staining. In 11 cases extensive *in situ* carcinoma was present, in 1 case the *in situ* carcinoma was completely ablated as well. A total of 7/8 tumours (88%) $<$2cm were completely ablated versus 1/6 (17%) tumours that were $\geq$2cm, p=0.026.

Nederlandse samenvatting

In dit proefschrift wordt de diagnostiek en minimaal invasieve chirurgische behandeling van het vroegstadium mammacarcinoom onderzocht. Hoewel de chirurgische behandeling van het mammacarcinoom de laatste jaren sterk verbeterd is, is er nog steeds ruimte voor verbetering. Aan de ene kant ligt de nadruk op het vroegstadium (nonpalpabele) mammacarcinoom, omdat dit door de noodzaak van preoperatieve lokalisatie, nog steeds een chirurgische uitdaging vormt. Aan de andere kant ligt de nadruk op eventuele toekomstige minimaal of non invasieve, lokale behandeling van het vroegstadium mammacarcinoom en de verbetering van adequate preoperatieve beeldvorming van de ziekte.

Beeldvorming

Om in staat te zijn het mammacarcinoom volledig te verwijderen of ableren, is adequate preoperatieve tumourgrootte schatting van essentieel belang. Het feit dat invasieve tumouren nieuwe bloedvoorziening ontwikkelen, maakt het mogelijk de uitbreiding van tumourweefsel met contrast versterkte echografie af te beelden. In **hoofdstuk 2**, worden de eerste resultaten van contrast versterkte echografie van het mammacarcinoom weergegeven. Reguliere echografie (US) onderschatte de histopathologische tumourgrootte in 6/9 casus (67%), terwijl contrast versterkte echografie (CEUS) slechts in 3/9 (33%) de histopathologische tumourgrootte onderschatte. CEUS bleek significant nauwkeuriger in tumourgrootte schatting. De grootste tumour dimensie gemeten met US was binnen 2mm van de pathologische tumourgrootte in slechts 2/9 casus (22%), terwijl dit met CEUS in 6/9 casus (67%) het geval was ($p<0.05$)

Volledige excisie van nonpalpabel mammacarcinomen is een uitdaging. Deze tumouren kunnen niet gepalpeerd of gezien worden tijdens de operatie. Een mogelijke verbetering in de chirurgische behandeling van deze patiënten zou kunnen liggen in het doen van een preoperatieve MRI scan, om zo de exacte uitbreiding van het tumourweefsel en mogelijke omringende *in situ* componenten te detecteren. In **hoofdstuk 3** worden de resultaten van de MONET trial beschreven. In deze trial werden 418 patiënten met een nonpalpabele BI-RADS 3-5 afwijking gerandomiseerd tussen de reguliere triple diagnostiek en de reguliere triple diagnostiek aangevuld met een extra MRI scan voor het biopt. Het doel was te bepalen of een extra MRI scan de volledige chirurgische excisie van de mammacarcinomen in deze groep zou verbeteren.

In de MRI groep hadden 74 patiënten, 83 maligne afwijkingen (41 DCIS, 42 invasieve carcinomen), in de controle groep hadden 75 patiënten, 80 maligne afwijkingen (41 DCIS, 42 invasieve carcinomen). In de MRI groep onderging een totaal van 53/78 (68%) een primair borstsparende behandeling (BCS) en 25/78 (32%) een primaire mastectomie. In de controle groep ondergingen 50/76 (66%) van de patiënten een primair BCS en 26/76 (34%) een primaire mastectomie. Het aantal en type initiële behandelingen was vergelijkbaar tussen de groepen ($p=0.776$).

Het aantal re-excisies in verband met tumour positieve resectiemarges na primair BCS was groter in de MRI groep; 18/53 (34%) in de MRI groep, versus 6/50 (12%) in de controle groep ($p=0.008$). Het aantal conversies naar mastectomie na primaire BCS was kleiner in de MRI groep dan in de controle groep, 6/53 (11%) versus 8/50 (14%), maar haalde geen significantie ($p=0.489$). Overall was het aantal additionele chirurgische interventies na initiële BCS 24/53 (45%) in de MRI groep versus 14/50 (28%) in de controle groep ($p=0.069$).

Tumour lokalisatie

In **hoofdstuk 4** worden de resultaten van een grote cohort follow up studie gepresenteerd. In deze studie werden 833 patiënten met 841 nonpalpabele mammacarcinomen vervolgd. De initiële operatie was BCS voor 589 tumouren (70%) en mastectomie voor 242 tumouren (29%). Voor 10 tumouren is de initiële operatie onbekend. Na BCS was er voor 158/589 (27%) een re-excisie geïndiceerd, 116/337 (34%) voor *in situ* carcinomen en 63/504 (13% voor invasieve carcinomen (p=0.0001). Het aantal conversies van BCS naar mastectomie was 106/589 (18%), 66/241 (28%) bij *in situ* carcinomen en 40/348 (11%) bij invasieve carcinomen (p=0.0001).

Het mediane aantal dagen tot volledige excisie van het tumourweefsel was 28 dagen, dit was 38 dagen voor *in situ* carcinomen en 25 dagen voor invasieve carcinomen (p=0.0001)

Een mogelijke verbetering van de chirurgische behandeling van het nonpalpabele mammacarcinoom zou radioguided occult lesion localisation (ROLL) kunnen zijn. In **hoofdstuk 5** worden de resultaten van de eerste 40 patiënten die in ons instituut met de ROLL methode werden behandeld , beschreven. Bij 31 patiënten (78%) werd de invasieve tumour volledig verwijderd. In 2 casus (5%) was een re-excisie geïndiceerd in verband met onvolledig verwijderd *in situ* carcinoom en bij 3 patiënten (7.5%) waren zowel de *in situ* component als het invasieve carcinoom niet volledig verwijderd. Bij 35 patiënten (88%) werd de schildwachtklier (SN) gevonden en verwijderd. Om te bepalen wat de plaats van ROLL is ten opzichte van de conventionele draadgeleide excisie (WGL) is een gerandomiseerde trial nodig.

In **hoofdstuk 6** worden de ratio, de doelen en het ontwerp van de ROLL trial gepresenteerd. Het doel van deze studie is om de ROLL techniek te vergelijken met de gebruikelijke WGL bij de chirurgische behandeling van patiënten met een nonpalpabel mammacarcinoom. De uitkomst is gedefinieerd als het percentage tumourvrije marges, de kosten effectiviteit, patiëntvriendelijkheid en cosmetisch resultaat. De resultaten van de ROLL trial worden aan het einde van 2010 verwacht.

De schildwachtklier biopsie

De schildwachtklier biopsie (SNB) is een belangrijke peiler in de stadiëring van het mammacarcinoom. Zowel een ééndaagsprotocol als een tweedaagsprotocol kan gebruikt worden voor de preoperatieve lymfoscintigrafie. De totale stralingsbelasting voor zowel patiënt als arts is kleiner in het ééndaagsprotocol en patiënten wordt een extra ziekenhuisbezoek gespaard aan de andere kant biedt het tweedaagsprotocol de mogelijkheid meer patienten op dezelfde dag te behandelen. Het succespercentage van de SNB in het ééndaagsprotocol versus het tweedaagsprotocol bij patiënten met een nonpalpabel mammacarcinoom wordt beschreven in **hoofdstuk 7**.

Bij 57/67 (85%) van de patiënten behandeld in het ééndaagsprotocol en bij 51/56 (91%) van de patiënten in het tweedaagsprotocol werd de SNB succesvol opgespoord (p=0.311). Achttien (27%) patiënten in het ééndaagsprotocol hadden metastasen en 13 (23%) patiënten in het tweedaagsprotocol (p=0.975). Er bestaat geen significant verschil in de detectiegraad van de SNB in het ééndaagsprotocol ten opzichte van het tweedaagsprotocol bij patiënten met een nonpalpabel mammacarcinoom. Ten gevolge van het intratumouraal injecteren van ^{99m}Tc-nanocolloïd voor de ROLL procedure en de SNB, is de detectie van het aantal SN's in de parasternale lymfeklierketen (IMC) toegenomen. Een klein deel van deze patiënten tonen slechts drainage naar de IMC, zonder drainage naar de axilla. Dit stelt de behandelend chirurg voor een dilemma, omdat de noodzaak van axillaire stadiëring onduidelijk is.

In **hoofdstuk 8** proberen we een antwoord te vormen op deze vraag. In deze studie toonden 426/2203 (19%) van de onderzochte patiënten drainage naar de IMC, hiervan toonden 25/2203 (1.1%) patiënten drainage naar de IMC zonder drainage naar de axilla. Bij 16/25 patiënten werd de IMC SN succesvol geoogst en in 9/25 patiënten werd een additionele SN in de axilla gevonden met gebruikmaking van patent blauw. Bij 1 van deze patiënten werd een additionele axillaire klier gevonden op palpatie. De IMC-SN toonde geïsoleerde tumourcellen (ITC) bij 3 patiënten, micro metastasen in 1 patiënt en macro metastasen in 1 patiënt. Verder werden bij 3 patiënten metastasen in de additionele axillaire klier gevonden. Bij 1 patiënt betrof het een macro metastase, bij 1 patiënt een micro metastase en bij 1 patiënt een ITC.
Bij 1 patient was de IMC-SN vrij van metastasen, maar toonde de additionele axillaire SN een ITC. Bij 5 patienten werd geen axillaire of IMC-SN gevonden, 3 van deze patienten ondergingen een aanvullende axillaire dissectie (AD). Dit resulteerde in het vinden van micro metastasen bij 1 patient. De gemiddelde follow up was 26 maanden en 2/25 onderzochte patienten overleden ten gevolge van progressie van het mammacarcinoom, 1/25 patienten overleden door progressie van een simultaan oesofagus carcinoom. Er werden geen axillaire recidieven gevonden

Minimaal invasieve behandeling

In **hoofdstuk 9** wordt een overzicht van de beschikbare literatuur over minimaal invasieve behandeling van mammacarcinoom beschreven. Er werd een totaal van 24 artikelen gevonden, het level of evidence varieerde (2B-4). Er werden met name fase II studies met een zogenaamd treat and resect protocol geanalyseerd. Tot 100% volledige ablatie werd beschreven voor radiofrequente ablatie (RFA), cryochirurgie en gefocusseerd ultrageluid (FUS). De oncologische resultaten behoeven verdere evaluatie. Dynamisch versterkte MRI lijkt de beste methode voor het monitoren van de resultaten van de behandeling (77% sensitiviteit, 100% specificiteit). Echografie is geschikt voor het beeldgestuurd plaatsen van de probes in de tumour. Er is vooralsnog geen consensus voor wat betreft de timing van de SNB.

Uiteindelijk is het doel mammacarcinoom lokaal te ableren om op deze manier het cosmetisch resultaat van de behandeling te verbeteren. Onze eerste ervaring met echogeleide laserablatie (LITT) wordt beschreven in **hoofdstuk 10**. Veertien patiënten volbrachten de behandeling. De gemiddelde histopathologische tumourgrootte was 17mm (spreiding 8-37mm); 6/14 tumouren bleken histopathologisch groter dan de geplande drempel van 2cm. Het toegediende vermogen was in alle patiënten 7 Watt en de gemiddelde behandelingsduur was 21.4 minuten (spreiding 15-30 minuten). Bij 1 patiënt ontstond een brandwond van de huid en 1 patiënt ontwikkelde een gelokaliseerde pneumothorax die conservatief behandeld kon worden. Bij 7/14 patiënten (50%) bleek de tumour volledig geableerd, dit werd middels NADH kleuring bevestigd. In 11 casus bleek er sprake van uitgebreid omringend *in situ* carcinoom, bij 1 patiënt was het *in situ* carcinoom volledig geableerd. Een totaal van 7/8 (88%) tumouren kleiner dan 2cm werden volledig geableerd versus 1/6 (17%) van de tumouren ≥2cm, p=0.026.

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De leden van de beoordelingscommissie **prof. dr. W.P.Th.M. Mali, prof. dr, P.J. van Diest, prof. dr. EJ.Th. Rutgers en prof. I.H.M. Borel Rinkes**.

Prof. dr. I.H.M. Borel Rinkes, beste Inne, je interesse, scherpe analytische denken en vermogen om altijd de vinger op de gevoelige plek te leggen hebben een belangrijke bijdrage geleverd aan de totstandkoming van dit proefschrift. Daarnaast ben je natuurlijk samen met professor Mali en professor Peeters de grondlegger van het mamma onderzoek in het UMCU, door jullie jarenlange samenwerking is er een stevige onderzoeksband ontstaan tussen onze afdelingen.
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List of publications

1. **Axillary staging in patients with exclusive drainage to internal mammary chain**
   S. van Esser, E.V.E. Madsen, T. van Dalen, R. Koelemij, P.S.N. van Rossum, I.H.M. Borel Rinkes, R. van Hillegersberg, A.J. Witkamp
   Accepted for publication in the World journal of Surgery

2. **Ultrasound guided laser induced thermal therapy for small palpable breast carcinomas**
   S. van Esser, G. Stapper, P.J. van Diest, M.A.A.J. van den Bosch, J.H.G.M. Klaessens, W.P.Th.M. Mali, I.H.M. Borel Rinkes, R. van Hillegersberg
   Annals of Surgical Oncology. 2009 Aug;16(8):2259-63. Epub 2009 Jun 9

3. **Treatment outcome of patients with a core-biopsy proven non-palpable breast carcinoma**
   S. van Esser, N. Peters, M.A.A.J. van den Bosch, W.P.Th.M. Mali, I.H.M. Borel Rinkes, R. van Hillegersberg, P.H.M. Peeters
   Annals of Surgical Oncology. 2009 Aug;16(8):2252-8. Epub 2009 May 13.

4. **Lymphatic mapping and sentinel lymph node biopsy in patients with non-palpable breast cancer: one- or two-day protocol?**
   S. van Esser, M.G. Hobbelink, W.P.Th.M. Mali, I.H.M. Borel Rinkes, R. van Hillegersberg
   Eur J Nucl Med Mol Imaging. 2009 Sep;36(9):1383-7. Epub 2009 Mar 25

5. **Radio guided occult lesion localization (ROLL) for non palpable invasive breast cancer**
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6. **Invited review on minimally invasive therapies for invasive breast carcinomas in the Dutch journal of oncology**
   S. van Esser, J.H.G.M. Klaessens, P.J. van Diest, W.P.Th.M. Mali, I.H.M. Borel Rinkes, R. van Hillegersberg
   Dutch Journal of Oncology 2008 September: 5 (6): 269-277

7. **The efficacy of 'Radio guided Occult Lesion Localization' (ROLL) versus 'Wire-guided Localization' (WGL) in breast conserving surgery for non-palpable breast cancer: a randomized clinical trial - ROLL study**
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   BMC Surg. 2008 May 21;8(1):9

8. **Minimally invasive ablative therapies for invasive breast carcinomas. An overview of current literature**
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9. **Accuracy of contrast-enhanced breast ultrasound for pre-operative tumour size assessment in patients diagnosed with invasive ductal carcinoma of the breast**
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10. **Radiofrequency ablation for breast cancer: A review of the literature**
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    Eur J Surg Oncol. 2007 Aug;33(6):673-7

Curriculum vitae auctoris

Stijn van Esser was born on 26th of November 1979 in Roermond, the Netherlands. After graduating at the Stedelijk Lyceum in Roermond in 1998 he passed additional exams in chemistry at the James Boswell institute in Utrecht. The remaining part of the year he went to Israël to work in a Kibboets. In 1999 he started his medical training at Utrecht University. In 2003 he started as a student researcher in the research group of Prof. Dr. I.H.M. Borel Rinkes and Prof.Dr. R. van Hillegersberg. After obtaining his medical degree in 2006 he was able to start a PhD programme thanks to a grant from the Netherlands Organisation for Scientific Research (NWO-ZonMw). In January 2010 he started his residency program in general surgery in the St Antonius Hospital in Nieuwegein (dr. P.M.N.Y.H. Go). The last two years are scheduled in the University Medical Center under supervision of Prof.Dr. I.H.M. Borel Rinkes.