Localisation and staging of early stage breast cancer

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Localiseren and stadiëren van het vroeg stadium mammacarcinoom

(met een samenvatting in het Nederlands)

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Voor mijn vader

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CHAPTER 1

General introduction and outline of the thesis

Introduction

Breast cancer is the most common cancer among women. Worldwide, approximately 1,4 million women were diagnosed with breast cancer and almost 460,000 died from the disease in 2008.[1] In the western world, 1 in 9 women will develop breast cancer during her lifetime and with ageing of the population the number of cases is expected to keep rising. The breast cancer death rate has been declining steadily since the early nineties.[2,3] This has been attributed to profound changes in the clinical presentation and management of breast cancer due to screening, improvements in radiotherapy and surgery and implementation of effective adjuvant systemic treatment.[4,5]

Surgery is considered the primary treatment for breast cancer. In the past, mastectomy (according to Halsted) was the only accepted surgical option. After large randomised trials reported equivalent survival rates for women treated with mastectomy compared to those treated with lumpectomy followed by whole breast irradiation, breast-conserving therapy (BCT) has become an acceptable standard of care for women with early stage breast cancer.[6,7] In addition, surgical management for staging of the axilla in patients with clinically node negative cancer has made the transition from axillary lymph node dissection (ALND) to sentinel lymph node (SLN) biopsy, a minimally invasive and highly accurate staging procedure.[8] Recently, it was even shown that among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.[9]

Parallel to the improvement in surgical treatment, breast cancer screening was introduced and enhancement of the imaging modalities took place. The combination of both resulted in a substantial increase in the detection rate of small, often non-palpable, early stage breast cancers amenable to BCT.[10] When performing breast conserving surgery in patients with early stage breast cancer the two main objectives of the surgeon are; 1) complete primary tumour removal with negative margins and 2) excision of a minimal amount of healthy tissue for optimal cosmetic results. To achieve

these objectives, accurate information on the extent and the precise localisation of the tumour in the breast is essential for the surgeon. Therefore, in patients with non-palpable breast cancer, localisation tools are fundamental for successful treatment. In the majority of cases wire guided localisation is used and is considered standard procedure.

For optimal management of early stage breast cancer the work of the pathologist is of great importance. Nowadays, the vast majority of breast cancers is diagnosed by means of core needle biopsy. Although the tissue obtained only represents a small part of the cancer, histology assessment provides important information for further work-up and decision making.[11-14] Post-operative evaluation results of the surgical specimen are decisive for the choice of optimal adjuvant treatment.

Localisation of non-palpable breast cancer

Mammography screening and the improving quality of imaging are responsible for the fact that the incidence of early stage, non-palpable breast cancer is still rising. Most of these cancers are suitable for BCT. When however the tumour is not palpable, the risk of incomplete tumour excision is substantial, as the involved area is hard to pinpoint. For this reason, accurate tools for localisation are imperative. Wire-guided localisation (WGL) has proven to be a rather accurate and very useful localisation tool, it is however associated with several shortcomings. The wire tip gives no indication of the extent of the tumour and the amount of tissue to be excised is estimated by the surgeon intra-operatively, leading to a high risk of incomplete tumour resection. In addition, the wire insertion is time consuming, requires an extra mammography and is reported to be uncomfortable for the patient

Radioguided occult lesion localisation (ROLL) was introduced as a promising alternative for WGL. Here, an intra-tumoural injection of radioactive tracer is used to localise the lesion with a gamma probe during surgery. ROLL offers the opportunity to combine the localisation of the primary tumour with the sentinel node procedure (SNP), since the intra-tumoural injection can be used for lymphatic mapping and SNP.

Since ROLL and WGL were never properly compared in patients with proven breast cancer, we performed a randomised controlled trial (RCT) to determine if ROLL should replace WGL as the golden standard. In this thesis several aspects of this trial will be presented.

Sentinel lymph node biopsy

The concept of sentinel node biopsy is based upon two basic principles: the existence of an orderly and predictable pattern of lymphatic drainage to a regional lymph node basin, and the functioning of a first lymph node as an effective filter for tumour cells.[15] The first lymph node to receive drainage from the tumour (i.e. sentinel node) is identified by using a radiotracer and/or blue dye for lymphatic mapping and subsequent excision of the node. Histology assessment of this node is performed and in case of metastases, axillary lymph node dissection (ALND) is performed. ALND, with a substantial risk for associated morbidity, can be omitted when the sentinel node is found to be negative for tumour cells. Since it has been proven that sentinel lymph node biopsy is an accurate method for the staging of breast cancer, this procedure has replaced the complete axillary lymph node dissection in clinically node negative patients.[8,16] It has been proven that the sentinel node procedure is most successful with the use of a dual tracer; the optimal injection site of this tracer is nevertheless a subject of discussion. The benefit of superficial injection (subdermal or (peri) areolar) is the technical simplicity. Deep injection (peri-tumoural/ intra-tumoural) has the ability to reveal drainage to the extra-axillary lymph nodes.

The value of pathology assessment

In breast cancer, the pathology diagnosis is the foundation upon which further work-up or treatment decisions are made. Now that diagnostic excision biopsy has been replaced by large core needle biopsy, it is possible to assess certain clinically relevant tumour characteristics pre-operatively. Histopathological parameters identified in the surgical breast specimen are essential for deciding on adjuvant treatment following early breast cancer surgery. Besides age, the choice of further treatment is based on the tumour characteristics, margin status and status of the sentinel node. Previous

studies have shown that the histopathological assessment of breast and sentinel node specimens varies substantially between pathologists with discrepancies of up to 50%.[17-20] These can be as a result of technical factors or a different interpretation. Since histology assessment is crucial in order to provide an accurate adjuvant treatment advice, inter-observer variability may eventually affect the patient outcome.

Outline of the thesis

This thesis focuses on the management of early stage breast cancer and is divided into two parts.

PART 1: Localisation of non-palpable breast cancer

Chapter two through five focuses on the localisation of non-palpable breast carcinoma with the aim to determine if the golden standard, WGL, can be replaced by ROLL. In chapter two a literature overview is provided describing the various localisation techniques and the efficacy of these techniques. In chapter three we present the results of our randomised controlled trial comparing ROLL with WGL in patients with non-palpable breast cancer for breast conserving surgery. As cost-effectiveness is of great importance when choosing a certain technique, the cost-effectiveness of WGL and ROLL is compared in chapter four. In chapter five we present the patients in whom failure of localisation occurred. A multidisciplinary evaluation of all the cases and description of potential pitfalls and solutions is provided.

PART 2: Staging of early stage breast cancer

In case of pre or per- operative non-identification of a sentinel node, the surgeon is forced to perform axillary lymph node dissection (ALND) as staging of the cancer is essential for planning of further treatment. Chapter 6 studies the impact of site of dual tracer injection on the risk of unplanned ALND in patients with non-palpable breast cancer. Chapter 7 focuses on the clinical relevance of routine biopsy of the internal mammary sentinel node.

Histological diagnosis is crucial for accurate surgical management and adjuvant treatment advice in patients with early stage breast cancer. The objective of chapter 8 is to provide insight into the impact of inter-observer variability of the histological assessment of non-palpable, clinically node negative breast carcinomas upon further treatment strategy and prognosis prediction.

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PART 1

Localisation of non-palpable breast cancer

CHAPTER 2

Localisation of non-palpable breast lesions

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Abstract

The introduction of mammography screening and improvements in diagnostic tools resulted in a major increase of breast cancers detectable as small, non-palpable lesions suitable for breast conserving treatment. Accurate pre-operative localisation of these cancers is a necessity. Several methods are available for localisation, of which wire guided localisation is considered the current golden standard. Promising techniques are radioguided occult lesion localisation, radioactive seed localisation and ultrasound guided surgery.

In this review, an overview of the various localisation techniques is provided, describing advantages, shortcomings and effectiveness.

Introduction

With the introduction of mammography screening and improvements in diagnostic tools, the majority of breast cancers are detected as small, non-palpable lesions, which are amenable to breast conserving treatment (BCT). Accurate localisation of non-palpable breast cancers is the key to achieving the main objectives in BCT: 1. complete tumour removal with adequate margins and 2. excision of a small amount of tissue providing acceptable cosmetic results. In patients who undergo breast conserving surgery for non-palpable breast cancer, high percentages (up to 50%) of tumour positive margins and re-excisions are reported.[1-3]

Several techniques are available for lesion localisation, of which wire guided localisation (WGL) is considered the current golden standard. This technique depends on ultrasound or stereotactic imaging to insert a wire into the lesion enabling intra-operative localisation and excision. However, the precise location of the wire tip and volume of the excised tissue still have to be estimated by the surgeon resulting in relatively high rates of involved margins.[4-6] Due to the fact that the wire exits the patient's skin after insertion, it is preferable to perform surgery the same day, making scheduling of the operation more complicated.

These disadvantages have prompted development and implementation of alternative approaches, such as radioguided occult lesion localisation (ROLL), ultrasound guided surgery (UGS) and localisation by radioactive seed (RSL).

In this review, we provide an overview of the currently available techniques for localisation of non palpable breast cancer and discuss their advantages and shortcomings. Most reports published regarding these techniques enrolled patients with non palpable breast lesions (malignant and benign). In order to assess the effectiveness of the different localisation procedures in breast cancer only, we will focus on the cases with malignant lesions.

Wire-guided Localisation (WGL)

In 1965 Dodd et al. first described the use of a wire to guide the localisation of non-palpable breast lesions prior to breast conserving surgery. Shortly before surgery, a hook wire is inserted by the radiologist, guided by ultrasound or stereotactic X-ray guidance. (figure 1) Following insertion of the wire, correct placement is verified by mammography. (figure 2) The surgeon, guided by the wire and the mammographic images, then removes the tissue around the tip of the needle.[7]

Until now, WGL is the most used method for localisation of non-palpable breast lesions, but it is associated with a number of disadvantages. This technique involves two separate procedures involving different departments, i.e. localisation at the department of radiology and surgical removal in the operation theatre, which complicates planning. On a patient level, undergoing two different procedures in two different settings is often perceived as unpleasant, painful and sometimes traumatic.[8]

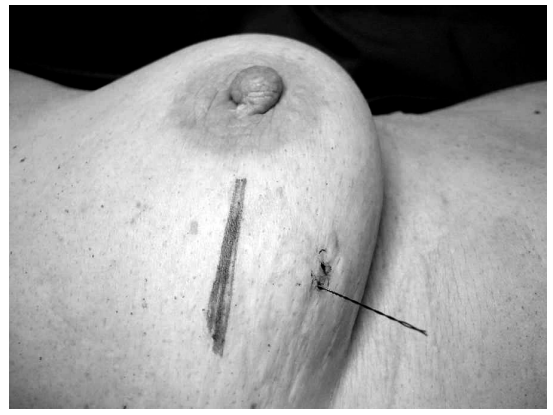

Figure 1 | Shortly before surgery, a hook wire is inserted by the radiologist, guided by ultra-sound or stereotactic X-ray guidance.

Also in some cases, the radiologist may insert the hook wire in such a way that the surgeon is forced to perform his incision elsewhere than desired for optimal cosmetic result.

Finally, there is a small chance of wire displacement during confirmatory mammography or transfer of the patient.[9,10]

Due to the limitations of WGL, emergence of alternative occult breast lesion localisation methods has taken place.

Radioguided occult lesion localisation (ROLL)

ROLL was introduced as a possible replacement for WGL at the European Institute of Oncology in Milan in 1996.[11] This technique utilizes the intra-lesion injected radiotracer that has already been used for the lymphatic mapping and sentinel node biopsy (SNB), to localize the primary lesion intra-operatively guided by a gamma probe.[12]

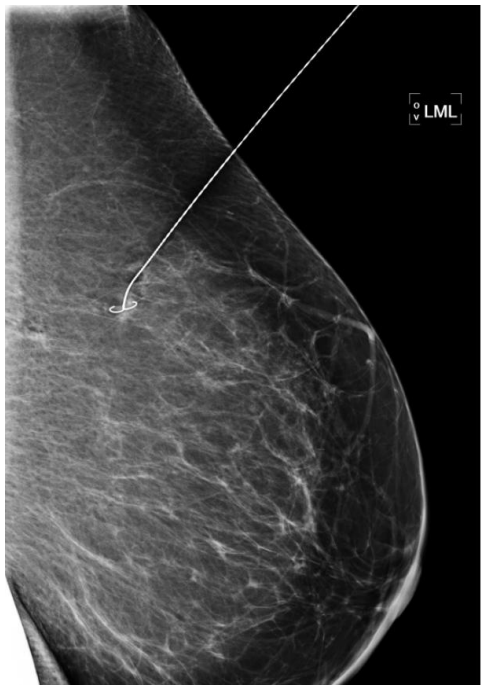

Figure 2 | Correct placement of the wire is verified by mammography.

During surgery the lesion can be localised at any time using the probe, resulting in the opportunity for the surgeon to choose the best route of access and to thereby perform a lumpectomy with tumour free margins, whilst removing minimal volume of tissue. (figure 3)

It also provides the possibility to check the residual tissue for radioactivity and thereby reduces the chance of an excision with tumour positive margins. The differing methods used for ROLL were previously described.[4,11]

A major advantage of the ROLL is that it utilizes the tracer that is injected for both the lesion localisation and the sentinel node biopsy without performing an extra procedure. Obviously this advantage is absent when a sentinel node procedure is not indicated (e.g. in ductal carcinoma in situ, DCIS, or proof of axillary lymph node involvement prior to surgery). A disadvantage is the chance of radioactive substance flowing into the mammary tissue adjacent to the tumour. This hinders localisation of the lesion itself with the gamma probe and may result in excessively large excision volumes.[13,14]

Non-controlled trials ROLL

Various studies report on experience with ROLL without comparing it to the WGL. Monti, et al. retrospectively analysed a dataset of 959 patients that were treated with the ROLL technique.[15] These were all patients with a histologically or cytologically proven malignancy. In 883 of the 959 patients (91.9%) the malignancy was completely removed with tumour free surgical margins. During the sentinel node procedure the radiotracer was injected sub-dermally. In only one patient the sentinel node could not be visualised with scintigraphy.

In a prospective study published in 2008 by Sarlos, et al., 100 patients with 120 proven malignant or pre-malignant lesions were treated with ROLL.[16] A sentinel node procedure was performed in 72 patients by placing a second injection of Tc 99 sub-dermally or peri-areolary and was successful in 98.6%. Complete tumour removal with negative margins was seen in 80% (55/69), taking only the invasive carcinomas

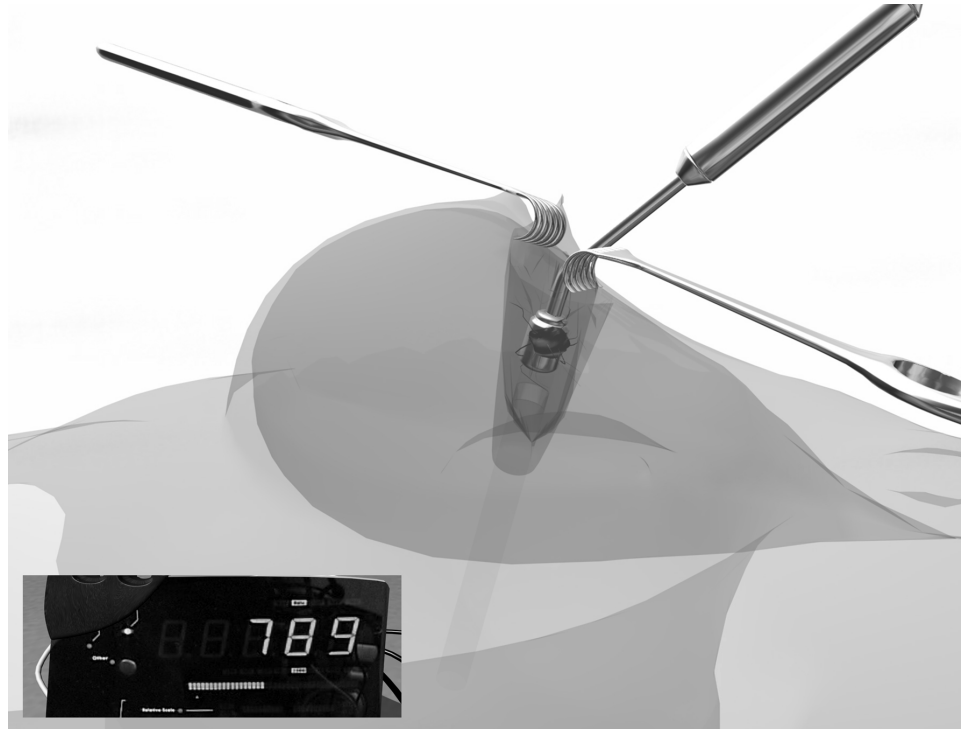

Figure 3 | Guided by the gammaprobe, the surgeon localizes and excises the lesion

into account. In patients with DCIS this was seen in 65% (17/26).

A group of 72 patients with non palpable suspicious lesions (BIRADS 4-5) was prospectively studied by Lavoué and co-workers.[17] For localisation of the lesions ROLL was applied, injecting the Tc99 peri-tumourally at the superficial and deeper pole of the lesion. In all cases the lesion was localised and removed. Pathological examinations showed involved margins in 7 of the 72 patients (10%). In four patients, a multi-focal tumour was identified resulting in 11 (15%) patients requiring re-excision. The sentinel node procedure was successful in 90% of the patients when combining the radioactive tracer with a peri-tumoural injection of blue dye during surgery.

Van Esser, et al. recruited patients with a core biopsy proven invasive carcinoma requiring breast conserving surgery and a sentinel node procedure.[18] One intra-tumoural injection was used for both localisation of the tumour as well as the sentinel node procedure, making this a population that benefits most from the ROLL technique. In 78% of the 40 enrolled patients complete excision of the tumour was achieved. The sentinel node was identified in 88% of the patients. An overview of the studies is provided in table 1.

ROLL versus WGL

Rampaul, et al. were the first to perform a randomised comparison between WGL and ROLL.[19] Patients with non- palpable breast lesions were enrolled and the ease of the different procedures and the patients' pain perception were assessed. ROLL was rated as easier to perform by the radiologists and surgeons and patients reported less pain. Unfortunately the rate of negative resection margins and re-excisions in patient with malignant disease were not reported. Moreno, et al. compared the ROLL technique with WGL in a randomised controlled trial using cosmetic results, post-operative pain and efficacy as outcome measures.[20] A total of 120 patients with suspicious non-palpable breast lesions who required diagnostic excision were included. Following randomisation, WGL was used for lesion localisation in 59 patients and ROLL in 61 patients. Comparison between the two techniques showed significant differences in favour of the ROLL. Taking perception of the patient into account, cosmetic results scored in the first month after surgery were significantly better ($p<0,001$). The percentage of clear margins in the ROLL group was higher (93% vs 87% $p<0,01$) for all lesions and the volume of the excised tissue was smaller (8,7 cm3 vs 23,2 cm3). This may explain the improved cosmetic results. However, there were only 10 patients in the ROLL and 16 patients in the WGL group with proven malignancy. When malignancy alone was assessed, a 90% clear margin rate was seen with ROLL versus 87.5 % utilizing WGL. This difference was not significant. The sentinel node procedure was not combined with the ROLL procedure.

Another randomised controlled trial was conducted by Martinez, et al.[21] Patients with core biopsy proven breast cancer (n=134) were randomised to ROLL or WGL. In the ROLL group sentinel procedure was combined. Patients in the WGL group received this same intra-tumoural injection of the isotope directly followed by insertion of the wire. Surgery was performed 3-22 hours after injection. Clear margins were obtained in 89% of ROLL patients versus 82% of WGL patients; this difference was not significant. Duration of the radiological procedure was significantly shorter. The sentinel node was detected in 91% in the ROLL group versus 84% in the WGL group.

Medina-Franco conducted a trial in which 100 patients with benign and malignant non-palpable breast lesions were randomised between ROLL and WGL.[22] Outcome measures were cosmetic results measured by a four point breast cosmesis scoring system and localisation time and ease of the procedures (rated by surgeon and radiologist). Furthermore the percentage of clear margins in the malignant lesions was assessed. In the ROLL group cosmetic results were better and the procedure was rated to be easier. In 8 of 9 (89.9%) ROLL patients and 5 of 8 (62.5%) WGL patients with malignant disease, complete tumour removal was achieved. The mixed patient population and the lack of data on the sentinel node procedure limit the conclusiveness of this study.

An overview of the studies is provided in table 2.

Table 1 | Non-Controlled studies localisation non palpable breast cancer

Study	Study design	Method	N=	Inclusion	Injection sentinel node	Clear margin	Specimen volume/ weight	Succes% SNP	LOE†
Monti (15)	Retrospective cohort	ROLL	959	Invasive carcinoma	Subdermal	92%	-	99.9%	3
Sarlos (16)	Prospective cohort	ROLL	69	Invasive carcinoma	Peri-aroleair	80%	48.4 gr	98.6%	2b
La Voue (17)	Prospective cohort	ROLL	72	BIRADS 4-5	Peri-tumoural	85%	-	90%	2b
van Esser (18)	Prospective cohort	ROLL	40	Invasive carcinoma	Intra-tumoural	78%	238 cm^3	88%	2b
Potter (27)	Prospective cohort	USG	31	Invasive carcinoma*	Intra-tumoural	90%	-	88%	2b
Ngo (28)	Retrospective cohort	USG	70	Invasive carcinoma*	Subdermal	92%	-	99.9%	3

* visible with ultrasonography

† OCEBM Levels of Evidence Working Group*. "The Oxford Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/

SNP: Sentinel Node Procedure
WGL: Wire Guided Localisation
ROLL : Radioguided Occult Lesion Localisation
USG: Ultrasound Guided Surgery
LOE: Level of evidence
a. volume was calculated by multiplying the three dimensions measured by the pathologist (length x height x width)

Ultrasound guided surgery (USG)

Ultrasound (US) guided excision uses real time ultrasound guidance to direct the surgeon during tumour excision. A major advantage of intra-operative ultrasound localisation is that it avoids the difficulties of the logistic organization between the department of radiology and department of surgery. Additionally, the patient does not have to undergo the placement of needle-wire which is often unpleasant for the patient.[23] This method of tumour localisation does not lengthen operating time and provides the possibility for the surgeon to adapt the excision guided by the real-time images.

A complicating factor is that this technique requires the presence of a physician with the skills to perform accurate ultrasound imaging (either radiologist or surgeon) to be present in the operating theatre. US-guided surgery is also hampered by the fact that ultrasound images often underestimate the size of the lesion and pre-malignant ductal carcinoma in situ components cannot be accurately visualised.[24-26] Underestimation of the lesion can be abolished by resecting the visualized lesion with an adequate margin (0.5- 1 cm).

Non-controlled trials USG

A prospective study was carried out by Potter et al. in 32 patients with mass lesions, which were well seen on ultrasound.[27] These patients underwent intra-operative US-guided localisation performed by one experienced surgeon. The percentage of clear margins was 90% in patients with a proven malignancy (n=31)). The tumours that were not completely excised were all lobular carcinomas.

Ngo and co-workers conducted a study in 70 patients with proven non-palpable invasive breast cancer.[28] Percentage of lesion identification and clear margins and the correlation between the histopathological tumour diameter and the diameter seen on the pre-operative US were assessed. The authors reported a sensitivity of 95,7% for US localisation and a percentage of 94% (66/70) with clear resection margins. The calculated correlation coefficient was 0.80 for pre-operative US dimensions. (table 1)

USG vs. WGL

In 2002 a comparison between WGL and USG was conducted by Rahusen and colleagues.[29] Twenty three patients were assigned to WGL and 26 patients to USG. The rate of adequate tumour excision was significantly higher when USG was performed. However, specimen volume and duration of surgery did not differ. Bennet, et al. performed a prospective controlled study in 103 patients with non palpable breast tumours.[30] All lesions were identified and correctly localised by ultrasound. When taking only malignant lesions into account, 39/42 (93%) malignancies were excised

Table 2 | Controlled studies localisation non palpable breast cancer

Study	RCT	Method	Number of malignant lesions (all lesions	Inclusion	Clear margin	P value	Specimen volume or weigt	P value	LOE†
Rampaul (19)	+	WGL	39 (47)	Non palpable	-	-	31 gr	0.298	2b
		ROLL	39 (48)	breast lesions	-		34 gr		
Moreno (20)	+	WGL	16 (59)	Non palpable	88%	0.067	20.3 cm^3	0.17	2b
		ROLL	10 (61)	breast lesions	90%		9.5 cm^3		
Martinez (21)	+	WGL	68	Invasive	82%	0.357	67.3 gr	0.913	1b
	+	ROLL	66	carcinoma	89%		68.1 gr		
Medina-Franco (22)	+	WGL	8 (50)	Non palpable	63%	0.04	-	-	2b
		ROLL	9 (50)	breast lesions	89%		-		
Rahusen (29)	-	WGL	23	Invasive	55%	0.007	53 gr	-	1b
	-	USG	26	carcinom	89%		51 gr		
Bennet (30)	-	WGL	28 (43)	Non palpable	83%	-	63.9 mm[a]	-	2b
		USG	42 (115)	breast lesions	93%		56.5 mm[a]		
Arentz (31)	-	WGL	38 (126)	Non palpable	52%	0.045	-	-	3
		USG	177 (329)	breast lesions	76%		-		
Haid (32)	-	WGL	61	Invasive	62%	0.002	-	-	2b
		US	299	carcinoma	81%		-		
Krekel (34)	-	WGL	117	Invasive	79%	0.023	54.9 $cm^{3\,b}$	0.16	3
		USG	52	carcinoma	96%		71.0 $cm^{3\,b}$		
		ROLL	32		75%		61.7 $cm^{3\,b}$		
Gray (39)		WGL	35 (51)	Non palpable	90%	0.01	-		2b
		RSL	26 (46)	breast lesions	76%				
Hughes (38)		WGL	79	Invasive	55%	0.001	-		2b
		RSL	306	carcinoma	73%				
Rao (40)		WGL	33	Invasive	46%	0.46	-		2b
		RSL	50	carcinoma	58%				

Calculations are based on patients with breast malignancies. ( ) patients in brackets stand for all non palpable breast lesions.

† OCEBM Levels of Evidence Working Group*. "The Oxford Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/

with clear margins. The authors reported a percentage of 83% clear margins in patients treated with WGL (N=43). The maximum diameter of the excised specimens did not differ significantly.

Post biopsy haematoma was used for tumour identification and localisation in a study performed by Arentz, et al.[31] Patients with non-palpable malignant and pre-malignant breast lesions were included and retrospectively analysed. In patients with malignant disease, US-guidance was performed in 177 patients and WGL in 38. A significantly higher margin clearance was reached when using US-guidance (76% vs. 52%). Data on the volume of the specimens are not reported.

Haid, et al. performed a prospective study in 360 patients, assessing the efficacy of US-guided surgery.[32] Based on the visibility of the lesion with US, 299 patients were allocated to the USG-group, 61 to the WGL-group. These were all patients with non palpable breast carcinomas. The USG group showed a significantly higher percentage of clear margins (81% in the USG group versus 62% in the WGL group), besides, the mean clear margin in the USG group was 4.8 mm versus 7.2 mm in the WGL group($p<0.001$). As in the two aforementioned studies, the choice of localisation procedure was based on the visibility of the lesion with US. The results are probably biased by selection, making them inconclusive.

Recently, a retrospective study was published by Krekel, et al (2010), evaluating the efficacy of WGL, ROLL and US-guided surgery in patients with non palpable invasive breast cancer.[33] In total 201 patients from 4 different centres were included. Of the excisions, 58% were performed by WGL, 26% by USG and 16% by ROLL. When comparing the rate of clear margins a significant difference was seen in favour of the USG-group. Here, 96% of the margins were clear from malignant tissue, whilst WGL and ROLL showed a rate of 79% and 75% respectively ($p<0.023$).

These percentages were based on the number of clear margins of the invasive tumour. When taking clear margins of unexpected DCIS into account, this difference

did not reach significance. When assessing the resection volumes, the calculated resection ratio (CRR) was used. This ratio was calculated by dividing the total resection volume by the optimal resection volume, consequently aiming for a ratio of 1. The CRR was significantly smaller when comparing WGL (2.8) to ROLL (3.8). The ratio calculated for the USG group did not differ significantly from the other groups (3.2).

Because all the data were retrospectively analysed, limitations of this study were the unbalanced number of patients spread over the different procedures and the selection bias. (table 2)

Radioactive 125I Seed localisation

In 1999 the first pilot study with radioactive seed localisation (RSL) of breast cancer was carried out by Dauway and colleagues.[34] This technique uses the radioactivity of a seed containing ^{125}I to localise the lesion. The radioactive seed is inserted into the breast lesion percutaneously prior to surgery guided by ultrasound or X-ray. During surgery, the lesion is localised by using a gammaprobe on the ^{125}I setting. For localisation of the sentinel lymph node, one uses the ^{99}TC setting. As a consequence, a gamma probe with the ability to detect radioactive isotopes with differing wavelengths should be available. After resection of the tissue, the gamma probe is used to verify if the ^{125}I activity is indeed present in the specimen. After inking the resection margins and sectioning the specimen, the seed is removed by the pathologist.[35]

A major advantage of localisation with an ^{125}I seed is that this isotope has a half-life of 60 days, so, contrary to the ROLL or WGL, there is no strict timing of this procedure and it can take place weeks before surgery. Another advantage is the fact that a ^{125}I seed is a point source and can therefore mark the lesion precisely, making it easier for the surgeon to perform a well placed incision. The surgeon is provided with constant real time feedback by using the gamma probe during the procedure, therefore he/she can adjust strategy at any time.[35,36]

A potential drawback in the use of RSL is the small chance of seed migration, causing the surgeon to perform an inadequate excision or even an excision without tumour tissue. Studies reported a seed migration rate in less than 2% of all cases.[36-38] Another limitation is that in contrast to the ROLL procedure, patients requiring a sentinel node procedure have to undergo an additional localisation procedure. Radioactive seed localisation also involves nuclear regulatory issues, which vary from country to country. Although the ^{125}I seeds have a short half-life and present little risk to the patient, they are radioactive and must be handled and disposed of correctly.[35]

Non controlled trials

Van Riet, et al. performed an uncontrolled prospective study including 325 patients with a histologically proven malignancy. Resection of the breast malignancies was done with RSL with a mean of 4 days between placement and removal of the seed. The resection margins were free from tumour in 95.4 % of the patients.[36] Mean volume of the specimen was 113 cm^3. (table 1)

RSL vs. WGL

Gray and co-workers carried out a trial comparing R SL with WGL.[39] In 2001 they randomised 97 women, with a non palpable breast lesion, for either RSL or WGL. In patients with malignant disease a significant difference (p=0.02) was seen in the rate of complete tumour removal with clear margins (RSL 74.3% vs. WGL 42.3%). No significant difference was seen in the volume of the excised tissue (RSL 55.7 ml vs. WGL 73.5ml).

In 2008 Hughes et al. compared the percentage of negative resection margins and pain and convenience scores between a group of 99 consecutive patients treated with WGL followed by a consecutive group of 383 patients treated with RSL.[38] Placement of the seed was performed ≥1 day prior to surgery in 69% of the patients. RSL had a significantly higher rate of clear resection margins, 73% vs 54% (p< 0.001) and a significantly better convenience score. The sentinel node success rate in both groups was 100%.

Rao, et al. implemented RSL in a public health care delivery system for a primarily minority and low income population.[40] Despite the difficulties encountered i.e. seed loss (2%) and lack of appropriate probes, RSL was still the preferred method of localisation based on the convenience of scheduling for patients, radiologists, and surgeons. The re-excision percentages of RSL and WGL were compared in a retrospective matched-pair analysis and showed a decrease, albeit insignificant, in the number of re-excisions when applying RSL. (table 2)

Expert commentary and five year view

In the past, high impact studies demonstrated that breast conserving surgery followed by postoperative radiotherapy should be considered golden standard treatment of patient with localized breast cancer.[41,42] Obtainment of clear resection margins during breast conserving surgery is the primary goal of the surgeon, as this is the most predictive factor for preventing local recurrence.[43] In order to perform an accurate surgical excision, exact localisation of the tumour is essential.

As a consequence of the rising number of non-palpable breast lesions, several localisation techniques have emerged over the past decades. Although some new localisation techniques show promising results and wire guided localisation is associated with many disadvantages, it is still the technique of choice for many breast surgeons. Studies on US guided localisation report good results, showing a range of 78- 96% adequate excisions.[27,28,30,32,33,44] However, this localisation technique can only be performed when the lesion is visible sonographically. Components of pre-malignant micro calcifications will be missed and tumour size is frequently underestimated, so patients undergoing this form of localisation should be selected based upon the radiological tumour characteristics in order to achieve clear resection margins. To overcome this disadvantage, various markers that are visible with US are being developed. These markers can be inserted at the site of the diagnostic biopsy directly after the (stereotactic guided) biopsy is performed, providing US detection of the lesion. During USG it is a necessity to have a well trained surgeon or radiologist performing the sonography. However, studies show that ultrasound imaging skills can be acquired by every surgeon in a short time.[45,46]

Localisation techniques based on radioactive substances are promising, but until now no conclusive studies have been published on the efficacy of these techniques due to the lack of randomisation and the small numbers of patients.

A relatively new radioguided surgical procedure is RSL. This localisation procedure is performed using the same technique as the WGL, excepting the localisation device itself; a seed instead of a hook wire. Because the seed is radioactive, this mode of localisation is hampered by regulations.[35] However, this technique has major advantages. Because the time between localisation and surgery is flexible, this technique has obvious logistic benefits. Besides, the technique allows for constant orientation of the tumour in the resection specimen, having a favourable impact on achieving negative resection margins. The former advantage also applies to the ROLL procedure, another promising radioguided localisation procedure. The ROLL procedure offers the important advantage of combining the sentinel node with the localisation procedure.

Presently, a multicentre randomised controlled trial is being conducted by our group comparing the ROLL technique with the WGL in order to determine if radioguided surgery is to be implemented as the standard of care.[47] Primary endpoints are the number of re-excisions and the volume of the specimen. Additionally, the ease of the procedure for the involved specialists will be assessed. Patients will be followed up to six months after surgery to obtain data on cosmetic outcome, quality of life and cost-effectiveness. Results of this study are expected at the end of 2011.

As both the ROLL and the ^{125}I seed have their specific advantages and disadvantages, the choice for one of these techniques should be patient and institution based, taking (dis)advantages into account. Conducting a well set up randomised controlled trial is essential for ascertaining which of these techniques is more precise and results in clear margins combined with good cosmesis.

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CHAPTER 3

Efficacy of 'radioguided occult lesion localisation' (ROLL) versus 'wire-guided localisation' (WGL) in breast conserving surgery for non-palpable breast cancer: a randomised controlled multicentre trial

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Abstract

Background

For the management of non-palpable breast cancer, accurate pre-operative localisation is essential to achieve complete resection with optimal cosmetic results. Radioguided occult lesions localisation (ROLL) uses the radiotracer, injected intra-tumourally for sentinel lymph node identification to guide surgical excision of the primary tumour. In a multicentre randomised controlled trial, we determined if ROLL is superior to the standard of care (i.e. wire-guided localisation, WGL) for preoperative tumour localisation.

Methods

Women (>18 yrs.) with histologically proven non-palpable breast cancer and eligible for breast conserving treatment (BCT) with sentinel node procedure were randomised to ROLL or WGL. Patients allocated to ROLL received an intra-tumoural dose of 120 Mbq technetium-99m nanocolloid. The tumour was surgically removed guided by gamma probe detection. In the WGL group, ultrasound or mammography guided insertion of a hooked wire provided surgical guidance for excision of the primary tumour. Primary outcome measures were the proportion of complete tumour excisions (i.e. with negative margins), the proportion of patients requiring re-excision and the volume of tissue removed. Data were analyzed according to intention to treat principle. This study is registered at ClinincalTrials.gov, number NCT00539474.

Findings

In total, 314 patients with 316 invasive breast cancers were enrolled. Complete tumour removal with negative margins was achieved in 140/162 (86%) patients in the ROLL group versus 134/152 (88%) patients in the WGL group (p=0.644). Re-excision was required in 19/162 (12%) patients in the ROLL group versus 15/152 (10%) (p=0.587) in the WGL group. Specimen volumes in the ROLL arm were significantly larger than those in the WGL arm (71 vs. 64 cm^3, p=0.017). No significant differences were seen in the duration and difficulty of the radiological and surgical procedures, the success rate of the sentinel node procedure, and cosmetic outcomes.

Interpretation

In this first multicentre randomised controlled comparison of ROLL versus WGL in patients with histologically proven breast cancer, ROLL is comparable to WGL in terms of complete tumour excision and re-excision rates. ROLL however, leads to excision of larger tissue volumes. Therefore ROLL cannot replace WGL as the standard of care.

Introduction

With the introduction of mammography screening and improvement of diagnostic methods, the majority of breast cancers are detected as small, non-palpable lesions, which are amenable to breast conserving treatment. When not palpable, the risk of incomplete tumour excision is substantial, as the involved area is hard to pinpoint. Therefore, accurate tools for localisation of non-palpable breast cancer are essential. The use of a hooked wire to guide surgeons for intra-operative localisation of non-palpable breast lesions was first described in 1965.[1] Even though wire-guided localisation (WGL) has proven to be a rather accurate and very useful localisation tool, it is associated with several shortcomings.[2] The wire tip gives no indication of the extent of the tumour and the amount of tissue to be excised is estimated by the surgeon intra-operatively. Therefore, WGL may lead to incomplete tumour resection in up to 50% of patients.[3-6] Moreover, wire insertion is time consuming, requires an extra mammography and is reported to be uncomfortable and painful for the patient.[7-11]

A promising alternative to wire localisation is radioguided occult lesion localisation (ROLL). Here, the intra-tumoural injection of radioactive tracer, already needed for lymphatic mapping and sentinel node biopsy (SNB) anyway, is used to localise the lesion with a gamma probe during surgery.[12] Several studies have reported the ROLL technique to be superior to WGL in achieving clear resection margins, cosmetic outcome and ease of the procedure for both surgeons and radiologists.[6,13,14] Nowadays however, clinical interpretation of these results is hampered by the fact that many of these studies compared ROLL with WGL in a diagnostic and non-randomised setting. Therefore, superiority of ROLL over WGL for the management of exclusively non-palpable breast cancer remains to be proven. The aim of this trial is to assess whether ROLL is superior to WGL in patients with invasive breast carcinoma requiring breast conserving surgery (BCS) with SNB.

Methods

Study design and patients

The methods of this study have been described in detail elsewhere.15 In short, patients were recruited at the outpatient surgical clinics of four sites in the Netherlands; three large community hospitals and one university medical centre. Women (>18 yrs) with biopsy proven non-palpable breast cancer and planned for BCS with SNB were eligible for inclusion.

The study was approved by the Medical Ethics Committee of all participating centres. All patients gave written informed consent. Pregnant or breastfeeding women, those with multifocal disease, in situ carcinoma only and women with breast implants were excluded from participation. All patients were treated according to a one-day protocol, where tracer injection, visualisation of the sentinel node and pre-operative tumour localisation were performed in the morning, and surgical excision of the breast tumour and sentinel lymph nodes in the afternoon.

Randomisation and masking

Patients were allocated to ROLL or WGL by an independent central telephone operator using centrally computerized randomisation, stratified per centre. Randomisation was performed after the patient was diagnosed with breast cancer. This being a pragmatic trial, masking was neither possible nor required.

Procedures

In order to guarantee the quality of the procedures a dedicated breast radiologist was available in all participating hospitals to provide a uniform protocol for the different procedures (i.e. intra-tumoural injection of the radiotracer and intra-tumoural placement of the wire). All surgeons participating in the study were dedicated breast surgeons, many of whom had experience with both ROLL and WGL before the start of the study. A dedicated breast surgeon, greatly experienced with the ROLL procedure, supervised the first ROLL procedure in each of the participating centres in order to ensure uniformly high quality and standard execution of the of ROLL procedures. The following ten ROLL procedures were attended by a member of the research team (resident surgeon / research nurse) and deviations to the protocol were reported to the surgeons.

ROLL procedure

All patients underwent intra-tumoural injection of the radiotracer (120 MBq 99mTc-nanocolloid in max 0,5 cc + air bubble) under stereotactic or ultrasound guidance (depending on the judgement of the dedicated breast radiologist). Scintigraphic imaging was performed 1-3 hours post injection and a dual head camera was used for acquiring images of the sentinel node. The skin projection of the sentinel node was marked by a nuclear medicine physician.

In the operating theatre, patent blue was injected peri-tumourally (guided by a handheld gammaprobe) at the site of the maximum count rate. The SNB and excision of the primary tumour were both guided by the gamma probe (Europrobe, Strassbourg, France). Correct excision of the tumour was verified by presence of a hot spot with maximal radioactivity in the surgical specimen.

Wire-guided localisation

Patients randomised to WGL underwent injection of the standard amount of radiotracer, either by peri-areolar injection or by means of an ultrasound or mammography guided intra-tumoural injection. Scintigraphy was performed 1-3 hours post-injection and the site of the sentinel node was marked as described above. In a next step, a guide wire was inserted into the tumour under stereotactic or ultrasound guidance.

Just before surgery, patent blue was injected either peri-tumourally (guided by maximum radioactivity counts) or peri-areolary. The gamma probe was not used for localisation of the carcinoma but for the SNB only. The inserted wire, together with mammographic images, was used as guidance during excision of the tumour.

Outcome measures

Patients were clinically assessed at baseline when clinical data and imaging abnormalities (lesion morphology, lesion site, BIRADS classification) were recorded.

Primary outcomes were the proportion of adequate excisions, the proportion of patients requiring re-excision and the volume of surgical breast specimens. An adequate excision was defined as complete removal of the tumour with tumour-free margins (i.e. no invasive carcinoma or DCIS at all the inked margins). For those with free margins, the distance (mm) from the cancer cells to the nearest inked margin of the specimen was recorded. Re-excision was defined as a second surgical intervention (i.e. relumpectomy or mastectomy) in the same breast within 6 months.

The total volume of the excised specimen was calculated with the ellipsoid formula using the three dimensions measured by the pathologist (4/3 π (0.5 length x 0.5 width x 0.5 height).[16] In case of fragmented breast lumps the volumes of the different fragments were totalled. All breast lump and sentinel node specimens underwent histological assessment according to a standard protocol. Central review of all surgical specimens was performed by two specialized breast reference pathologists (PJvD, SMW).

Secondary outcomes included patient reported outcomes, doctor reported outcomes and technical and medical complications.

Regarding patient reported outcomes, all women were asked to report their pain during tracer injection on a numeric visual analogue scale (VAS) (0 being not painful, 10 being very painful). When randomised for WGL, the patient was also asked to report the pain score during insertion of the wire. Cosmetic outcome was self-reported by the patient at baseline and at 6 months after surgery. Here, information regarding the patient's satisfaction with size and overall impression of the breasts and reported pain in the breasts was collected using an interviewer administered questionnaire (Likert scale).

Duration and difficulty of the (localisation) procedures performed at the imaging department were recorded by the radiologist. Duration was measured in minutes, difficulty was rated on a Likert- scale (1 being extremely easy and 10 extremely difficult). Difficulty and duration of the surgical procedures were rated by the surgeon on a similar rating scale.

Success rate of the sentinel node procedure (proportion of patients in whom a sentinel node was retrieved) was assessed and post-operative complications were prospectively collected following primary surgery and categorized according to Clavien Dindo's classification of surgical complications.[17]

Potential outcomes of the study were predefined.[15] Outcome of the study would be classified as negative when ROLL resulted in either lower proportions of tumour free margins, more tumour free margins in combination with larger resection volume or equal proportions of tumour free margins in both groups. A positive outcome was defined as more tumour free resection margins in combination with smaller resection specimens and equal tumour free margins in combination with smaller resection specimens. Other outcomes, i.e. more tumour free margins with an equal resection volumes or equal proportions of tumour free margins with smaller excised volumes would remain open to discussion.

Statistical analysis

Sample size calculation was based on the expected 15% difference in tumour free margins between the ROLL group and de WGL group in favour of the ROLL group.[13] At least 158 localisation procedures per group were needed to detect this difference with a two-sided α-level of 5% and a power of 80%.[15] All analyses were done in accordance with the intention-to-treat principle.[18] Normally distributed continuous variables were presented as means (standard deviation) and compared with independent t tests. Ordinal data and not-normally distributed data were presented as medians (range) and compared with the Mann Whitney U test. Chi square test was used to compare proportions of tumour free margins, re-excisions and successful

sentinel node procedures. Differences were considered significant when p< 0.05. This study is registered at ClinicalTrials.gov, number NCT00539474.

Role of funding source

This trial was funded by ZonMw. ZonMw had no role in study design, data collection, data analysis, data interpretation, or writing of the report. ELP, HMV and RvH had full access to all data and had final responsibility for the decision to submit for publication.

Results

Patients

Between Dec 1, 2007 and April 21st, 2011, 333 patients were recruited and randomised after informed consent. After randomisation, 19 (6%) patients withdrew. Of the remaining 314 patients with 316 non palpable breast carcinomas, 162 were allocated to ROLL and 152 were allocated to WGL. Two patients were diagnosed with bilateral non-palpable disease and underwent two localisation procedures. Due to technical or logistical reasons, four patients in the ROLL arm received WGL, while one patient in the WGL arm underwent a ROLL procedure. Retrieval of data on the primary outcome measures was 100% for the rate of inadequate excisions and re-excisions, and 97% for the volume of the lumpectomy specimen. Of the 314 patients enrolled, 277 (89%) completed the 6 months follow up questionnaire (figure 1). Patient, imaging and histological characteristics were well balanced between groups (table 1 and table 2). Mean patient age was 60.5 in the ROLL group and 61.1 years in the WGL group. In both groups the majority of the lesions was localised with ultrasound (92% vs. 95%). The average tumour size was 1.3 cm in the ROLL group and 1.2 cm in the WGL group. The percentage of invasive carcinoma with an in situ component did not differ with 55% in the ROLL group and 51% in the WGL group (p=0.42).

Primary outcome measures

No significant difference was observed in the proportion of adequate excisions: 140/162 (86%) in the ROLL arm versus 134/152 (88%) in the WGL arm (p=0.644) (table 3). Distance to the closest inked margin in specimens with free resection were comparable between groups, with a mean of 0.4 cm in the ROLL group and 0.5 cm in the WGL group. Re-excision (re-lumpectomy or mastectomy) was required in 19 (12%) of patients in the ROLL group versus 15 (10%) in the WGL group (p=0.582). The remaining 6 patients had focally involved margins and were treated with a radiotherapy boost.

The total amount of tissue excised during surgery was significantly larger in patients treated with ROLL; 71 cm^3 vs. 64 cm^3 in the WGL group (p=0.017). The maximal diameter of the ROLL specimen was 7.5 cm vs. 7.0 cm in the WGL specimen (p =0.001).

Patient reported outcomes

Patients experienced similar pain in both groups during injection of the technetium-99m nanocolloid, with a median score of 3 (range 1-10). Patients in the WGL group rated the wire insertion as moderately painful (score of 4, range 1-10).[19]

At baseline, women in both groups rated the cosmetic aspects of their breasts similarly in the two groups. Six months after surgery no significant differences were seen in the overall cosmetic results (table 4).

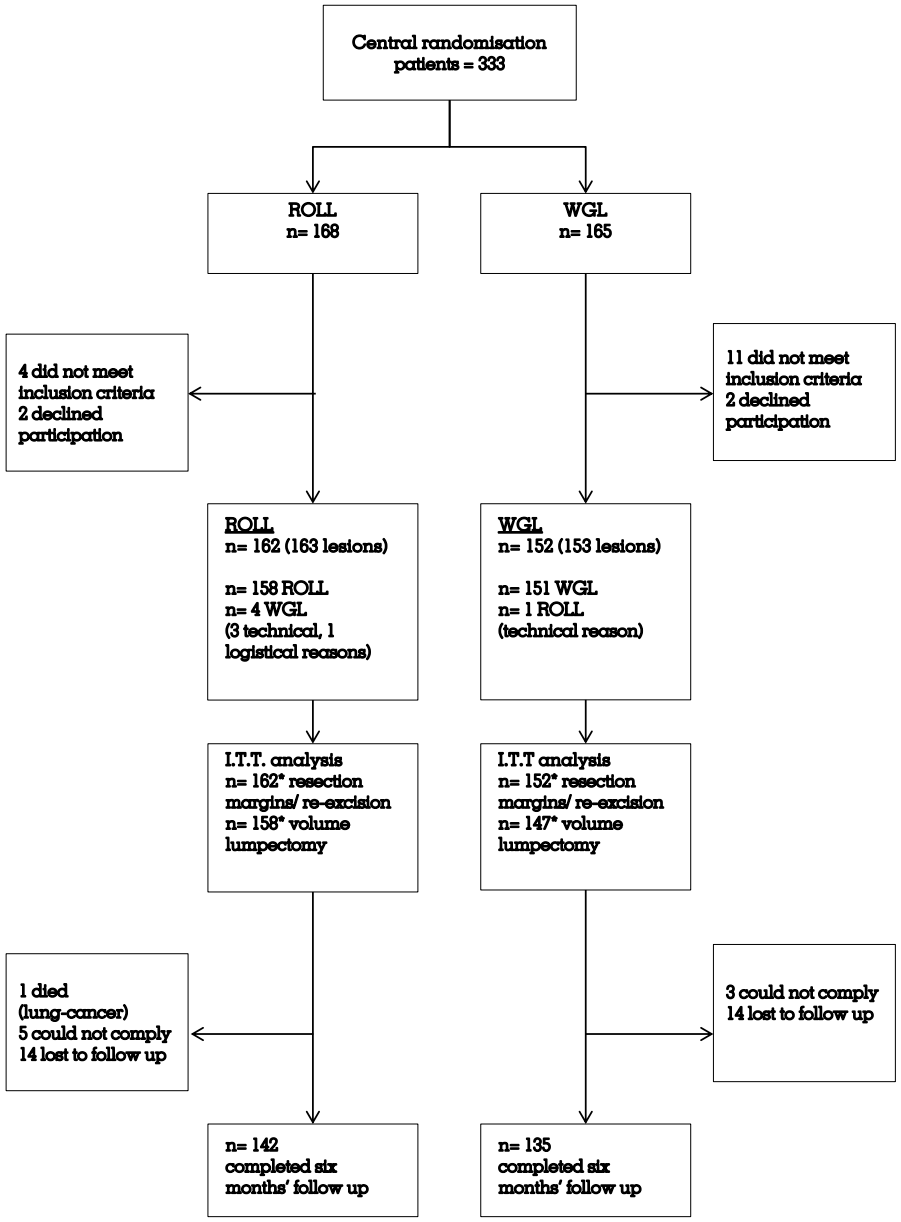
Doctor reported outcomes

Injection of the radioactive tracer was rated as equally difficult between the groups (score of 3 (range 1-10) for both groups). Also, no difference in duration of tracer injection was measured between the two groups. Wire insertion was rated as moderately difficult (4), and took 9 (range 1-60) minutes on average.

Duration of the surgical procedures did not differ between groups, nor did the difficulty of the sentinel node procedure or the lumpectomy (4, range 1-10 in both groups) (table 5).

Retrieval of the SNB during surgery was successful in 95% in both groups. When

Figure 1 | Trial profile ROLL trial



ROLL= radioguided occult lesion localisation, WGL = Wireguided localisation, I.T.T.= intention to treat.
*number of patients of which primary outcome measures were retrieved (adequacy excision, re-excision and volume of lumpectomy specimen)

unsuccessful, all but one patient (because of age) underwent axillary lymph node dissection.

The rate and severity of the post-operative complications were not significantly different between the groups.

Discussion

In this multicentre randomised trial, the first of its kind in patients with proven breast cancer, we show that ROLL is not superior to WGL in terms of complete tumour excision and re-excision rates and leads to removal of larger tissue volumes, with no measurable impact on cosmetic outcome. As predefined in our study protocol, this result is considered a negative one.20 For this reason, ROLL cannot replace WGL as the standard of care.

The outcome of our study contradicts several earlier studies, which showed more favourable results of the ROLL procedure, including higher rates of complete excision and smaller removal of tissue volumes.6,13,14 There are several explanations for this discrepancy between our findings and the positive findings from the literature.

First, most previous studies were performed in patients requiring excisional biopsy for diagnostic purposes. Those results are not very useful for current clinical practice, since most patients undergo preoperative core needle biopsy. Diagnostic surgical biopsy is hardly ever performed, as international guidelines state that more than 90% of patients with breast cancer should receive a diagnosis prior to surgery.

Only one randomised clinical trial compared ROLL to WGL in exclusively patients with proven breast cancer.[21] They found similar results for ROLL and WGL in terms of complete tumour excision with tumour free margins (89.4% vs. 82.4% respectively, p=0.730), but shorter duration of the ROLL procedure. However this was a single centre study, including only 134 patients with invasive as well as in situ cancer. In patients with in situ cancer, there is hardly any indication to perform a SNB, except

Table 1 | Patient and imaging characteristics at baseline

	ROLL group (n=162; 163 lesions)		WGL group (n=152; 153 lesions)	
Mean Age (standard deviation)	**6.0 (7.7) yrs**		**61.1 (9.7) yrs**	
Menopausal status				
Pre menopausal	15	**9%**	20	**13%**
Post menopausal	136	**84%**	124	**82%**
Not reported	11	**7%**	8	**5%**
Detection primary tumour				
Organised Screening Program	124	**77%**	112	**74%**
High risk* screening	12	**7%**	8	**5%**
Clinical symptoms	8	**5%**	6	**4%**
Not reported	18	**11%**	26	**17%**
Number of lesions				
1	161	**99%**	151	**99%**
2	1	**1%**	1	**1%**
Visible on				
Mammography + ultrasound	150	**93%**	142	**94%**
Ultrasound only	8	**5%**	6	**4%**
Mammography only	4	**3%**	5	**3%**
Findings Mammography				
Density	115	**70%**	114	**74%**
Density + microcalcification	24	**15%**	20	**13%**
Microcalcifications	5	**3%**	3	**2%**
Visible on US only	8	**5%**	4	**3%**
Unknowns	11	**7%**	12	**8%**
Site tumour				
ULQ	60	**37%**	63	**41%**
UMQ	22	**13%**	20	**13%**
LLQ	20	**12%**	10	**7%**
LMQ	12	**7%**	15	**10%**
Central	45	**27%**	37	**24%**
Axillary	1	**1%**	0	**0%**
Not reported	3	**2%**	8	**5%**
BIRADS classification				
BIRADS I-3	8	**5%**	12	**9%**
BIRADS 4	66	**40%**	70	**45%**
BIRADS 5	70	**43%**	66	**43%**
Not reported	19	**11%**	5	**3%**
Method of tumour localisation				
Ultrasound	150	**92%**	146	**95%**
Mammography	13	**8%**	7	**5%**

Imaging characteristics (visible on, mammographic findings, tumour site, BIRADS, method of localisation) are given on lesion level (n=316). BIRADS= Breast Imaging Reporting and Data System. ULQ= upper lateral quadrant, UMQ= upper medial quadrant, LLQ=lower lateral quadrant, LMQ= lower medial quadrant*Genetic predisposition, hormone treatment, follow up after breast cancer

Table 2 | Tumour characteristics and nodal stage

	ROLL (n=163)		WGL (n=153)	
Tumour characteristics				
Median size invasive carcinoma (range)	**1.30 (0.1-3.5) cm**		**1.25 (0.3-6.0) cm**	
Histologic type				
Ductal	135	**83%**	137	**90%**
Lobular	14	**9%**	7	**5%**
Ductolobular	9	**5%**	7	**5%**
Other	5	**3%**	2	**1%**
Bloom and Richardson				
Grade I	67	**41%**	71	**46%**
Grade II	71	**44%**	58	**38%**
Grade III	18	**11%**	23	**15%**
Not reported	7	**4%**	1	**1%**
DCIS component				
Yes	90	**55%**	78	**51%**
No	66	**41%**	70	**46%**
Unknown	7	**4%**	5	**3%**
Estrogen receptor status				
Positive	145	**89%**	140	**91%**
Negative	10	**6%**	11	**7%**
Not reported	8	**5%**	2	**1%**
Progesterone receptor status				
Positive	128	**78%**	127	**83%**
Negative	27	**17%**	23	**15%**
Not reported	8	**5%**	3	**2%**
Her2Neu receptor status				
Positive	13	**8%**	8	**5%**
Negative	139	**85%**	143	**94%**
Not reported	11	**7%**	2	**1%**
Sentinel node				
Tumour free	118	**72%**	118	**77%**
Macrometastases	23	**14%**	17	**11%**
Micrometastes	11	**7%**	9	**6%**
Isolated tumourcells	10	**6%**	8	**5%**
No lymph nodes dissected	1	**1%**	1	**1%**

Data are numbers with percentage of group total and given on lesion level (n=316).

DCIS: ductal carcinoma in situ

for larger palpable or grade 3 lesions. We therefore do not consider this a suitable indication for a ROLL procedure.

Another explanation for the absence of superiority of ROLL over WGL found in our study may be related to the good results that were obtained by the standard intervention, WGL. Compared to the literature, the proportion of complete excisions in the ROLL group is in line with other studies (78-92%).[6,14] However, the proportion of adequate excisions in the WGL group in our study, i.e. 86%, is substantially higher than those reported previously (i.e. 50-88%).[6,13,21-24] As the share of non palpable breast cancers has increased over the last few years in The Netherlands, the experience of the physicians with the WGL procedure is substantial, possibly causing this relatively high rate of clear resection margins in the WGL group.

A straightforward explanation for excision of larger tissue volumes in the ROLL group is difficult to find. Potentially, a hooked wire is more helpful for a surgeon to exactly pinpoint the centre of the lesion, while the maximal amount of counts (used as guidance during the ROLL procedure) is often more diffuse. In addition, surgeons may have the tendency to continue removing additional tissue when radioactivity is still traceable within the breast.

Ideally, excised tissue volume is measured by submerging the specimen in water and measuring the volume of water displaced. As an alternative, we calculated the specimen volumes with the ellipsoid formula, using the three dimensions reported by the pathologist. We chose to use these measurements as they are routinely performed in every patient, making our results easy to reproduce and compare/apply in future- or retrospective studies.

We acknowledge that this method has its limitations. The formula applied for calculation is based on the assumption that breast specimens are commonly ellipsoid or spherical.[16] In reality the shape of the excised specimen may vary, making this method of calculation less accurate in a part of the patients. Also, possible shrinkage of the specimen between surgery and histopathological assessment is not taken into consideration.[25,26] Krekel, et al. quantitatively assessed the difference between surgical and pathological estimates of specimen volumes in 68 patients. A discrepancy of 2.1cm^3 between the actual volume (water displacement) and the ellipsoid specimen volume calculations (measurement by pathologist) was observed.[27]

Given the fact that calculation of the excised volumes was performed similarly in both study arms, a possible difference between the calculated volume and the actual volume will be evened out between both trial groups, resulting in the same outcome, namely that ROLL leads to excision of more tissue volume. This assumption is supported by our additional analyses comparing the maximum diameter and cubical volume between both group. Both show equal results, that is significantly higher figures in the ROLL group.

Assessment of the secondary outcomes showed no significant differences between the groups. A benefit of ROLL over WGL is that it avoids one extra, moderately painful procedure, i.e. wire placement. Interestingly, despite the larger amount of breast tissue removed, the cosmetic outcomes were not significantly different. Reason for this could be that the surgeon is free to choose the optimal site of the incision (without interference of a hooked wire) and can therefore acquire the same cosmetic results, despite excising more volume. At the same time, the mean maximal size of the excised specimen differed by only 5 mm, which is probably not clinically relevant with respect to cosmetic outcome.

Over the past years, other techniques, in particular radioactive seed localisation (RSL) are increasingly being introduced as alternatives to WGL. With RSL, an Iodine^{125} seed is placed in the breast lesion, which is used by the surgeon to guide the tumour

excision. Advantage of RSL is that the seed can be placed up to 14 days prior to surgery, making the entire procedure logistically less challenging.[28] In a multicenter randomised controlled trial, Lovrics and co-workers recently compared RSL with WGL. RSL and WGL showed similar rates of positive margins (RSL 10.5% vs. WGL 11.8%) and re-operation, and RSL was rated as less difficult by the surgeon, making it an acceptable localisation method.[29] To date, none of the emerging localisation methods have well proven to be superior to the standard WGL. To conclude, in patients with histologically proven breast cancer ROLL is not superior to WGL in terms of complete tumour excision and re-excision rates and a larger volume of tissue is excised with ROLL. For this reason ROLL cannot replace WGL as the standard of care for localising non-palpable breast cancer.

Table 3 | Inadequate excision rates, re-excision rates, volume and maximum diameter lumpectomy specimens, success rate SNB and postoperative complications.

	ROLL (n=162)		WGL (n=152)		P value
Inadequate excision*					
Overall	22	**14%**	18	**12%**	**0.644**
Invasive carcinoma	21	**12%**	13	**8%**	**0.340**
DCIS	1	**1%**	5	**3%**	**0.081**
Re-excisions**					
Overall	19	**12%**	15	**10%**	**0.582**
Re-lumpectomy	13	**8%**	13	**9%**	**0.841**
Mastectomy	6	**4%**	2	**1%**	**0.185**
Specimen volume (median with range)†	**71(50-101) cm^3**		**64 (39-91) cm^3**		**0.017**
Max diameter specimen (median with range)†	**7.5 (6.0-8.5) cm**		**7.0 (5.6-8) cm**		**0.001**
Sentinel node biopsy					
Succesfull	154	**95%**	143	**94%**	**0.681**
Postoperative complications					
Hematoma	6	**4%**	3	**2%**	**0.359**
Seroma	7	**4%**	8	**5%**	**0.696**
Infection	12	**7%**	9	**6%**	**0.598**

Data are number and % of group total. *inadequate excision= malignant (DCIS/invasive) cells in one of the margins or carcinoma not in specimen. ** re-excision = second surgery (relumpectomy or mastectomy) in the same breast within two months. † ROLL n=158, WGL n=147. Hematoma= a clinically evident collection of blood filling the lumpectomy cavity in the breast or axillary, requiring aspiration or re-operation. Seroma= a clinically evident collection of fluid filling the cavity in the breast or axillary requiring aspiration. Infection= an infection due to lumpectomy or sentinel node procedure, requiring antibiotic treatment

Table 4 | Patient reported outcomes (cosmetic results and pain) at baseline versus 6 months

	Baseline					6 months				
	ROLL (n=158)		WGL (n=148)		p value	ROLL (n=142)		WGL (n=135)		p value
Overall cosmetic score	8 (1-10)		7 (1-10)		**0.871**	8 (1-10)		8 (1-10)		**0.554**
Satisfaction breast size					**0.792**					**0.199**
Not satisfied	4	**3%**	6	**4%**		9	**6%**	9	**7%**	
A Little	25	**16%**	19	**13%**		27	**19%**	15	**11%**	
Quite	80	**51%**	76	**51%**		75	**53%**	86	**64%**	
Very	49	**31%**	47	**32%**		31	**22%**	25	**19%**	
Pain in breast					**0.578**					**0.851**
None	100	**63%**	101	**68%**		42	**30%**	45	**33%**	
Rarely	45	**28%**	40	**27%**		79	**49%**	69	**51%**	
Frequently	12	**8%**	6	**4%**		17	**13%**	17	**13%**	
Most of the time	1	**<1%**	1	**<1%**		3	**2%**	4	**3%**	

Overall cosmetic score: scored on a 1-10 scale (1 very dissatisfied- 10 very satisfied). Data are median (range), or number and % of the group, or p value.

Table 5 | Doctor reported outcomes

	ROLL group (n=162)	WGL group (n=152)	Pvalue
Radiological procedures	2 (1-10)	2 (1-8)	**0.642**
Difficulty injection radiotracer (median with range)		3 (1-10)	-
Difficulty insertion Wire (median with range)	5 (1-45)	5 (1-30)	**0.747**
Duration injection radiotracer (median with range)		7 (1-60)	-
Duration insertion wire (median with range)			
Surgical procedures	4 (1-10)	5 (1-10)	**0.548**
Difficulty sentinel node biopsy (median with range)	4 (1-10)	4 (1-10)	**0.996**
Difficulty lumpectomy (median with range)	13 (3-75)	15 (3-90)	**0.156**
Duration sentinel node biopsy (median with range)	18 (7-50)	16 (6-80	**0.133**
Mean duration lumpectomy (median with range)	32 (13-98)	31 (13-106)	**0.867**
Total duration (median with range)			

Procedures were scored by the doctor performing the procedure. Difficulty was rated on a Likert type scale (1 very easy – 10 very difficult). Duration of the procedures was recorded in minutes.

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CHAPTER 4

Cost-effectiveness of 'radioguided occult lesion localisation' (ROLL) versus 'wire-guided localisation' (WGL) in breast conserving surgery for non-palpable breast cancer: results from a randomised controlled multicentre trial

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Abstract

Background

Accurate pre-operative localisation of non-palpable breast cancer is essential to achieve complete resection. Radioguided occult lesion localisation (ROLL) has been introduced as an alternative for wire-guided localisation (WGL). Although efficacy of ROLL has been established in a RCT, cost-effectiveness of ROLL compared with WGL is not yet known. The objective of this study was to determine whether ROLL has acceptable cost-effectiveness compared with WGL.

Methods

An economic evaluation was performed alongside a randomised controlled trial (ClinicalTrials.gov, number NCT00539474). Women (>18 years) with histological proven non-palpable breast cancer and eligible for breast conserving treatment with sentinel node procedure were randomised to ROLL (n=162) or WGL (n=152). Empirical data regarding direct medical costs was collected, and changes in quality of life were measured over a 6 months period. Bootstrapping was used to assess uncertainty in cost-effectiveness estimates, and sensitivity of the results to the missing data approach was investigated.

Results

In total, 314 patients with 316 invasive breast cancers were enrolled. On average ROLL required the same time as WGL for the surgical procedure (119 vs. 118 min.), resulted in a 7% higher re-interventions risk and 13% more complications. Quality of life effects were similar (difference 0.00 QALYs 95% CI (-0.04 to 0.05). Total costs were also similar for ROLL and WGL (+ €26 per patient 95% CI -250 to 311).

Conclusion

ROLL is comparable to WGL with respect to both costs and quality of life effects as measured with the EQ5D, and will therefore not lead to more cost-effective medical care.

Introduction

In the Netherlands, 13,000 women are newly diagnosed with breast cancer every year.[1] Up to 30% of these breast cancers (approximately 4,000) are detected as small, non-palpable lesions which are suitable for breast conserving treatment. As the lesion is non-palpable, the involved area is hard to pinpoint and the risk of incomplete tumour excision increases. Consequently, a second surgical intervention is often required for complete clearance of malignant cells.[2-6]

Re-intervention and the associated hospitalization of the patients leads to a substantial increase in costs. In general, wire guided localisation (WGL) is applied to guide excision of non-palpable breast cancers.[7] Although this is a helpful localisation tool it is known to have several disadvantages and is associated with a high risk (up to 50%) of re-excision.[2,3,5,6,8-13]

Radio-guided occult lesion localisation (ROLL) is an alternative localisation tool that offers the advantage of combining sentinel node detection and the localisation of the carcinoma intra-operatively. Per patient, on average €114 (costs material, personnel) can be saved by combining these procedures. Recently, we determined the efficacy of ROLL compared to WGL in a randomised controlled trial (RCT).[14] We concluded that ROLL is not superior to WGL in oncologic outcomes and can therefore not replace WGL as standard localisation procedure. Cost effectiveness of ROLL is however yet to be determined. As such, we conducted an economic evaluation alongside our RCT to assess the cost-effectiveness of ROLL compared with WGL in patients with non-palpable breast cancer.

Methods

Study design and patients

Shortly, in this RCT, patients were recruited from surgical outpatient clinics at four sites in the Netherlands; three large community hospitals and one university medical center. The study was approved by the Medical Ethical Committee of all participating hospitals. Women (>18 years) with biopsy proven non-palpable breast cancer and planned for breast conserving surgery (BCS) with sentinel node biopsy (SNB) were eligible for inclusion. Patients were randomly allocated to ROLL or WGL. At baseline, patients were clinically assessed and clinical data and imaging abnormalities (lesion morphology, lesion site, BIRADS classification) were recorded.

In the ROLL arm the radiotracer, injected intra-tumourally for sentinel lymph node identification, was also used to guide surgical excision of the primary tumour. In this arm, the SNB and excision of the primary tumour were both guided by the gamma probe (Europrobe, Strassbourg, France). Correct excision of the tumour was verified by presence of a hot spot with maximal radioactivity within the surgical specimen.

Patients in the WGL arm underwent injection of the standard amount of radiotracer. In the next step, a guide wire was inserted into the tumour under stereotactic or

Table 1 | Patient characteristics and imaging at baseline

	ROLL (n=162)		missing	ROLL (n=152)		missing
Mean Age (standard deviation)	60.5 (7.7) yrs		0%	61.1 (9.7) yrs		0%
Detection primary tumour			11%			17%
Organised Screening Program	124	77%		112	74%	
High risk screening	12	7%		8	5%	
Clinical symptoms	8	5%		6	4%	
Visible on			0%			0%
Mammography + ultrasound	150	93%		141	93%	
Ultrasound only	8	5%		6	4%	
Mammography only	4	3%		5	3%	
Findings Mammography			7%			8%
Density	115	70%		114	74%	
Density + microcalcification	24	15%		20	13%	
Microcalcifications	5	3%		3	2%	
Visible on US only	8	5%		5	3%	
Method of tumour localisation			0%			0%
Ultrasound	149	92%		145	95%	
Mammography	13	8%		7	5%	
Mean EQ5D T=0 (SD)	0.861 (0.16)		2%	0.831 (0.18)		3%
Mean EQVAS T=0 (SD)	76.9(12.4)		2%	75.1(14.9)		3%

Table 2 | Outcomes of the localisation- and surgical procedures, and 6 months' follow up

	ROLL (n=162)		missing	WGL (n=152)		missing	Pvalue
Duration wire loc. (median, range)				7 (1-60)		25%	-
Duration SNB (median, range)	13 (3-75)		17%	15 (3-90)		23%	0.156
Duration lump (median, range)	18 (7-50)		15%	16 (6-80)		21%	0.133
Lump + SNB (median, range)	32 (13-98)		16%	31 (13-106)		21%	0.867
Total duration surgery (median, range)	122 (77-194)		80%†	132 (72-218)		79%†	0.150
Inadequate excision*			0%			0%	
Overall	22	14%		18	12%		0.644
Invasive carcinom	21	12%		13	8%		0.340
DCIS	1	1%		5	3%		0.081
Re-excisions**			0%			0%	
Overall	19	12%		15	10%		0.582
Re-lumpectomy	13	8%		13	9%		0.841
Mastectomy	6	4%		2	1%		0.185
ALND	25	15%		19	13%		0.454
Complications***			0%			0%	
Hematoma surgical	5	3%		1	1%		0.118
Hematoma, puncture	1	1%		2	1%		0.521
Seroma surgical	1	1%		0	1%		0.334
Seroma puncture	24	15%		14	9%		0.133
Infection, antibiotics	25	16%		14	9%		0.099
Infection, surgical	1	1%		0	0%		0.334
Chemotherapy	48	30%	<1%	34	22%	2%	0.153
Mean EQ5D							
T=6	0.850(0.19)		0%	0.828(0.20)		0%	0.134
T=12	0.835(0.19)		7%	0.801(0.20)		7%	0.142
T=26	0.825(0.16)		9%	0.796(0.19)		9%	0.182
Mean EQVAS							
T=6	73.0 (14.3)		0%	73.5 (12.3)		0%	0.772
T=12	72.0 (13.0)		7%	71.6 (14.1)		7%	0.788
T=26	72.4 (13.6)		9%	72.0 (13.5)		9%	0.840

*inadequate excision= malignant (DCIS/invasive) cells in margins or carcinoma not in specimen. ** re-excision = second surgery (relumpectomy or mastectomy) in the same breast within two months. *** Complications reported up to 6 months after surgery. Wire loc: image guided wire localisation . ALND: axillary lymph node dissection. Lump: lumpectomy. †This variable was only registered in one hospital, the percentage missing is given over the whole patient group

ultrasound guidance.

The SNB was guided by gamma probe. The inserted wire, together with mammographic images, was used as guidance during excision of the tumour. All randomised women were included in this economic evaluation and were analyzed according to the intention to treat principle. The methods of this study have been described in detail elsewhere.[15]

Outcomes

Quality of life was measured utilizing two methods: the EQ5D questionnaire and the EQ5D visual analog scale (EQVAS).[16] Data on EQ5D and EQVAS score were collected at baseline and at 6, 12, and 26 weeks following surgery. For our analysis we used quality of life as calculated from the EQ5D questionnaire. To assess the robustness of our results, we repeated our analysis using EQVAS data.

Duration of the various procedures (i.e. wire placement, radiotracer injection, SNB and lumpectomy) was routinely recorded. Durations of the localisation procedures (i.e. injection radiotracer and wire placement) performed at the imaging department were recorded by the radiologist. Durations of the surgical procedures (i.e. SNB and lumpectomy) were recorded by the surgeon. Registration of the total duration of the initial surgical procedure (actual OR time) was performed in one centre in 70 patients. For patients from the other centers, total duration of surgery was estimated based on the duration of their separate procedures (table 2).

For all patients, data were collected regarding time required for the radiological and surgical procedures. Throughout the first 6 months after surgery, data on re-interventions (i.e. re-lumpectomy, mastectomy, and axillary lymph node dissection) and complications, such as hematomas, seromas, and wound infections, were registered. Total costs per patient were calculated based on the unit costs for specific medical personnel required, materials used, and use of the operation room, multiplied by the registered time periods and volumes. All unit costs were based on internal cost

calculations performed at the University Medical Centre Utrecht, and shown in table 3, with additional details provided in the appendix.

Table 3 | Global overview of cost components.

PROCEDURE	COSTS*	
	Set costs	Variable costs (costs/hour)
Lumpectomy*	€ 584.00	€770.00 (surgeon, OR)
Wire localisation*	€ 96.00	€200.00 (radiologist)
Re-lumpectomy	€ 1354.00	-
Mastectomy	€ 2522.00	-
Re-excision with ALND	€ 1739.00	-
ALND	€ 1097.00	-
Complication related costs		
Surgical treatment	€ 1161.50	-
Puncture (drainage hematoma or seroma)	€ 107.30	-
Antibiotics (wound infection)	€ 112.70	-

All unit costs were based on internal cost calculations performed at the University Medical Centre Utrecht.

* Cost for the primary surgery and wire placement were calculated by adding up the set cost and the costs per hour multiplied by the duration of the procedure. ALND: Axillary lymph node dissection. For additional details see the appendix.

Analysis

Health related quality of life assessments collected with the EQ-5D instrument were converted to utility scores. To assess the effect of missing values on our cost-effectiveness estimates, we repeated our analysis using three well known mechanisms to deal with missing values: 1) complete case analysis, 2) mean imputation, and 3) multiple imputation.[17,18] For complete case analysis we first selected all patients without missing values. Subsequently, bootstrapping of these complete cases was used to estimate cost-effectiveness. For mean and multiple imputation the full dataset was bootstrapped and missing values were subsequently imputed either by the mean value (separately for the ROLL and WGL groups), or based on the multiple imputation model (with 10 imputation sets). Bootstrapping was performed using 5,000 samples. Single imputation was also performed, but due to the large number of bootstrap samples the results were identical for single and multiple imputation, so results are only shown for multiple imputation. It has been shown that multiple imputation consistently yields the most valid results.[17,19] Therefore, we focus here on the cost-effectiveness results obtained by multiple imputation.

For the cost-effectiveness analysis we assumed that once tumour free margins of excision are obtained, the prognosis of patients in both groups will be similar. Consequently, a long-term analysis of costs and effects will not provide additional insight, which justifies our time horizon of 6 months. Given the assumption of similar prognosis, all (in)direct medical costs as well as (in)direct non-medical costs were assumed to be similar in both groups after 6 months. Discounting was not applied because of the short time horizon. Based on the difference in health benefits and costs in the bootstrap samples, we calculated the Net Monetary Benefit (NMB) instead of the incremental cost-effectiveness ratio (ICER) to avoid unstable estimates due to very small differences in health effects. The NMB is defined as the difference in health benefits multiplied by the ceiling ratio, i.e. the accepted cost threshold to gain one QALY, minus the difference in costs. We calculated the NMB for ceiling ratios of € 20,000/QALY and € 80,000/QALY, the thresholds currently applied in the Netherlands. A positive NMB value implies that the balance between additional health effects and additional costs is favourable, whereas a negative NMB value implies that this balance is unfavourable. Results were represented in a cost-effectiveness plane and a cost-effectiveness acceptability curve.[20]

Results

Data of all 314 patients were available for analysis. Baseline patient and imaging characteristics were comparable between both groups.

Clinical outcomes

The EQ5D and EQVAS scores were registered for >90% of the patients at all four time points table 1). At baseline, quality of life scores were well balanced between both groups; the EQ5D was 0.861 in the ROLL and 0.831 in de WGL group. The EQVAS was 76.9 versus 75.1 respectively. (table 1) Duration of the separate procedures was

Figure 1A | The cost-effectiveness plane for ROLL compared with WGL.

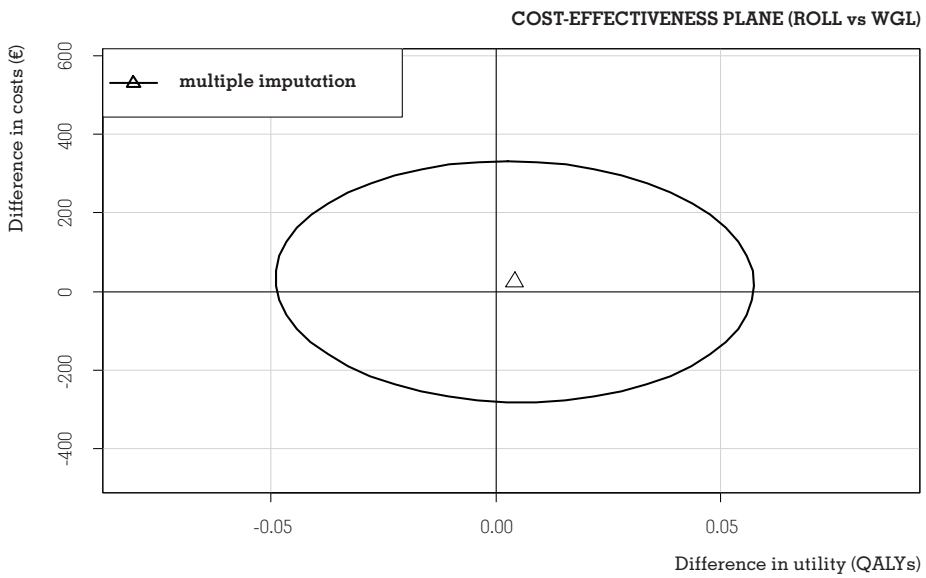

Figure 1A shows the difference in costs and effects for ROLL compared with WGL. Here, the ellipse represents the 95% CI, and the marker the corresponding mean value.

Figure 1B | The cost-effectiveness acceptability curve for ROLL compared with WGL.

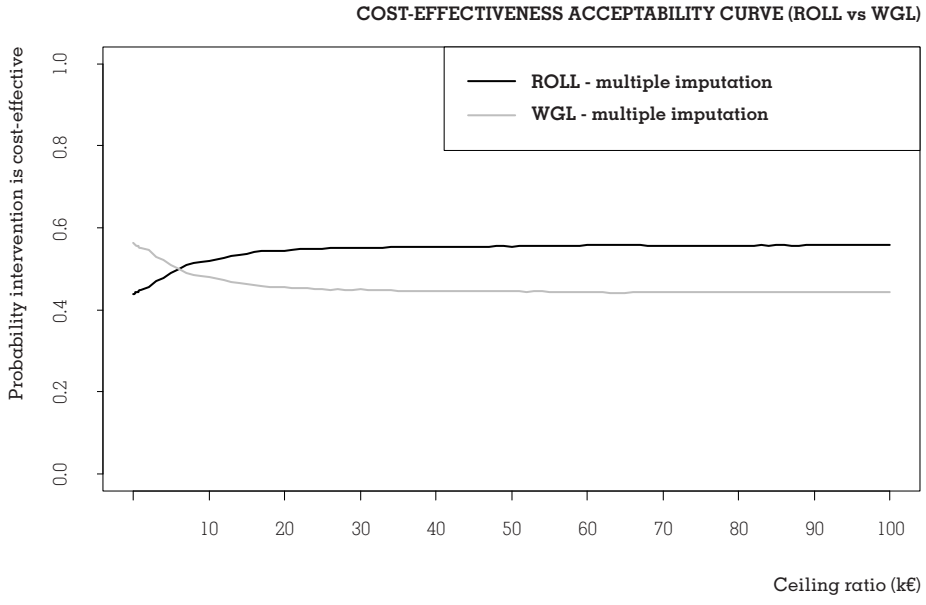

Figure 1B shows the probability that the cost-effectiveness of ROLL compared with WGL is acceptable, for a range of values of the maximum acceptable ceiling ratio, that is, for the maximum amount of money policy makers would be willing to pay for one additional quality-adjusted life year.

available for analysis in 75 to 85% of the patients. The total duration of the initial surgical procedure was similar for ROLL and WGL (table 4). The risk of complications up to 6 months after surgery was higher for ROLL than for WGL (30% vs. 17%, p=0.006) (table 4). There was no difference between groups in change between baseline and the 6 month follow up EQ5D score. The costs of the initial procedure are roughly similar given that both procedures require the same amount of time (table 4).

Cost- effectiveness analysis

Although the costs of tumour localisation were lower for ROLL (a cost-saving of € 114 per patient (95%CI € 111-117)), these savings were offset by higher costs due to re-interventions and complications of € 108 and € 48 on average per patient. Consequently, the ROLL procedure does not appear to be cost saving compared to the WGL procedure and results in similar health related quality of life benefits as measured by the EQ5D.

The confidence ellipse shown in the incremental cost-effectiveness plane indicates that the use of ROLL is not more preferable regarding costs and quality of life related health benefits than WGL (figure 1a). Table 4 also shows the actual probabilities that the one intervention would be more or less costly and more or less effective than the other, which range from 18% to 31%.

Figure 1b shows the probability that ROLL has acceptable cost-effectiveness for a chosen range of ceiling ratios. Apart from very low values for the ceiling ratio (< € 6,000 per QALY) it is clear that ROLL does not have a high probability of having acceptable cost-effectiveness compared to WGL and vice versa. When repeating our analysis with the EQVAS quality of life estimates instead of the EQ5D score, results were similar. In addition, repeating the analysis and applying complete case analysis and mean imputation analysis again resulted in similar cost-effectiveness outcomes, with complete case analysis indicating larger uncertainty in all outcomes due to the fact that all patients with any missing data were excluded (results not shown).

Table 4 | Differences in outcomes for ROLL and WGL and summary of cost-effectiveness.

Outcomes	WGL procedure		ROLL procedure			
	estimate	95%CI	estimate	95%CI	estimate	95%CI
Risk of complications (total)	0.17	0.11 to 0.24	0.30	0.23 to 0.37	0.13	0.04 to 0.22
Haematoma surgically treated	0.01	0.00 to 0.02	0.03	0.01 to 0.06	0.2	0.00 to 0.05
Haematoma treated with puncture	0.01	0.00 to 0.03	0.01	0.00 to 0.02	- 0.01	- 0.03 to 0.01
Seroma surgically treated	0.00	0.00 to 0.00	0.01	0.00 to 0.02	0.01	0.00 to 0.02
Seroma treated with puncture	0.09	0.05 to 0.14	0.15	0.10 to 0.20	0.06	- 0.02 to 0.13
Infection treated with antibiotics	0.09	0.05 to 0.14	0.15	0.10 to 0.21	0.06	- 0.01 to 0.13
Infection surgically treated	0.00	0.00 to 0.00	0.01	0.00 to 0.02	0.01	0.00 to 0.02
Risk of reintervention (total)	0.20	0.14 to 0.26	0.27	0.20 to 0.34	0.07	- 0.02 to 0.17
Mastectomy	0.01	0.00 to 0.03	0.04	0.01 to 0.07	0.02	- 0.01 to 0.06
Re-excision	0.06	0.03 to 0.10	0.08	0.04 to 0.13	0.02	- 0.04 to 0.08
Re-excision with ALND	0.02	0.00 to 0.04	0.00	0.00 to 0.00	- 0.02	- 0.04 to 0.00
ALND	0.11	0.06 to 0.16	0.15	0.10 to 0.21	0.05	- 0.02 to 0.12
Change in quality of life (QALYs)						
EQ5D week 6 vs week 0	0.00	-0.04 to 0.03	- 0.01	- 0.04 to 0.02	- 0.01	- 0.06 to 0.04
EQ5D week 12 vs week 0	- 0.03	-0.07 to 0.00	- 0.02	- 0.06 to 0.01	0.01	- 0.04 to 0.06
EQ5D week 26 vs week 0	- 0.04	-0.08 to 0.00	- 0.04	- 0.07 to -0.01	0.00	- 0.04 to 0.05
Time and costs						
Time for initial procedure (min)	119	107 to 133	118	103 to 136	- 1	- 18 to 17
Cost of initial procedure (€)	2113	1952 to 2297	2098	1909 to 2324	- 15	- 236 to 221
Cost of tumor localisation (€)	114	111 to 117	0	0 to 0	- 114	- 107 to - 111
Cost of complications (€)	29	15 to 48	77	45 to 114	48	11 to 88
Cost of reinterventions (€)	265	180 to 357	373	277 to 479	108	- 29 to 244
Total costs (€)	2521	2335 to 2728	2548	2325 to 2796	26	- 250 to 311
Summary of cost-effectiveness (ROLL vs WGL)						
P(ROLL is more effective AND more expensive)				31%		
P(ROLL is less effective AND more expensive)				25%		
P(ROLL is more effective AND less expensive)				18%		
P(ROLL is more effective AND less expensive)				25%		
P(Cost-effectiveness of ROLL is favorable)						
Ceiling ratio is €0 per QALY				44%		
Ceiling ratio is €20,000 per QALY				54%		
Ceiling ratio is €80,000 per QALY				56%		

ALND - axillary lymph node dissection

Discussion

We performed the first economic evaluation comparing ROLL with WGL in a randomised setting. and show that health related quality of life benefits observed up to 6 months after surgery are similar for ROLL and WGL when scored with the EQ5D or EQVAS. In addition, the total time required for the initial surgical procedure is similar for ROLL and WGL. The costs saved by ROLL being a one-step procedure, are offset by the slightly higher costs of re-interventions and complications after ROLL, making the total costs for ROLL and WGL similar. These observations result in cost-effectiveness estimates indicating that there is no apparent benefit from replacing WGL with ROLL. Our results are robust with respect to the three methods applied to handle missing data.

Previous studies evaluating ROLL often suggest that ROLL is a more cost-effective method than WGL.[21,22] This presumption is made based on the fact that ROLL does not require a localisation wire or a post-localisation mammogram. Besides, some studies report fewer patients requiring a costly re-excision with ROLL in comparison to WGL.[23-25] In this randomised evaluation we however found no direct economic benefit for ROLL.

Recently, we demonstrated a similar percentage of re-excisions for ROLL and WGL; as such, no costs are saved with ROLL with regard to this aspect.[14] The apparent costs saved by omitting placement of the localisation wire (i.e. material costs, personnel costs) were nullified by the costs made due to a slightly higher number of complications and re-excisions in patients treated with ROLL. It must be mentioned that the postoperative complication rate (complications caused by primary surgery) was similar in both groups.[14] These results are conform previous performed studies. However, when taking all complications into consideration that occurred up to 6 months after surgery we found a higher complication rate in the ROLL group. Since we are the first to assess the complication rate 6 months after surgery, our results cannot be compared to with other results and should be interpreted with care. Probably the slightly higher number (not significant) of re-excisions and axillary

lymph node dissections in the ROLL group (table 2) can partly explain the higher number of complications. A straightforward explanation for the higher complication rate in the ROLL group is however hard to find. It is noteworthy that the clinical results of our recently performed RCT show that ROLL is not superior to WGL as it leads to larger excision volumes while the adequate excision and re-excision rate are similar. The cosmetic scores however did not differ between both groups. Equally, quality of life scores used for this current evaluation did not show a difference between both groups.

In this evaluation we used the EQ5D score to assess the impact on the quality of life. As this score may not adequately capture every (small) difference in quality of life, we also investigated the collected EQVAS score. Similar to the EQ5D results, this alternative measurement showed no significant differences between the two groups at any time point. Still, both scores are quite rough estimates for the quality of life in our study population. Although very useful for a cost-effectiveness analysis, one should interpret these quality of life results with care, as small differences may not have been captured.

Our study has certain limitations. Most notably, data on the total duration of the initial surgical procedure was not collected in all participating hospitals. However, data on the separate parts of the procedure was collected routinely in all hospitals and all evidence on durations could be used effectively in our multiple imputation analysis. Furthermore, recording of the duration of all procedures would probably have been more precise when performed by an independent person given that the treating physician is primarily focused on patient care. In addition, the internal cost calculations to determine the relevant unit costs did not allow assessment of uncertainty. Therefore in our analysis uncertainty in costs was only due to uncertainty in volumes and durations and not to uncertainty in unit costs. Hence, the uncertainty in our cost-effectiveness estimates was underestimated.

In this era of healthcare and especially in the field of breast cancer, where patient volume is large and still increasing, it is of increasing importance to study the cost-effectiveness of novel techniques. The choice for a certain localisation technique still however primarily depends upon the efficacy of the technique (i.e. adequate excision rate, lumpectomy volumina) as this is of major importance in the surgical care of oncology patients. The cost-effectiveness is of secondary importance in this group of patients.

A promising new technique is radioactive seed localisation (RSL). Here, a radioactive seed is introduced with a needle using standard ultrasound or mammographic guidance. It has been shown that RSL and WGL are equally effective in surgical treatment of non-palpable breast cancers.[26] Since the seed can be placed days in advance of the surgical procedure because of its long half-time, this technique provides scheduling benefits. Also, the surgical procedure is reported to be shorter with RSL.[26] Both will probably result in cost savings. On the other hand, the costs for radioactive seed itself are higher than for a guide wire and the nuclear regulatory issues that come with RSL can increase the costs.[27] Further studies should be performed to determine if RSL would lead to more cost-effective care.

ROLL is not more cost-effective than WGL and therefore, replacement of WGL by ROLL is unlikely to lead to more cost-effective medical care. This study adds to our previous conclusions that ROLL cannot replace WGL as the standard of care.

COST DETAILS

	Costs	Details of the cost components)
1 Hour OR time	€770.00	1 hour OR (€650.00) 1 hour surgeon (€120.00)
Lumpectomy*	€ 584.00	Day care admission (1 day)
	…….	xx hour OR time (variable)
Wire localization*	€ 96.00	Mammography (€48.00) Placement wire by radiologist and guide wire (€48.00)
	……	xx hour radiologist (€120.00)
Re-lumpectomy	€ 1354.00	1 hour OR time (€770.00) Day care admission (€584.00)
Mastectomy	€ 2522.00	1 hour OR time (€770.00) 3 days admission (€1822.00)
Re-excision with ALND	€ 1739.00	1.5 hour OR time (€1155.00) 1 day admission (€584.00)
ALND	€ 1097.00	40 min OR time (€513.00) 1 day admission (€584.00)
Complication related costs		
Surgical treatment	€ 1161.50	45 min OR time (€577.50) 1 day admission (€584.00)
Puncture (drainage hematoma or seroma)	€ 107.30	2 extra visits outpatient clinic (€94.00) 10 min surgeon/nurse time for puncture (€13.30)
Antibiotics (wound infection)	€ 112.70	2 extra visits outpatient clinic (€94.00) Antibiotics (€11.27a) Culturing (€7.50)

All unit costs were based on internal cost calculations performed at the University Medical Centre Utrecht.
* Cost for the primary surgery and wire placement were calculated by adding up the set cost and the costs per hour multiplied by the duration of the procedure. ALND: Axillary lymph node dissection a Medicijnkosten.nl

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CHAPTER 5

Localisation failures with radioguided occult lesion localisation (ROLL) in non-palpable breast cancer; pitfalls and solutions

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Abstract

Background

Success of radioguided occult lesion localisation (ROLL) procedure for non-palpable breast cancer is highly dependent upon the exact radiological localisation of the tumour, correct injection of the radiopharmaceutical and proper surgical excision technique. In the context of a prospective study investigating the accuracy of ROLL and wire-guided localisation (WGL) of non-palpable breast cancers, we specifically evaluated the cases in which failures of localisation occurred.

Methods

Of the in total 314 women with non-palpable breast cancer eligible for breast conserving treatment with sentinel node procedure, 159 were randomly allocated to ROLL and 155 to WGL. Patient, imaging and tumour characteristics were prospectively collected. Failure of localisation was defined as <25% of the primary invasive carcinoma in the resection specimen. In a multidisciplinary setting, we evaluated reasons for failure of the localisation procedures.

Results

Failure of localisation occurred in 5/159 (3%) of the ROLL procedures. In 4 patients, failure was ascribed to incorrect pre-operative placement of the radiopharmaceutical injection. In 1 patient, dispersion of the radiopharmaceutical was identified as the cause of incorrect localisation. Patient, imaging or histological characteristics did not explain the failures. A re-operation was required in all 5 patients; 4 underwent a re-excision and mastectomy was performed in 1 patient. No localisation failures occurred in the WGL group.

Conclusion

Inadequate excision of breast cancer due to failure of the localisation procedure is a rare (<5%), but serious complication of the ROLL procedure, which should be prevented at any time. This study suggests that incorrect localisations may be avoided by the use of a contrast medium mixed with the radiopharmaceutical for

injection followed by check mammography, allowing early detection of failure and intervention.

Introduction

Surgical treatment of non-palpable breast carcinoma is challenging. Various methods of tumour localisation have been introduced to enable accurate surgical tumour removal. Radioguided occult lesion localisation (ROLL) was introduced in 1998.[1] Here, human serum albumine labelled with technetium-99 is injected intra-tumourally (guided by ultrasound or mammographic images) and facilitates both the sentinel node biopsy (SNB) and the tumour localisation procedure. A handheld gamma probe guides the surgeon to the area of concern and provides continuous feedback during excision of the tumour and sentinel node(s). Besides the advantage of ROLL being a one-step procedure, it also provides the possibility of ensuring that the primary lesion is completely removed by checking the surgical cavity for focal accumulation of radioactivity.

The use of ROLL for the localisation of non-palpable breast lesions has been studied by several. When compared to the standard method of localisation, that is wire guided localisation (WGL), ROLL leads to improved cosmetic results, lower re-excision rates, shorter duration of surgery and more patient comfort.[2-4] We recently performed a randomised multicentre trial comparing ROLL with WGL. Here, 314 patients with proven invasive breast carcinoma requiring breast conserving surgery and SNP were enrolled and prospectively evaluated. Of the patients treated with ROLL (n=159), 5 patients appeared to have no tumour or only a small part of the tumour in the excised tissue at histological examination. Consequently, re-excision was necessary in these patients to (completely) remove the cancer. In this appraisal we carefully evaluate the cases in which an incorrect localisation occurred.

Methods

This study was conducted within the context of the multi-centre randomised ROLL trial and the study was approved by the ethical committee of participating centres.[5] Details of eligibility criteria, method of randomisation, study procedures, follow up and definition and assessment of outcome measures have been described elsewhere. Briefly, women (>18 yrs) with biopsy proven non-palpable breast cancer

and scheduled for BCS with SNB gave their informed consent and were randomly allocated to treatment with ROLL or WGL. With ROLL, patients underwent intra-tumoural injection of the radiopharmaceutical (120 MBq 99mTc-nanocolloid in max 0.5 cc + air bubble) under stereotactic or ultrasound guidance. When US guidance was used, the lesion was localised by the radiologist with the patient in supine position and a needle was placed intra-tumourally for injection of the radiopharmaceutical. After confirmation of correct placement of the needle a syringe with 99mTc-nanocolloid was attached and the radiopharmaceutical was injected by the nuclear medicine physician. Scintigraphic imaging was performed and the skin projection of the sentinel node was marked. With WGL, patients first underwent an intra-tumoural or peri-areolar injection of radiopharmaceutical for lymphatic mapping. After detection and marking of the sentinel node with scintigraphic imaging, the radiologist inserted a guide wire in or near the lesion guided by ultrasound or mammographic images. A check mammography was performed to confirm the localisation of the wire in relation to the tumour. The patient was brought to the operating theatre 3-7 hours after injection of the radiopharmaceutical and here, patent blue was injected peri-tumourally (guided by a handheld gammaprobe) at the site of the maximum count rate. With WGL, the SNB was guided by the gamma probe. The wire was used for excision of the tumour. With ROLL, the SNB and excision of the primary tumour were both guided by the gamma probe (Europrobe, Strassbourg, France). The SNB was performed firstly in most of the cases. In cases where the tumour was localised close to the sentinel node, the surgeon chose to first remove the tumour, avoiding interference of its intense radioactive signal with the sentinel node radioactivity. In patients treated with ROLL correct excision was verified by presence of a hot spot with maximal radioactivity in the surgical specimen and by low or no residual radioactivity in the surgical cavity.

Histopathology examination

The resected specimens and sentinel nodes were evaluated by routine histology. An adequate excision was defined as complete removal of the tumour with tumour-free margins (i.e. no invasive carcinoma or DCIS at the inked margin). Failure of localisation was defined as <25% of the primary invasive carcinoma in the resection specimen.

Evaluation of the localisation failures

For the cases in whom failure of localisation occurred, patient characteristics, imaging features, and surgical reports were scrutinized by a radiologist, nuclear medicine physician and surgeon vastly experienced with both the WGL and ROLL method, to elucidate the reasons of failure. There were not enough events to perform a multivariable analysis examining the association of certain characteristics with failure of localization.

Results

Failure of the localisation procedure occurred in 5/159 (3%) of the patients treated with ROLL; after histology assessment no invasive tumour cells were found in the specimen of 4 patients, and only a small part (20%) of the invasive tumour in 1 patient. No localisation failures occurred in the WGL group. Incorrect placement or displacement of the wire occurred in 3/155 (2%) patients, but this was detected by mammography and did not lead to localisation failure. In all 3 patients a second wire was inserted successfully.

Among the patients in whom failure of localisation occurred, age varied from 53-76 years. All 5 patients had a breast density score of 2 and the size of the target lesion varied from 6-16 mm. Ultrasound was used in all cases for pre-operative localisation. (table 1) In 4 patients a radioactive hotspot was found in the excised specimen and no high residual radioactivity was detected in the surgical cavity assuring that the surgeon excised the tissue that was injected by the radiologist. For this reason all 4 failures were ascribed to incorrect pre-operative localisation of the tumour, i.e. incorrect placement of the radiopharmaceutical injection. In one case, dispersion of the technetium into the mammary gland tissue after injection was identified as the cause of incorrect localisation. Figure 1 shows the diffuse spot of radioactivity on lymphoscintigraphy.

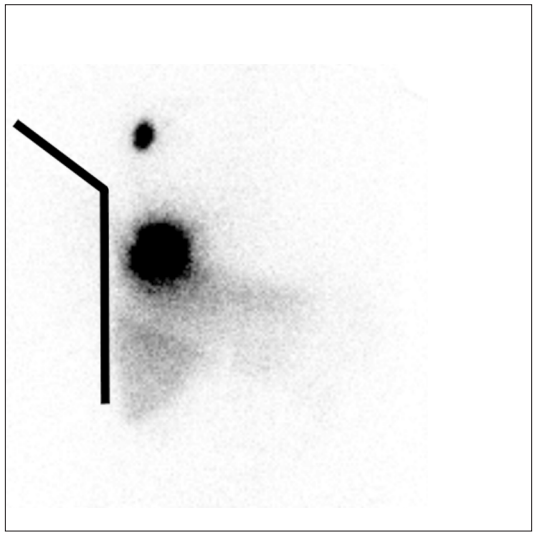

Figure 1 | Scintigraphy performed after injection of the radiopharmaceutical. Evidently, dispersion of the radiopharmaceutical occurred as a diffuse spot of radioactivity is seen.

Due to the small number of localisation failures, it was not possible to statistically determine risk factors for failure in patients treated with ROLL. Four out of 5 localisations occurred in the first year after onset of the study (total duration of study was 41 months). All patients underwent reoperation. Re-excision was required in 4 patients, mastectomy in 1 patient.

Discussion

In our series of 159 patients that underwent ROLL for the surgical treatment of an invasive non-palpable breast carcinoma, 5 patients were identified that underwent an inadequate surgical excision of the tumour due to failure of the ROLL procedure. In the 155 patients that underwent WGL no localisation failures were encountered.

The proportion of ROLL procedure failures reported in this study is in line with the literature. In 2010, Lovrics and colleagues performed a meta-analysis of studies assessing radioguided localisation of non-palpable breast cancer and reported failure rates between 0-5% with the ROLL procedure.[4] Recently, Bernardi and colleagues retrospectively analysed a large cohort of patients (n=579) with a non-palpable breast lesion that underwent localisation by ROLL . The incidence of ROLL failure was reported to be 4% (23/579). After multivariate analysis the authors demonstrated that radiological lesion size <5mm, central localisation in the breast and inexperience of the radiologists were predictive factors for ROLL failure.[6] As this study is retrospective, the authors propose that a prospective cohort is required to confirm their findings.

Table 1 | Patient and imaging characteristics

N	Age (yrs)	Year of study	Tumor size	Tumor site	Breast density score	Cup size	Localisation guidance	US	Verification with probe*		Volume excised tissue	Reason for failure	Re-intervention
									HS	CA			
1	55	1	8 mm	LLQ	2	A	US	Mass	+	-	51 cm3	Dispersion 99 Tc	Lumpectomy
2	53	1	15 mm	LLQ	2	C	US	Mass	+	+	43cm3	Incorrect 99 Tc injection	Lumpectomy
3	62	1	6 mm	LLQ	2	D	US	Mass	+	+	88cm3	Incorrect 99 Tc injection	Lumpectomy
4	70	1	16mm	Central	2	D	US	Mass	+	+	100cm3	Incorrect 99 Tc injection	Mastectomy
5	76	2	10 mm	UMQ	2	C	US	Mass	+	+	43cm3	Incorrect 99 Tc injection	Lumpectomy

Table 1. Patients in whom incorrect localisation occurred. UMQ= upper medial quadrant LLQ=lateral lower quadrant. Breast density according to ACR classification. US= ultrasound, * verification probe: HS=radioactivity hotspot in specimen CA=low/no residual radioactivity in surgical cavity. Experience= number of years after onset trial, total duration of trial 41 months.

Our prospective data show a comparable failure rate and although all involved teams consisted of experienced breast radiologists, similar to the series of Bernardi, a learning curve of the involved radiologists with the ROLL technique also may have played a role in our study.

Failure of localisation with WGL is reported in up to 3%.[4] However, the gross of these failures do not lead to an inadequate excision during surgery as most pre-operative localisation failures are detected by control mammography. In our series, incorrect placement or displacement of the wire occurred in 3 patients, but did not lead to localisation failure as this was detected with mammography and a second wire could be inserted to correctly guide the surgeon.

When treating patients for non-palpable breast carcinoma with breast conserving surgery, adequate pre-operative localisation of the tumour is crucial. Once pre-operative localisation fails, the risk of an inadequate excision is substantial and can consequently lead to a re-operation. Due to the multidisciplinary character of a localisation method such as ROLL, various aspects of the procedure can lead to an unsuccessful localisation procedure. In the context of this study we assessed all different aspects and steps. In the first step, the radiologist should always ensure that the lesion planned for injection is indeed the target lesion. It is also important that the radiologist delivers continuous pressure to the breast with the ultrasound probe during injection of the radiopharmaceutical. If this is not done there is a risk of the lesion relocating while the needle remains at the same site. As a consequence the radiopharmaceutical is injected outside the lesion. In the following step, that is after injection of the radiopharmaceutical, dispersion over a large part of the mammary gland tissue can occur. This has been reported in a small proportion of the patients that underwent ROLL and makes precise localisation of the tumour difficult.[6-8] Dispersion of the radiopharmaceutical can be seen on lymphoscintigraphy, and if so, one should consider using another localisation method depending on the extensiveness of the dispersion. Regarding the last step of performing surgery, the surgeon should verify the presence of the radioactive hotspot in the specimen and ensure that no high radioactivity is detected in the surgical cavity. By following the above mentioned steps we attempted to minimize the chance of failure.

The use of contrast medium mixed with the radiopharmaceutical followed by check mammography to allow early detection of dispersion of the radiopharmaceutical into the mammary tissue was first advocated by Rampaul and colleagues.[7] This technique can also be used to verify injection of the radiopharmaceutical at the correct site and is used frequently by others performing ROLL.[8-10] In our series we chose not to apply this technique, considering the extra mammography the patient has to undergo. However, we now suggest to use this technique in the future as the gross of our failures potentially could have been avoided by using this technique.

Conclusion

Failure of intra operative localisation is a rare, but serious complication of the ROLL procedure. The failure rate (3%) could be minimized with the use of a contrast medium mixed with the radiopharmaceutical for injection followed by control mammography, allowing early detection of failure and intervention.

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PART 2

Staging

CHAPTER 6

Non-identification of the sentinel node in non-palpable breast cancer; the influence of injection site

Submitted

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Abstract

Background

Sentinel node biopsy (SNB) is the standard procedure in patients with early stage breast cancer. In case of intra-operative non-identification of a sentinel node, the surgeon is forced to perform axillary lymph node dissection (ALND), associated with a substantially higher morbidity. We studied the impact of the site of dual tracer injection upon the risk of unplanned ALND in patients with non-palpable breast cancer.

Methods

Patients with non-palpable breast cancer, eligible for breast conserving surgery and SNB were included (n=314). Injection of technetium and patent blue was performed by peri-areolar injection in 68 patients and by intra/peri-tumoural injection in 246 patients. We compared success rates of SNB and the number of ALNDs due to non-visualization of a sentinel node between both groups. Logistic regression analysis was applied to estimate the adjusted effect of injection site on risk of unplanned ALND.

Results

The probability of detecting an axillary sentinel node on lymphoscintigraphy was lower in patients with intra/peri-tumoural injection (81%) than in those with peri-areolar injection (94%) (p=0.02). Unplanned ALND was performed in 1% (1/67) of the patients with peri-areolar injection compared to 7% (18/249) of patients with intra/peri-tumoural injection (p=0.055). Through multivariate analysis the most predictive factors for unplanned ALND in patients undergoing SNB were increasing age (OR 1.08 95% CI 1.0-1.1) and intra/peri-tumoural tracer injection (OR 7.0 95% CI 0.9-55.2).

Conclusion

Among patients with non-palpable breast cancer, intra/peri-tumoural injection of the dual tracer increases the risk of unplanned ALND.

Introduction

Sentinel lymph node biopsy (SNB) allows accurate staging of the axillary nodal status while evading surgical excision of all axillary lymph nodes.[1] Dual mapping of the lymphatic drainage using both radiotracer and blue dye has proven to be superior to mapping by means of either approach alone; a 95-100% success rate of sentinel node detection is reached when these two methods are combined.[2] Optimal injection site is still subject of discussion. The benefit of superficial injection (subdermal or (peri) areolar) is the technical simplicity. Deep injection (peri-tumoural or intra-tumoural) however has the ability to reveal drainage to the extra-axillary lymph nodes.

In cases of non-detection of an axillary sentinel node intraoperatively, the surgeon is urged to perform axillary lymph node dissection (ALND) in order to perform accurate staging of the breast cancer. Compared to SNB, ALND requires a more extensive excision and exploration of the axillary region, thereby increasing the risk of persistent lymph oedema, seroma and paraesthesia.[3,4] As such, one should avoid performing this procedure and aim for a high success rate of the sentinel node procedure.

Until now, no studies have reported on the optimal injection site in patients with non-palpable breast cancer. This patient group may differ with respect to lymphatic invasion and metastatic tumour spread. Recently, we performed a randomised controlled trial in which patients with non-palpable breast cancer and eligible for breast conserving surgery and sentinel node procedure were allocated to either radioguided occult lesion localisation (ROLL) or wire guided localisation (WGL) to guide the tumour excision . In the context of this trial, patients received a single intra/peri-tumoural injection or peri-areolar injection of the radiotracer and patent blue.

As such, we had the opportunity to compare the different methods of radiotracer and patent blue injection in a homogeneous series of early non-palpable breast cancer patients. We primarily focused on the proportion of patients that underwent axillary lymph node dissection due to failure of the SNP, as this procedure has relevant clinical implications.

Methods

Clinical and histological data were collected in the context of the multi-centre randomised controlled ROLL trial (ClinicalTrials.gov, number NCT00539474). Institutional review boards at each participating centre approved the protocol and all patients provided informed consent. Details of eligibility criteria, method of randomisation, study procedures, follow up and definition and assessment of outcome measures have been described elsewhere.[5]

In brief, this series consisted of 314 patients with non-palpable, histology proven breast cancer that were eligible for breast conserving surgery and sentinel node procedure. Patients were randomly allocated to radioguided occult lesion localisation (ROLL) or wire-guided localisation (WGL).

Radiotracer injection and lymphoscintigraphy

In the WGL arm, 68/152 patients received a peri-areolar (PA) injection of radiotracer (120 MBq 99mTc-nanocolloid), this group will be referred to as the peri-areolar group. Intra or peri-tumoural (IT/PT) injection of the radiotracer under stereotactic or ultrasound guidance was used in all 162 patients allocated to ROLL and 84/152 patients allocated to WGL. After radiological confirmation of correct placement of the needle, a syringe with 99mTc-nanocolloid was attached and the radiotracer (120 MBq 99mTc-nanocolloid in max 0.5 cc + air bubble) was injected by the nuclear medicine physician. If too much resistance was experienced while injecting the radiotracer intratumourally, the (remainder of) radiotracer was injected peri-tumourally. These patients (n=246) will be referred to as the intra/peri-tumoural group. In all patients, scintigraphic imaging was performed 1-3 hours postinjection. The nuclear medicine physician marked the skin projection of the sentinel node(s).

Surgical procedures

The patient was brought to the operating theatre 3-7 hours following injection of the nanocolloid. Patients in the intra/peri-tumoural group received a peri-tumoural injection of 2 ml patent blue (guided by a handheld gammaprobe) at the site of the

maximum count rate. The patients in the peri-areolar group received an injection with patent blue in the peri-areolar area.

The patent blue and a gamma detecting probe (Europrobe, Strassbourg, France) were used to identify the sentinel node(s). Axillary as well as internal mammary chain (IMC) sentinel nodes were excised whenever possible. In case of non-identification of an axillary sentinel node, axillary lymph node dissection was performed in the same setting.

Histological evaluation

All sentinel nodes were bisected if their size was > 0.5cm. Both parts were formalin fixed and step sections were made at 250 µm-intervals. H&E staining was performed. Additional immunohistochemical staining was performed if H&E staining proved negative. If metastases were present, they were classified as macro metastases, defined as a metastatic depot of more than 2 mm in size; as micro metastases, defined as a metastatic depot of 0.2–2 mm in size; or as isolated tumour cells, defined as a single tumour cell or a cluster of tumour cells of less than 0.2 mm in size.[6]

Statistical analysis

Summary statistics were provided for baseline variables by site of injection (i.e. intra/peri-tumoural group versus peri-areolar group). Groups were compared for occurrence of unplanned ALND and potential determinants of ALND. Here, normally distributed continuous variables were presented as means (standard deviation) and compared with independent t tests. Ordinal data and not normally distributed data were presented as medians (range) and compared with the Mann Whitney U test. Chi-square test or Fisher's exact test was used to compare proportions.

Initially the variables were entered in univariate logistic regression models, with unplanned axillary lymph node dissection as outcome. We then entered variables associated with unplanned ALND with a p-value <0.25 in a multivariate logistic regression model and applied manual stepwise backward regression to identify factors independently associated with ALND. All analyses were performed with SPSS software version 17.0.

Results

Mean age of patients in the intra/peri-tumoural group was 60.6 yrs versus 62.1 yrs in the peri-areolar group (table 1). A higher proportion of (ducto)lobular carcinomas was seen in the intra/peri-tumoural group (13% versus 5%). Tumour size, site and grade were comparable between both groups.

Thirty one (13%) patients in the intra/peri-tumoural group compared to two (3%) in the peri-areolar group did not show any drainage on lymphoschintigraphy (p=0.02). (table 2) Detection of an axillary sentinel node on lymphoscintigraphy was seen in 202 (81%) patients with intra/peri-tumoural injection versus 64 (94%) with peri-areolar injection (p=0.01). The proportion of patients in whom IMC nodes were visualized was significantly higher with intra/peri-tumoural injection (26% vs. 1%, p<0.01). The median number of harvested nodes was 1.98 with intra/peri-tumoural injection versus 1.94 with peri-areolar injection (p=0.51). Unplanned axillary lymph node dissection due to failure of the sentinel node procedure was performed in 7% (18/246) of the patients with intra/peri-tumoural injection versus 1% (1/68) with peri-areolar injection (p=0.055). Restriction of our analyses to only patients who underwent WGL gave similar results; 8 (11%) unplanned ALNDs in the intra/peri-tumoural group versus 1 (1%) in the peri-areolar group (p=0.039).

In multivariate analysis we found that increasing age was independently and significantly associated with increased risk of unplanned ALND (OR 1.08 95% CI 1.01-1.12). (table 3) Intra/peri tumoural injection was associated with unplanned ALND with an odds ratio of 6.98 95% CI 0.88-55.15, p=0.065). Tumour grade and size did not modify the risk of unplanned ALND.

Of the patients with drainage to the internal mammary nodes, 15/67 patients underwent biopsy of this node. Pathology assessment revealed micrometastases

Table 1 | Baseline patient and imaging characteristics of patients with non-palpable breast cancer planned for breast conserving surgery and sentinel node procedure.

		IT/PT injection (n=246)		PA injection (n=68)	
Mean Age (SD)		60.6 (7.7) yrs		62.1 (8.6) yrs	
Median tumour size (range)		1.2 (0.1-6.0) cm		1.30 (0.5-3.1) cm	
Site	ULQ	92	37%	29	43%
	UMQ	35	14%	6	9%
	LLQ	25	10%	5	7%
	LMQ	20	8%	9	13%
	Central	63	26%	18	26%
	Axillary	1	<1%	0	0%
	Not reported	10	4%	3	4%
Bloom and Richardson					
	Grade I	106	43%	31	46%
	Grade II	102	41%	27	40%
	Grade III	30	12%	10	15%
	Not reported	8	3%	0	0%
Tumour type					
	Ductal	208	85%	64	94%
	Lobular	18	7%	3	4%
	Ductolobular	14	6%	1	1%
	Other	6	2%	0	0%
Axillary lymph node status					
	pN0	181	74%	55	80%
	ITC	16	6%	2	3%
	Micrometastases	17	7%	3	4%
	Macrometastases	32	13%	8	12%
IMC lymph node status					
	No biopsy	231	93%	68	100%
	pN0	13	5%	0	0%
	ITC	1	1%	0	0%
	Micrometastases	1	1%	0	0%
	Macrometastases	0	0%	0	0%

Data are numbers with percentage of group total. IT/P intra/peri-tumoral, PA= peri-areolar, SD= standard deviation, ULQ= upper lateral quadrant, UMQ= upper medial quadrant, LLQ=lower lateral quadrant, LMQ= lower medial quadrant
IMC=internal mammary chain

Table 2 | Sentinel lymph node detection lymphoscintigraphy; drainage and number of sentinel nodes on lymphoscintigraphy, number of sentinel nodes harvested during surgery, number of ALNDS during the initial surgical procedure.

	IT/PT injection(n=246)		PA Injection (n=68)		Pvalue
Drainage on LS					
Axillary	202	81%	64	94%	0.02
Internal mammary	67	27%	1	1%	<0.01
Elsewhere	17	6%	2	3%	0.06
No drainage on LS	31	13%	2	3%	0.02
SNs detected on LS (median, range)	1.4 (1-6)		1.2 (1-4)		0.07
SNs harvested (median, range)	1.98 (1-12)		1.94 (1-13)		0.51
Unplanned ALNDs	18	7%	1	1%	0.055*

Data are numbers with percentage of group total. LS= lymphoscintigraphy, SN= sentinel node, ALND= axillary lymph node dissection during the primary surgery. * Fishers exact 1 sided

Table 3 | Univariate and multivariate analysis of factors associated with unplanned axillary lymph node dissection due to failure of the sentinel node procedure

	ALND (n=19)		No ALND (n=295)		P value	Crude OR (CI 95%)	Adjusted OR (CI 95%)
Age*	64 (45-78)		62 (38-85)		0.063	1.057 (0.99-1.12)	1.08 (1.01-1.15)
Size invasive carcinoma*	1.3 (0.6-6.0) cm		1.2 (0.1-5.2) cm		0.106	1.53 (0.90-2.60)	1.57 (0.85-2.92)
Site of injection*							
I/P-tumoural	18	**95%**	228	**77%**	0.055¥	1 (ref)	1 (ref)
Peri-areolar	1	**5%**	67	**23%**		5.3 (0.69-40.59)	6.98 (0.88-55.2)
B & R*							
Grade I	5	**26%**	132	**45%**	0.217	1 (ref)	
Grade II	10	**53%**	119	**40%**		2.21 (0.73-6.67)	1.94(0.63-5.96)
Grade III	4	**21%**	36	**12%**		2.93 (0.75-11.49)	2.48 (0.56-10.90)
Not reported	0	**0%**	8	**3%**		na	
Localisation							
ROLL	10	**52%**	152	**52%**	0.925	1 (ref)	
WGL	9	**48%**	143	**48%**		0.96 (0.38-2.42)	
Tumour type	18	**95%**	249	**84%**	0.855	1 (ref)	
Ductal	1	**5%**	20	**7%**		0.69 (0.09-5.45)	
Lobular Ductolobular	0	**0%**	15	**5%**		na	
Other	0	**0%**	11	**4%**		na	
Tumour site	3	**16%**	78	**26%**	0.622	1 (ref)	
Central	6	**32%**	62	**21%**		2.51 (0.61-10.47)	
Medial Lateral	9	**48%**	143	**48%**		1.63 (0.43-6.22)	
Not reported	1	**5%**	12	**4%**			

* Factors included in our multivariate model. Age and size invasive carcinoma are given in medians with range, I/P= intra/peri, B&R: Bloom and Richardson, ROLL: Radioguided occult lesion localisation, WGL: Wire-guided localisation. na: not applicable. Factors with a p value <0.25 were included in our multivariate model.

in one patient and isolated tumour cells in another. These findings did not affect locoregional and systemic therapy. All these patients had received an intra/peri-tumoural injection.

Axillary involvement was seen in 26% in the intra/peri-tumoural injection group vs. 20% in the peri-areolar group. Of all patients that underwent unplanned ALND (n=19), assessment of the removed nodes showed axillary metastases in 4.

Discussion

This study shows that in patients with early stage non-palpable breast cancer intra or peri-tumoural injection of radiotracer leads to a lower axillary SN detection rate on lymphoscintigraphy compared to peri-areolar injection. Deeper (intra or peri-tumoural) injection of radiotracer is associated with a higher risk of unplanned ALND rate when compared to peri-areolar injection. Intra/peri-tumoural injection does however reveal drainage to the IMC with lymphoscintigraphy in a larger proportion of the patients.

Since its introduction in the early nineties, SNB for patients with early breast cancer has been studied extensively. Dual tracer injection is proven to be most effective compared to a single injection of radiotracer or blue dye.[7,8] However, there is no consensus on the optimal site of injection despite the large amount of studies addressing this aspect of sentinel node procedure. [9-13] As the incidence of non-palpable breast cancer is rising, it is of great importance to evaluate this aspect in this selected group.

One can distinguish two categories of injection sites; that is deep (peri-tumoural, subtumoural, intratumoural) and superficial (intradermal, subdermal, subareolar).[14] The rationale for superficial injection is that the breast parenchyma and the overlying skin drain to a joint node in the axilla because of their common embryological origin. The advantages of injecting superficially instead of intraparenchymally are the ease and the short duration of the procedure and the high probability of finding the SN.[10-12] Most importantly, in cases of non-palpable lesions, it allows injection without the need for preoperative imaging. Superficial injection however, rarely leads to identification of extra- axillary nodes.

Opponents of superficial injection point out that the intraparenchymal injection technique visualises the actual lymph drainage and is therefore more accurate. Some studies have suggested that different parts of the breast drain to different nodes as deep injections show extra-axillary nodes in up to 30% or the patients.[15-18] Although several studies demonstrate that lymphatic drainage of the breast is indeed more complex than superficial drainage, it was never shown that the deeper injection technique leads to less false-negative cases. Recently Pesek, et al. performed a meta-analysis to assess which method of SNP has achieved the lowest false-negative rate.[9] In this analysis 183 studies were included (n=9306). Articles were grouped according to injection material and site of injection. False-negative rates were assessed per grouping and by the year of publication. The authors concluded that the combining of blue dye and a radioactive tracer leads to the lowest false negative rate. Site of the injection does not significantly impact the false-negative rate of the SNB.

Another argument used by proponents of the deep injection technique is that when visualised, SNB of extra-axillary nodes leads to more accurate staging. In the past, histological assessment of the extra-axillary harvested nodes lead to a change in systemic treatment in up to 20%.[18,19] Nowadays, the presence of unfavourable primary tumour characteristics such as high grade, size >1 cm have become a sufficient indication for adjuvant systemic treatment. As such, the clinical value of determining the internal mammary SN status with regard to the systemic treatment has decreased. Recently, our group performed a study that confirms this; in a large cohort of patients (n=493) in whom internal mammary sentinel node biopsy was routinely performed, systemic treatment was not changed in any of the patients. Radiotherapy was frequently adjusted (in 11% of the patients) based on the histology of the internal mammary sentinel node, however solid scientific evidence for this adjustment is lacking.[20] Pathology assessment of the internal mammary node in our study revealed

micro metastases in 1 patient and isolated tumour cells in another. According to the most recent guidelines , these findings did not affect systemic and/or radiotherapeutic treatment.[21]

In this study only patients with non-palpable breast cancers were included. Non palpable breast cancers show significantly more drainage to extra-axillary nodes than palpable breast cancers.[22] A probable explanation for this finding is that these non-palpable cancers are located deeply and therefore are less accessible for palpation. Anatomical studies show that the lymphatics arising from deeper mammary tissue (pectoral muscle and fascia) supply the extra-axillary (internal mammary and interpectoral) nodes. Consequently, more extra axillary drainage is seen in non-palpable breast cancers when compared to palpable lesions.

Sentinel node biopsy is a minimal invasive procedure designed to detect and excise the lymph node (s) that is/are affected primarily. When failure of this procedure occurs, ALND needs to be performed to assure accurate staging. Compared to SNB, ALND requires a larger incision with extensive tissue dissection and disruption of the lymphatic system. Consequently the risk of post-operative wound infection and seroma is significantly higher after ALND. Besides, the rate of potentially (chronic) disabling complications such as lymph oedema and paraesthesia is reported to be significantly higher in patients who underwent ALND (5 vs. 13%).[23] The reason for this is the removal of more axillary nodes and the more extensive damaging of the lymphatic drainage with ALND. Paraesthesia is often caused by transection of the intercostobrachial nerve; this is four times more reported with ALND than with SNP.[24] For this reason, one should attempt avoiding failure of the SNB at any time.

This study shows that the use of peri-areolar injection in patients with non-palpable breast cancer decreases the risk for failure of the SNB and concurrent ALND. In patients with non-palpable breast cancer, peri-areolar injection offers the important advantage of being time and cost saving as a radiologist and preoperative imaging of the tumour is not needed. The above mentioned, accompanied by the fact that the site of injection does not influence the false-negative rate with SNB indicates that peri-areolar injection would be our method of choice in patients with non-palpable breast cancer.

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CHAPTER 7

Sentinel lymph node biopsy of the intra mammary chain in breast cancer

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Abstract

Background

Routine removal of the internal mammary chain sentinel node in breast cancer patients remains a subject of discussion.

Objective

The aim of this study was to determine the impact of routinely performed IMC sentinel node biopsy on the systemic and locoregional treatment plan.

Methods

All patients with biopsy proven breast cancer who underwent a sentinel node procedure between 2002 and 2011 were included in a prospective database. In cases of IMC drainage, successful exploration of the IMC (i.e. sentinel node removed) and surgical complications were registered. If the removed sentinel node contained malignant cells we determined if this altered the treatment plan when practising the current guidelines.

Results

In total, 119 of the 493 included patients showed IMC drainage on lymphoscintigraphy. Exploration of the IMC was performed in 107 (89%) patients; in 86/107 (80%) exploration was successful. In 14/107 patients (13%) the IMC SN was tumour positive. Macro metastases were found in 8 patients , micro metastases in 6 patients. In the group of patients that underwent surgical exploration of the IMC, systemic treatment was changed in none, radiotherapy treatment in 13/107 patients (11%).

Conclusion

Routine SNB of the IMC does not alter the systemic treatment. Radiotherapy treatment is altered in a small proportion of the patients, however, solid scientific evidence for this adjustment is lacking.

Introduction

Sentinel lymph node (SLN) biopsy is a standard procedure for axillary assessment of patients presenting with clinically node-negative early breast cancer.[1-4] Depending on the technique of injecting the nanocolloid and the site of the tumour, extra axillary lymph drainage to the internal mammary chain (IMC) is found in up to 30% of breast cancer patients.[5-7] There is however no consensus on the added diagnostic or prognostic value of retrieving SLNs from the IMC when seen on pre-operative lymphoscintigraphy. Opponents point out that harvesting these nodes has no clinical relevance because tumour positive IMC SLNs rarely influence adjuvant systemic treatment strategy and because there is no evidence supporting an effect of radiotherapy (RT) to the IMC.[8,9] Besides, they state that the increased radiation dose that is administered to the cardiac and pulmonary tissue might lead to increased morbidity and mortality. Proponents of routine IMC SLN biopsy advocate that the presence of lymph node metastases in the IMC is associated with a poorer prognosis in a small but substantial patient group and that these metastases should therefore be treated with appropriate systemic therapy and IMC RT.[6,7,10-13] As a reflection of this on-going debate, Dutch national guidelines on the treatment of breast cancer do not recommend routine biopsy of the IMC SLNs. Adjuvant chemotherapeutic treatment and IMC RT is however indicated when a tumour positive IMC lymph node is found.[14]

In this historical cohort study, we evaluated the impact of IMC sentinel node biopsy (which is routinely performed in our hospital) upon the systemic and locoregional treatment strategy.

Methods

Between January 2002 and August 2011 all patients with biopsy proven cT1-2 cN0 invasive breast cancer underwent surgical treatment including sentinel node biopsy. All patients were included in a prospective database. Patient who did not show drainage on lymphoscintigraphy, who received neo-adjuvant systemic treatment, in whom the tumour was multicentric or those with recent surgery to the ipsilateral axilla or breast were excluded from our analysis.

Sentinel node procedure

A mean dose of 120MBq Tc-99m nanocolloid in a 0.5cc physiological saline was administered through 4 peri-tumoural injections. A higher dose (370 MBq) was administered when the sentinel node procedure was performed according to a 2-day protocol. Early and late static images (anterior and lateral) were acquired with a single or dual head gamma camera one and two hours post-injection. If no sentinel node was depicted, an extra series of late images was performed often after administration of additional TC-99m nanocolloid. The sentinel node was marked on the skin. In patients with non-palpable tumours the radiotracer was injected intratumourally guided by either ultrasound or stereotaxis, depending on the visibility of the tumour.

Surgery

Lymphatic mapping procedure was performed the previous day or on the same day as surgery. In the operating theatre 1-2 ml Patent Blue was injected peri-tumourally. The sentinel node was identified with the aid of blue dye and the gamma probe. Axillary as well as IMC sentinel nodes were excised whenever possible.

Histological examination

All sentinel nodes were bisected if their size was > 0.5cm. Both parts were formalin fixed and step sections were made at 250 µm-intervals. H&E staining was performed. Additional immunohistochemical staining was performed if H&E staining proved negative. If metastases were present, they were classified as macro metastases, defined as a metastatic depot of more than 2 mm in size; as micro metastases, defined as a metastatic depot of 0.2–2 mm in size; or as isolated tumour cells, defined as a single tumour cell or a cluster of tumour cells of less than 0.2 mm in size.[15]

Outcome measures

For each patient, information on patient and tumour characteristics was gathered. We analysed the lymphatic drainage pattern and determined the proportion of patients with IMC drainage. In this selection of patients, evaluation of the number of successful

IMC sentinel node biopsies during surgery, intra-operative complications due to the attempt of harvesting the IMC sentinel node and the frequency of metastases in the IMC node was performed. We then analysed the effect of the IMC sentinel node histology on the adjuvant treatment according to the most recent Dutch guideline on the treatment of breast cancer.[14]

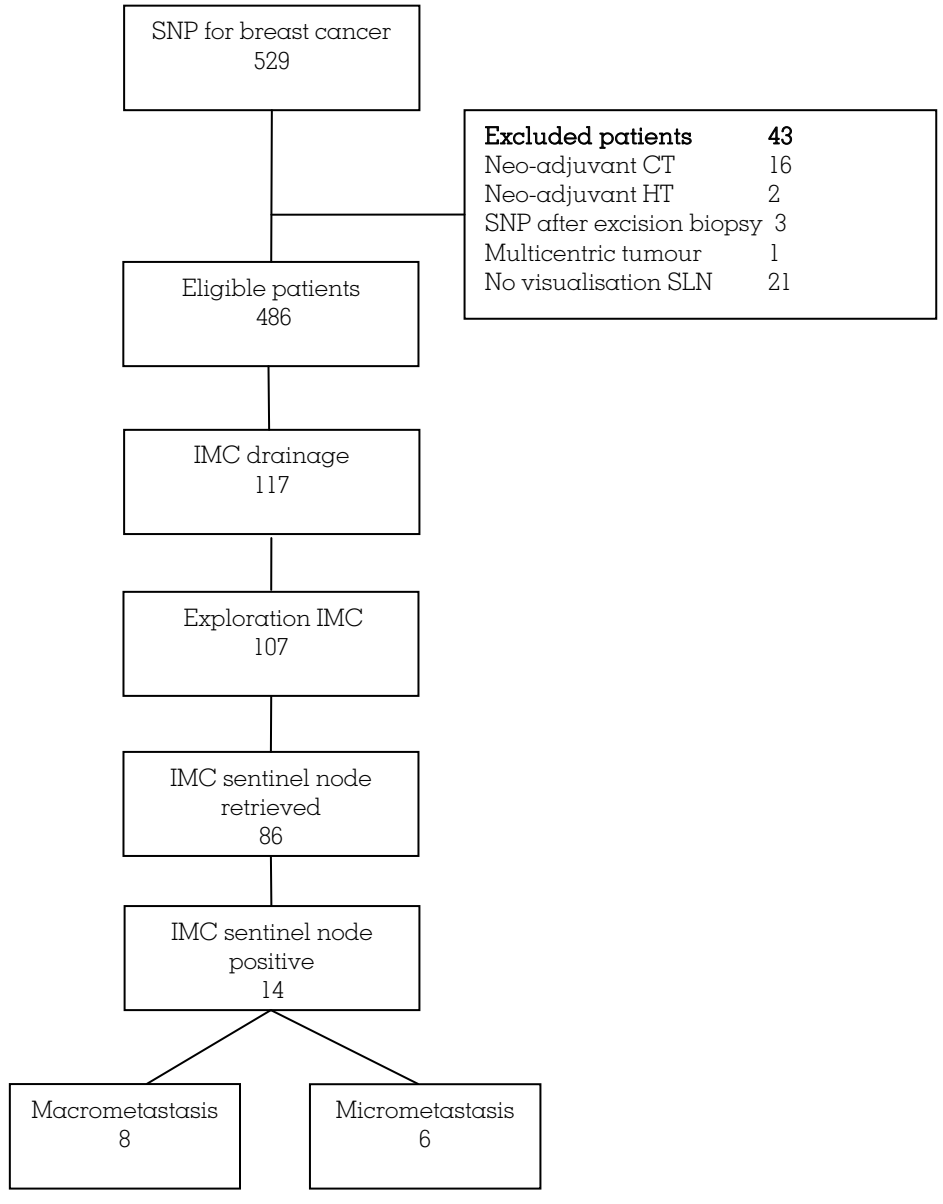
Statistical analysis

Normally distributed continuous variables were presented as means (standard deviation) and compared with independent t tests. Not normally distributed data were presented as medians (range) and compared with the Mann Whitney U test. Chi-square test was used to compare proportions. Differences were considered significant when $p< 0.05$.

Results

In total, 486 patients who underwent 493 sentinel node procedures were included in this retrospective analysis. (fig. 1) Forty three patients were excluded; 3 patients underwent a SNP after excisional biopsy, 18 patients received neo-adjuvant systemic treatment, in 1 patient the tumour was multicentric and 21 patients did not show drainage on lymphoscintigraphic imaging. Lymphoscintigraphic imaging showed axillary drainage in 479 (99%) patients. An IMC drainage pattern was seen in 119 of 486 (24%) patients; 112 with concomitant drainage to the axillary nodes and 7 with drainage to the IMC exclusively. IMC drainage was associated with a smaller tumour size, non palpability and a medial localization of the tumour (table 1). The axillary biopsy of the SN was succesfull in 478/481 (99%) and contained metastases in 164/478 (34%) of the cases. Biopsy of the IM SLN was successful in 86/119 (72%) of the patients with drainage to the IMC. In 12 patients exploration of the IMC region was not attempted because the radioactivity count was considered too low in this region intra-operatively. In the remaining 21 patients, exploration of the parasternal region was attempted, but unsuccessful. The IMC sentinel node contained metastases in 14 patients; histopathology examination showed macro metastatic disease in 8 patients and micro metastatic disease in 6 patients.

Figure 1 | Flowchart sentinel lymph node procedures.



SNP = sentinel lymph node procedure
IMC = intra mammary chain
CT = chemotherapy
HT = hormonal therapy

Table 1 | Patient and tumour characteristics

		All patients* N=486	IMC Drainage N=119	NO IMC Drainage N=367	P Value
Mean Age (SD)		58 (22-86)	56 (53-81)	59 (22-86)	0.101
Median tumour size in cm (SD)		1.9 (1.2)	1.7 (0.9)	2 .0 (1.2)	0.044
Tumour localisation	Central	54 (11%)	14 (12%)	40 (11%)	<0.001
	ULQ	218 (45%)	27 (22%)	191 (52%)	
	UMQ	68 (14%)	29 (24%)	39 (11%)	
	LLQ	52 (11%	16 (13%)	36 (10%)	
	LMQ	48 (10%)	18 (15%)	30 (8%)	
	Cranial	19 (4%)	7 (6%)	12 (3%)	
	Caudal	5 (1%)	3 (3%)	2 (1%)	
	Medial	5 (1%)	3 (3%)	2 (1%)	
	Lateral	17 (3%)	2 (2%)	16 (4%)	
B & R grading	1	107 (22%)	22 (18%)	85 (23%)	0.283
	2	179 (37%)	50 (42%)	129 (35%)	
	3	149 (31%)	38 (32%)	111 (30%)	
	unknown	51 (10%)	9 (8%)	42 (11%)	
Tumour histology	IDC	382 (78%)	94 (77%)	288 (76%)	0.824
	ILC	38 (8%)	7 (6%)	30 (8%)	
	IDLC	51 (10%)	12 (10%)	39 (11%)	
	Other	27 (6%)	5 (3%)	10 (2%)	
Axillary involvement	N 0	322 (66%)	87 (73%)	235 (64%)	0.069
	N +	164 (34%)	32 (27%)	132 (36%)	
ER	Positive	405 (83%)	94 (80%)	311 (85%)	0.385
	Negative	60 (12%)	17 (14%)	43 (12%)	
	Missing	21 (5%)	8 (3%)	13 (4%)	
PR	Positive	328 (66%)	77 (65%)	251 (68%)	0.757
	Negative	137 (28%)	34 (29%)	103 (28%)	
	Missing	19 (5%)	8 (7%)	11 (5%)	
Palpable	Yes	308 (63%)	66 (58%)	242 (66%)	0.027
	No	174 (36%)	53 (42%)	121 (33%)	
	missing	4 (1%)	0 (0%)	4(1%)	
Bilateral SNP		7 (1%)	0 (0%)	7(2%)	0.113

* In patients with bilateral disease, data of the first diagnosed tumour was used for analysis.
ULQ=Upper lateral quadrant UMQ=Upper medial quadrant LLQ=Lower lateral quadrant LMQ=Lateral medial quadrant

Of the 14 patients with IM SLN metastases 7 (50%) presented with concomitant axillary lymph node involvement. Conversely 7/165 patients (2%) with axillary metastases, showed IMC involvement.

IMC sentinel node biopsy

Surgical exploration of the IMC was performed in 107 patients. In 94 patients information regarding the incision for IMC exploration was reported; an extra incision was necessary in 86 patients and in 8 patients exploration was performed using the lumpectomy or mastectomy incision. Serious complications were reported in 3/107 patients (3%); in 2 patients re-exploration was necessary due to post-operative bleeding, 1 patient developed a haematothorax after surgery. In 6 patients minor injury to the pleura during surgery was reported; all patients were treated conservatively. Intra-operative bleeding from the internal mammary artery occurred in 4 patients, but was stopped successfully.

Change in systemic treatment strategy

Based on unfavourable primary tumour characteristics or involvement of the axillary SLN status, hormonal treatment was indicated in 13 patients and chemotherapy in 11 patients. The IMC sentinel node histology did not affect the adjuvant treatment in any of the patients. (table 2)

Change in radiotherapy treatment

A change in the RT plan was seen in 13 patients due to a tumour positive IMC node. IMC and medial peri-clavicular lymph nodes were irradiated in these patients. One patient presented with 7 positive axillary lymph nodes. As such, she already had an indication for loco-regional radiotherapy of the parasternal and medial peri-clavicular area.

Discussion

In the group of patients studied, lymphatic drainage pattern to the IMC was seen

in 24%. The majority (72%) of explorations of the IMC was successful. Intra and postoperative complications related to this procedure were reported in 13/107 (12%) of the patients. Histologic examination of the retrieved IMC sentinel nodes revealed metastases in 17% of the patients. This rate is conform with other studies, considering the use of peri-tumoural or intra-tumoural injection of the radiotracer.[6,7,9,11] The proportion of patients with IMC metastases and concomitant axillary metastases (50%) is however low compared to results reported by others.[6,7,12,16-18] According to current guidelines, exploration of the IMC lead to adjustment of the systemic treatment in none of the patients. However, adjustment of RT was seen frequently (11%) .

Several studies reported that prognosis of patients with medially located tumours is inferior to that of patients with laterally located tumours.[19,20] Since it is known that medial tumours more often drain to the IMC, the rationale for harvesting IMC SLNs is the assumption that the poorer prognosis of patients with medially located tumours is a result of understaging of IMC lymph node metastases with the consequence of omitting adjuvant treatment in this patient group.[11,21,22] As sentinel lymph node biopsy of the IMC leads to a greater degree of staging accuracy, it provides a guidance for a more specific tailored therapy. Studies evaluating the effect of the IMC SLN biopsy on the treatment strategy in patients with an IMC drainage pattern report change of treatment in 2-9%.[5,7,11,21] Since adjuvant systemic treatment in this small but substantial patient group is likely to improve prognosis, authors of these studies recommend routine biopsy of IMC SLN's.

Despite these considerations, the clinical value of IMC SLN biopsy remains heavily debated. Since unfavourable primary tumour characteristics solely have become a sufficient indication for adjuvant systemic treatment, the proportion of patients with an indication for systemic treatment has increased substantially. Moreover, solely IMC metastases changing the N0 to an N+ status are rare. Rates of 2-8% have been reported by others.[6,7,11,17] We observed seven patients with IMC metastases without axillary involvement, representing only 1% of our study population. Although biopsy of the IMC SN leads to upstaging in these patients, systemic treatment was not affected as all patients already would have received systemic treatment based on unfavourable tumour characteristics. Consequently, the clinical value of determining the IMC SLN status with regard to the systemic treatment has decreased. Our study confirms this, as the systemic treatment plan was not changed in any of the patients.

Regarding the RT adjustments; for every nine patients in whom biopsy of the IMC SLN was attempted, one patient was identified eligible for additional (loco-regional) RT treatment. Straightforward evidence of the value of RT in terms of improving long-term prognosis is however, lacking. Romestaing et al. randomised patients to RT versus no RT of the IMC after surgery. In total, 1334 early stage breast cancer patients with node-positive disease (75%) and/or medially located tumours that underwent mastectomy and RT to the chest wall, axilla and peri-clavicular area were enrolled. No significant difference was found in 10 year overall survival. As the IMC lymph nodes were not pathologically evaluated, it is likely that only a small proportion of these patients have actual tumour positive IMC lymph nodes.[23] This means that the study is possibly underpowered for showing a significant difference in the recurrence or survival rate. Another randomised comparison was carried out by Kaija, et al. evaluating the (dis)advantages of IMC RT. Radiation of the IMC did not lead to an increase in complications. No difference in disease recurrence was found however, follow up time was too short to be conclusive.[24]

Results of an on-going study (EORTC trial 22922) investigating the role of internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III stage breast cancer are awaited.[25] However, inclusion criteria (high risk patients/no histopathology of the IMC SLN) mean that this study will not adequately address the question of the additional value of IMC irradiation in patients with a tumour positive IMC SLN.

Several trials evaluated the effect of loco-regional RT in high risk patients and showed that loco-regional RT leads to a substantial improvement in loco-regional control and a less substantial, but still significant improvement in long term survival.[26-29]

(table 3) This indicates that in widespread locoregional disease chemotherapy alone inadequately eliminates metastatic disease and an additional therapeutic effect is achieved by loco-regional therapy. In these studies however, patients were treated with outdated chemotherapy regimens and underwent incomplete axillary lymph node dissection, rendering these results not applicable to current breast cancer patients. The on-going NCIC-CTG MA-20 trial reports on 1832 high risk node negative and node positive patients that underwent breast conserving surgery and systemic therapy between 2000 and 2007.[30] Patients were randomly allocated to undergo regional radiotherapy or not. Interim analysis after five years of follow-up shows that additional RNI reduces the risk of loco-regional and distant recurrences, and improves the disease free survival with a trend towards improved overall survival.

Consideration should be given to the fact that in our study 6 of the 14 IMC SLN positive patients presented with micro metastatic disease only. As the prognostic value of this finding is still questionable, it is unlikely that radiotherapeutic treatment in case of micro metastatic disease will result in a significantly improved prognosis.[31,32]

Irradiation of the IMC is accompanied by extra morbidity. Besides a marginally increased risk of secondary malignancy and radiation induced lung injury, cardiac toxicity is a well-known side effect of radiotherapy. Some studies show a significant increase in non-breast cancer mortality and long term mortality from heart disease in breast cancer patients that underwent RT.[33,34] Although modern CT based RT planning techniques have proven to significantly decrease the irradiated heart dose and volume, long-term decreased cardiotoxicity has not yet been demonstrated. The fact that more aggressive systemic therapy regimens (including cardiotoxic agents) are frequently used nowadays and the long term effect of RT in combination with these agents is not yet known, should also be considered. In our opinion, evidence of the additional value of IMC irradiation is not sufficient enough to legitimate the accompanying toxicity. Surgically staging by exploration of the IMC could be omitted by improving pre-operative staging. FDG PET/CT is shown to be a valuable instrument besides conventional modalities for the detection of extra-axillary lymph node macro metastases, also in regions that cannot be evaluated by ultrasound.[35]

Exploration of the IMC is an extra procedure that carries an additional risk of intra and postoperative complications and a less satisfactory cosmetic outcome. Since the adjustment rate of systemic treatment based on the finding of this procedure is minimal and there is no sufficient ground for adjustment of RT, we believe that biopsy of the IMC SLN should not be performed routinely. As FDG PET/CT is of additional value for pre-operative staging and thus for selection of patients for RT, we advocate performing this procedure in high risk patients (medially located tumour or N+).

Table 2 | Patients with IMC lymph node metastases (n=14). Patient characteristics, primary tumour characteristics and therapeutic consequences when practising current guidelines.

Pt	IMC SLN	Age	Size	BR	HR	Ax +	Ind CT	Ind HT	Ind CT	Ind LRRT	Change
1	**1 macro**	73	1.9	III	E+P+	0	-	+	-	No	LRRT
2	**1 macro**	71	1.2	II	E+P-	1	-	+	-	No	LRRT
3	**1 micro**	73	2.5	II	E+P+	1	-	+	-	No	LRRT
4	**1 macro**	32	1.3	NR	E+P+	0	+	+	PTC/age	No	LRRT
5	**1 macro**	50	2.1	III	E-P-	7	+	-	PTC + AX	Yes	No
6	**1 macro**	65	2.5	III	E+P-	2	+	+	PTC + AX	No	LRRT
7	**1 micro**	57	2.6	II	E+P+	1	+	+	PTC + AX	No	LRRT
8	**1 macro**	47	0.5	II	E+P+	1	+	+	AX	No	LRRT
9	**2 micro**	64	1.7	III	E+P+	0	+	+	PTC	No	LRRT
10	**1 macro**	57	1.5	II	E+P+	0	+	+	PTC	No	LRRT
11	**2 macro**	61	1.5	III	E+P+	0	+	+	PTC	No	LRRT
12	**1 micro**	46	2.0	III	E+P+	0	+	+	PTC	No	LRRT
13	**1 micro**	50	1.3	III	E+P+	0	+	+	PTC	No	LRRT
14	**1 micro**	36	3.5	III	E+P+	1	+	+	Size+AX	No	LRRT

IMC SLN= intra mammary chain sentinel lymph node (histologic outcome), Size= tumour size in cm, BR:Bloom and Richardson grade, HR: hormone receptor status, E+/- estrogen receptor positive/negative, P+/-= progeston receptor positive/negative Ax += axillary lymph node metastases CT= chemotherapy LRRT=locoregional radiotherapy

Table 3 | Overview of studies evaluating the effect of locoregional RT in high risk patients

Study	N=	patients	FU	ST	outcome	GRM+RT	GRM	P value
Ragaz	318	N+	20	CMF	Overall survival	47%	37%	0.002
					Locoreg. RFS			0.03
Overgaard*	1375	SII/III	10	Tam	Locoreg. Recurrence	8%	35%	<0.001
					Overall survival	45%	36%	0.03
Overgaard*	1708	SII/III	10	CMF	Locoreg. Recurrence	9%	32%	<0.001
					Overall survival	54%	45%	<0.001
Clarke**	1428	N0	5	Var.	Locoreg.	2.3	6.3	2p=0.0002
	8505	N+	5	Var.	Recurrence	5.8	22.8	2p=0.0002
	1428	N0	15	Var.	Rate	31%	28%	NS
	8505	N+	15	Var.	Breast cancer mortality	55%	60%	2p=0.0002

*Incomplete axillary lymph node dissection: a median number of 7 lymph nodes were removed

**Meta-analyses in which the studies by Overgaard were included

FU: Follow-up (years), ST: Systemic therapy, GRM+RT: Modified radical mastectomy + radiotherapy, GRM: Modified radical mastectomy, var=various, N+: Node positive disease,

N0: Node negative disease, SII/III: stage II/III breast cancer, RFS: recurrence free survival,

Tam: Tamoxifen CMF: cyclophosphamide, methotrexate, 5-FU

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CHAPTER 8

Discrepancy between routine and expert pathologists' assessment of non-palpable breast cancer and its impact on locoregional and systemic treatment

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Abstract

Background

Histopathological parameters are essential for deciding on adjuvant treatment following breast cancer surgery. We assessed the impact of inter-observer variability on treatment strategy in patients operated for clinically node negative, non-palpable breast carcinomas.

Methods

In the context of a multicentre randomised controlled trial, clinical and histological data of 310 patients with clinically node negative non-palpable invasive breast cancer were prospectively collected. Histological assessment of the primary tumour and sentinel nodes was first performed in a routine setting, subsequently central review took place. In case of discordance between local en central assessments, we determined the impact upon locoregional and systemic treatment strategy.

Results

Discordance between local and central review was observed in 13% of the patients for type (kappa 0.60, 95% CI 0.50-0.71), in 12% for grade (k=0.796, 95% CI 0.73-0.86), in 1% for ER status (k=0.898, 95% CI 0.80-1.0), in 2% for PR status (k=0.940 95% CI 0.89-0.99). Discrepancy in the assessment of the sentinel node(s) was seen in 2% of the patients (k=0.954, 95% CI 0.92-0.98). Applying current Dutch guidelines, central review would have affected locoregional treatment in 2% (7/310), systemic treatment in 5% (16/310) and both in 1% (2/310) of the patients.

For the 9 (3%) patients in whom central review would have led to additional systemic treatment, Adjuvant! predicted 10 years mortality and recurrence rate would have decreased with a median of 4.6% and 15%, respectively.

Conclusion

Discordance between routine histological assessment and central review of non-palpable breast carcinoma specimens and sentinel nodes was observed in 24% of

patients. This inter observer variation would have impacted locoregional and/or systemic treatment strategies in 8% of the patients.

Introduction

Adequate surgical excision followed by whole breast irradiation is the first step in the treatment of early stage breast cancer. Further adjuvant treatment decisions are predominantly based on the pathology findings. Besides age, the choice of treatment depends on the tumour characteristics such as grade, hormone receptor status and HER2 status and lymph node and margin status as these are prognostic and/or predictive factors.[1]

In cases of lymph node metastases, adjuvant systemic treatment is advised in the vast majority of patients, as this is an important indicator of adverse prognosis. Identification of node negative patients requiring adjuvant systemic treatment requires further stratification using the additional prognostic and predictive factors. Here, clinical-pathological guidelines like Adjuvant!Online can be applied.

Post-operative locoregional treatment strategy depends on the margin status of the excised tissue and the nodal stage. Tumour positive margins increase the risk of local recurrence and therefore require re-operation or a radiotherapy boost. In cases of sentinel lymph node metastases, one may decide to perform an axillary lymph node dissection or to administer radiotherapy to the axilla.

Reproducible and accurate histopathological diagnosis of breast cancers is therefore of crucial importance. Previous studies have shown that the histopathological assessment of breast specimens varies substantially between pathologists with discrepancies of up to 50%.[2-5] Studies evaluating the inter-observer variability for sentinel node status show fair to excellent agreement (kappa 0.39-0.95).[6-8] Variation can occur due to technical differences of the procedures performed for the assessment of these factors or due to differences in interpretation.

Since a histological diagnosis is crucial for accurate adjuvant treatment advice, inter-observer variability may eventually affect the patient outcome. In the present study, we aim to determine the impact of inter-observer variability in the histological assessment of non-palpable, clinically node negative, breast carcinomas on further treatment strategy and prognosis prediction.

Methods

Patients and recruitment

This study was conducted within the context of the ROLL trial, a multicenter randomised trial designed to compare the efficacy of wire-guided localisation (WGL) and radioguided occult lesion localisation (ROLL). Detailed methods have been described previously.[9] In brief, women (>18 years) with histological proven non-palpable breast cancer and eligible for breast conserving surgery with sentinel node biopsy were enrolled. Approval of the institutional review boards at all 4 participating centres was acquired and all enrolled patients gave informed consent prior to randomisation. All patients underwent sentinel node biopsy and breast conserving surgery guided by either ROLL or WGL.

Histopathology evaluation

All specimens were initially evaluated in a routine setting at one of the four participating hospitals.

All formalin fixed paraffin embedded tissue sections were H&E stained and assessed by a local pathologist. Central review of all slides was exclusively performed by a dedicated breast pathologist (PvD or SMW). Tumours were histologically graded according to the Bloom and Richardson grading system. Immunohistochemical stainings for ER (clone 1 B5, Dako), PR (PgR636, Dako) and HER2 (SP3, Neomarkers) were performed according to manufacturers' protocols. ER and PR were considered as positive if at least 10% of the tumour cells showed nuclear positivity. Immunohistochemical HER2 status was scored as previously described.10 In case of a 2+ score for HER2 with immunohistochemistry, additional FISH/CISH for HER2 was performed and scored as decribed.[10]

Resection margins were annotated as negative (i.e. no tumour cells extending to the margin), focally positive margins (i.e. tumour cells present in the resection margins over less than 2 mm.), more than focally positive (i.e. tumour cells present in the resection margins over more than 2 mm.).

The sentinel nodes were evaluated with H&E and cytokeratin immunohistochemistry. If metastases were present, they were classified as macro metastases, defined as a metastatic depot of >2 mm in size; as micro metastases, defined as a metastatic depot of 0.2–2 mm in size; or as isolated tumour cells, defined as a single tumour cell or a cluster of tumour cells of <0.2 mm in size.[11]

Outcomes

Clinical and pathological data of all patients were collected prospectively. Local and central pathology diagnoses were compared. We assessed the impact of central review on the loco-regional and systemic treatment by applying the most recent Dutch guidelines on the treatment of breast cancer.[1] In cases where central review led to an indication for additional systemic treatment where local assessment did not, the impact of the change in treatment on the predicted 10 year recurrence and mortality rates by Adjuvant!Online was determined.

Statistical analysis

Normally distributed continuous variables were presented as means (standard deviation) and not normally distributed data were presented as medians (range). The level of inter-observer agreement between the original and central review was expressed as Cohen's Kappa. Kappa scores between 0.00-0.20 indicate poor agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement and 0.81-1.0 excellent agreement.[12] Kappa statistics and 95% confidence intervals (CIs) were calculated using SPSS version 16.0.

Results

Discrepancy between expert- and routine pathologist histological assessment

Of the 314 patients included in the ROLL trial, routine and central histology data of 310 patients were available for analysis. In 24% of the patients some sort of inconsistency was observed. Discrepancy between the routine and central review with regard to the margin status was seen in 2% (7/310) of the patients. Five cases with tumour negative margins at routine assessment showed involved margins (n=3) or focally involved margins (n=2) at central review. Conversely, in three patients with margins originally deemed tumour positive, tumour negative margins were reported at central review. Histological tumour type was not concordant in 9% (286/310) of the patients (k=0.70 95% CI 0.60-0.80); 7% (18/266) of the tumours initially defined as ductal were reported as a (ducto)lobular or another type (i.e. tubular, medullary, cribriform) after central review. The tumour grade was discordant in 12% (37/298) with a kappa score of 0.80 (95% CI 0.73-0.86). At central review, 4% of tumours that were assessed as grade 2 by routine pathologists were upgraded to grade 3, while 13% was downgraded to grade 1.

The level of inter-observer agreement for the hormone receptor status was excellent. Assessment of the hormone receptor status differed in only 4/302 (1%) of the patients for ER, with a high kappa score of 0.90 (95% CI 0.79-0.99) and for 5 /283 (2%) of patients for PR with again a high kappa score (k=0.94 95% CI 0.89-0.99).

Local and central review data regarding the nodal stage were available in 303 patients; concordance was seen in 98% of the patients with a kappa score of 0.954 (95% CI 0.92-0.99). Originally 222 patients were deemed pN0, but after central review 2 of them were restaged as pN0 (i+) and 1 as pN1mic. In one of the 18 patients originally staged as pN0(i+), a micro metastasis was reported at central review. Of the 19 patients originally reported as pN1mic, one patient was restaged into pN0(i+). Forty one patients were originally staged pN1+, and one of them was restaged as pN1mic at central review.

Impact on systemic and loco-regional treatment

According to the Dutch CBO guidelines 2012, the results of central review would have led to a change in treatment in 27/310 (9%) patients. (table 3)

Adjuvant systemic treatment (i.e. hormone therapy and chemotherapy) was advised in 10 patients based on routine pathology assessment, whilst systemic treatment could have been omitted based on the central review. Conversely, in seven patients, systemic treatment was not indicated based upon routine pathology, while central review would have resulted in proposing chemo and hormonal treatment. After central review, 2 patients obtained an indication and one lost her indication for hormone therapy only. With regard to locoregional treatment, in three patients re-excision and in two patients radiotherapy boost would have been required based on central review, but not according to routine assessment. Conversely, in three patients re-excision could have been omitted based on central review.

Impact on prognosis

Nine patients (3%) did not receive systemic adjuvant treatment based on local evaluation, but adjuvant systemic therapy would have been advised based upon central review findings. Assessment of the impact of omitting adjuvant treatment showed a median increase in Adjuvant!Online predicted 10 year mortality of 4.6% (1.7-7.4%) and a median increase in Adjuvant!Online predicted 10 year recurrence of 15.2% (10.5-20.0%) by omitting systemic therapy in these patients. (table 3b)

Discussion

With this study we show a substantial amount of discrepancy in histol ogical assessment of early stage non palpable breast cancer between routine and expert pathologists. In 24% of the patients, central review led to differences in reporting of grade, margin status, hormone status, which would have affected locoregional treatment in 3% and systemic treatment in 6% of our patients according to Dutch guidelines.

In 12% of the patients, we found discrepancy in histological grading between the routine setting and central review. B&R grade 2 carcinomas were most sensitive to inter-observer differences. This level of inter-observer variability was still low compared to other studies, where discordance was found in 15-40% of the cases.[4,13-15] Inter-observer variability for ER and PR status was also lower compared to other studies; we found 1% for ER status and 2% for PR status, while others report percentages of up to 5% and 18%, respectively.[15,16] This was possibly caused by the fact that the originally stained slides were used for review, avoiding discrepancies due to technical issues. Histological tumour type was most liable to inter-observer variation; in 13% of the patients a different type was reported at central review. Most of tumours were reclassified from ductal carcinoma to ductolobular, lobular, or as a less common type of carcinoma (i.e. tubular, medullary, papillary). Still, discrepancy in histologic tumour type would not have altered systemic or locoregional treatment strategies.

Lymph node status is an important prognostic factor and therefore an essential decision tool in the adjuvant treatment strategy of breast cancer. The discrepancy between pathologists regarding sentinel node status assessment has been studied previously, showing kappa scores ranging from 0.39 to 0.95. When the number of tumour cells in a SN decreases, discordance seems to increase.[7,8] Vestjens and colleagues assessed the impact of central review of the nodal status in 2842 patients with early breast cancer (pN0, pN0 (i+) or pN1mic). Central review changed the nodal status in 24% of the patients. Most of them were upstaged, with potentially clinical relevance.[6] We showed an excellent inter-observer agreement score for SN status (k=0.95), with no specific nodal stage being more sensitive for inter-observer variability.

Data on the concordance between pathologists regarding margin status of the tissue specimen is scarce. Newman, et al reported a change of the surgical margin status in 5% of the patients after review by a dedicated pathologist.[17] Staradub and colleagues found that second opinion leads to altering of the initially reported margin status in 4% of the patients.[18] Three per cent of the patients in our cohort showed a discrepancy for margin status. Prognosis is substantially influenced by the margin status; in cases of

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tumour positive margins recurrence is reported in up to 30% of the patients compared to 7% of the patients with tumour negative margins. [4,13-15] Therefore, patients in our cohort that were potentially undertreated (i.e. would have underwent re-excision or radiotherapy boost based on central review) have a substantially less favourable prognosis. Conversely, surgical over-treatment carries the risk of complications and impairs cosmetic outcome.[19]

Bueno- de Mesquita, et al. assessed the impact of inter-observer variability on adjuvant systemic treatment strategy in 694 patients with primary unilateral T1-4N0M0 cancer using the 2004 CBO guidelines (CBO 2004). Pathological re-examination of the tumour was performed; nodal status was not taken into consideration. Change in systemic adjuvant treatment was reported in 15% of the patients. Compared to our results, the inter-observer agreement variability for histological grade was considerably lower (kappa 0.561) leading to a larger proportion of patients being assigned to a different treatment group. In the most recent guidelines the criteria indicative for systemic therapy are broader compared to the CBO 2004 guidelines.[20] Therefore, the direct impact of differences in pathological parameters on the systemic treatment has possibly decreased. Recently, Kennecke and colleagues retrospectively assessed a large cohort of patients (n=906) with node negative, invasive or in situ breast cancer and evaluable nodes which was referred to the British Columbia Cancer Agency (BCCA). Pathology review was not performed systematically; only in a subgroup (405/906) pathology was re-assessed by a BCCA pathologist. Women who were reviewed were younger and more likely to have involved margins compared to the women who were not reviewed. Changes in the pathological assessment were seen in 20% of the patients, changing the treatment strategy in 6% of the patients.[5]

In our series nine patients (3%) were potentially undertreated systemically (i.e. chemotherapy and/or hormone therapy) when taking the central review as golden standard. The calculated Adjuvant! 10 yrs mortality and recurrence rates showed that undertreatment leads to a substantial difference in prognosis. Overtreatment effects are hard to calculate. It is however well known that systemic treatment, especially chemotherapy, causes a decrease in the quality of life and causes higher rates of morbidity and mortality (Berg 2001,). In our cohort 10 patients were possibly overtreated with chemotherapy (taking central review as golden standard).

This studies shows that in patients with non-palpable, node negative, breast cancer pathology review frequently reveals discrepancies in the histology assessment. These discrepancies eventually lead to a different choice of treatment in 8% of the patients. These differences can be of major influence on the prognosis. With these data we show that accurate histology assessment is of major importance for optimal treatment of breast cancer patients. For this reason we suggest that histology assessment should only be performed by pathologists vastly experienced with breast pathology or, when performed by a less experienced pathologist, review should be performed.

Conclusion

Discordance between routine histological assessment and central review of non-palpable breast carcinoma specimens and sentinel nodes occurred in 24% of patients. Inter observer variation in the histological assessment of non-palpable breast carcinoma specimens and sentinel nodes is in the order of 24% and results in a different locoregional or systemic treatment advice in 8% of the patients. The possible effect on the prognosis of these patients is considerable.

Table 1 | Baseline and tumour characteristics

	All patients (N=310)	
Mean Age (standard deviation)	61 (8.0) yrs	
Menopausal status		
Pre menopausal	35	11%
Post menopausal	260	83%
Not reported	15	6%
Visible on		
Mammography + ultrasound	290	94%
Ultrasound only	12	4%
Mammography only	8	3%
Median size invasive carcinoma (range)	1•25 (0•1-6) cm	
Histologic type		
Ductal	266	86%
Lobular	21	7%
Ductolobular	17	5%
Other	6	2%
Bloom and Richardson		
Grade I	135	43%
Grade II	129	41%
Grade III	40	13%
Not reported	6	3%
Ductal carcinoma in situ component		
Yes	173	56%
No	127	41%
Not reported	10	4%
Estrogen receptor status		
Positive	282	91%
Negative	21	7%
Not reported	7	2%
Progesterone receptor status		
Positive	248	80%
Negative	53	17%
Not reported	9	3%
HER2 receptor status		
Positive	20	6%
Negative	280	90%
Not reported	10	3%
Sentinel node		
Tumour free	230	74%
Isolated tumour cells	18	6%
Micrometastes	19	6%
Macrometastases	41	13%
No lymph nodes dissected/missing	2	1%

Table 2 | Histological diagnosis based on routine assessment (vertically) and central review (horizontally) of 310 patients with surgical excision of non-palpable breast cancer

2a. Histological tumour type

Routine / Central	Ductal	Lobular	Ducto-lobular	Papillary	Medullar	Cribri-form	Tubular	Other	Total
Ductal	236	2	14	3	2	3	5	1	266
Lobular	2	15	4						21
Ductolobular	2		15						17
Papillary	1			1					2
Tubular							1	1	2
Other								2	2
Total	241	17	33	4	2	3	6	5	310

2b. Bloom and Richardson grade

Routine / Central	B&R grade 1	B&R grade 2	B&R grade 3	Total
B&R grade 1	120	12	2	134
B&R grade 2	16	105	5	126
B&R grade 3		2	36	38
Total	136	119	43	298

2c. Nodal stage

Routine / Central	pN0	pN0 (i+)	pN1mic	pN1	Total
pN0	222	2	1		225
pN0 (i+)		17	1		18
pN1mic		1	18		19
pN1			1	40	41
Total	222	20	21	40	303

2d. Oestrogen Receptor status

Routine / Central	Positive	Negative	Total
Positive	276	2	278
Negative	2	19	21
Total	278	21	299

2e. Progesterone Receptor status

Routine / Central	Positive	Negative	Total
Positive	227		227
Negative	5	48	53
Total	232	48	280

2f. Margin status

Routine / Central	Positive	Negative	Total
Positive	268	5	273
Negative	3	34	37
Total	271	39	310

Tumour type: kappa=0.601 (95% CI 0.50-0.71)
Tumour grade: kappa=0.796 (95% CI 0.73-0.86)
Oestrogen receptor status: kappa=0.898 (95% CI
Progesterone receptor status: kappa=0.940 (95% CI 0.89-0.99)
Nodal stage: kappa= 0.954 (95% CI 0.92-0.98)
Margin status: kappa = 0.88 (95% CI 0.80-0.96)

Table 3

3a. Altering of post-operative treatment based on central review

Change	Reason	N=	% of all patients
+ CT and HT	B&R upgrading	6	2%
	SN	1	<1%
- CT and HT	B&R downgrading	10	3%
+ HT	ER	2	1%
- HT	ER	1	<1%
+ Boost	Margins	2	1%
Re-excision	Margins	3	1%
No re-excision	Margins	3	1%
Total		28	9%

*For the patients in the grey cells, central review led to an indication for systemic treatment
CT +/-= Chemotherapy yes/no, HT +/-= Hormone therapy yes/no

3b. Impact of inter observer variability on Adjuvant! Online predicted survival for the cases in which central review led to an indication for systemic treatment (chemo and/or hormone therapy).

	Age (yrs)	Change	Reason	10-yrs. rec. without ST	10 yrs. rec. with ST	Δ 10yr. rec.	10 yr. mort. without ST	10 yr. mort with ST	Δ10 yr mort.	Ind LRRT	Change
1	**63**	ST	B&R	17.2%	6.7%	10.5%	2.9%	1.3%	1.6%	No	LRRT
2	**64**	ST	B&R	23.3%	9.3%	14.0%	7.5%	3.4%	4.1%	No	LRRT
3	**57**	ST	B&R	24.2%	8.2%	16.0%	7.7%	3.1%	4.6%	No	LRRT
4	**50**	ST	B&R	24.6%	6.4%	18.2%	7.9%	3.1%	4.8%	No	LRRT
5	**41**	ST	B&R	24.8%	6.9%	17.9%	7.9%	3.6%	4.3%	Yes	No
6	**59**	ST	SN	25.0%	10.0%	15.0%	8.7%	3.8%	4.9%	No	LRRT
7	**59**	HT	ER	30.9%	20.2%	10.7%	12.5%	9.2%	3.3%	No	LRRT
8	**57**	ST	B&R	30.9%	10.9%	20.0%	12.5%	5.1%	7.4%	No	LRRT
9	**48**	HT	ER	44.3%	29.8%	14.5%	23.6%	16.8%	6.8%	No	LRRT

ST= systemic therapy: chemo- and hormone therapy; HT= Hormone Therapy; B&R=Bloom and Richardson grade, SN=Sentinel node, ER= Oestrogen Receptor

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CHAPTER 9

Localisation of non-palpable breast cancer; current situation and future perspectives

Currently in the Netherlands, there is no uniformity regarding the localisation of non-palpable breast cancer. A short mail survey assessing the current situation of localisation of non-palpable breast cancer amongst oncological surgeons in the Netherlands showed that various different techniques are being utilized. The survey was sent to 420 Dutch oncological surgeons of which 145 (35%) responded. The results showed that the most important outcomes of breast surgery considered by surgeons were: 1) obtaining tumour negative margins, 2) volume of excised tissue, 3) patient comfort, 4) logistics and 5) ease of the procedure for the surgeon.

The vast majority (83%) of the oncological surgeons use wire-guided localisation (WGL). Radioguided occult lesion localisation (ROLL) is used by 9%, radioactive seed localisation (RSL) by 11% and ultrasound guided localisation (USG) by 5%. Ninety-one per cent of the surgeons indicated a willingness to try an alternative localisation technique. Based on our findings one can conclude that WGL seems to be the standard for the surgical treatment of non-palpable breast cancer in the Netherlands, but that other techniques are applied by a substantial number of surgeons. The scientific evidence supporting the use of alternatives to WGL, however, is limited. Results of the WGL localisation technique have improved over time showing a decrease in tumour positive margins from 40% in early reports to 12% in more recent studies.[1-4] As the proportion of non-palpable breast cancers has increased over the last few years in the Netherlands, experience with WGL is substantial which may explain these improved rates of clear resection margins. Improvements in the imaging techniques for detection and delineation of non-palpable breast cancer may also have contributed. One should however bear in mind that the definition of involved resection margins differs per country and has changed substantially over time. In the Netherlands margins are considered involved when tumour cells are present in the inked surgical margin. In some other countries, an involved margin is defined as tumour cells <5 mm (or more) from the inked margin. As such, the improvement in margin negative resections may be partially due to differences and changes in definitions.

Despite the improvements seen with WGL, it is associated with a number of disadvantages and as such, alternative methods have been proposed.[1-5] Until now, none of the novel techniques have proven to be superior to WGL. Even though it is hard to introduce an alternative that comes close to the results achieved with WGL, there still is room for improvement. Currently, still more than 10% of patients require re-excision and excessive resection volumes of healthy tissue are reported.[6] ROLL has been touted as an effective method to improve both aforementioned aspects. When performing ROLL, the surgeon is provided with feedback regarding localisation and depth of the tumour during the whole surgical procedure. Additionally, the surgeon is free to select the most optimal place of incision without interference of a hook wire. These aspects have led to the expectation that the use of ROLL decreases re-excision rates whilst reducing the volumes of excised (healthy) tissue. The results of the ROLL trial however, showed that ROLL does not lead to decreased re-excision rates and even increases the excised tissue volumes. Therefore, ROLL cannot replace WGL as the standard of care. Considering the results of previous performed studies and the opinion of surgeons vastly experienced with ROLL, our results were unexpected.

The findings of the ROLL trial underline once again the importance of performing well designed, clinical evaluations of new techniques preferably by means of multicentre randomised trials before implementing new surgical techniques in routine care. Often novel techniques are touted as an effective technique without the drawbacks of the standard treatment and consequently implemented as the new standard of care without performing a thorough comparison with the traditional technique. One should however keep in mind that novel techniques carry their own drawbacks and (still) unknown risks. Also, where single centre studies often represent 'best practice', multicentre trials approximate results in daily care. As breast cancer is an "everyday" diagnosis, results from multicentre trials are of major value.

Radioactive seed localisation (RSL) is increasingly proposed as a promising alternative to WGL. A radioactive seed is introduced by a needle using standard ultrasound or mammographic guidance. The seed can be placed days in advance of the surgical procedure because of its long half-time, providing logistical benefits. Since radioactive seed localisation offers the opportunity of easier scheduling, less waiting time for surgery is likely. This technique is already used in a few centres in the Netherlands and several centres are planning on implementing RSL in the near future. Recently, Lovrics and colleagues performed a multicentre randomised controlled trial that demonstrated that RSL is at least equivalent to WGL in obtaining negative resection margins and avoiding a second intervention.[2] Also specimen sizes were similar for both groups (184 cm^3 vs. 191 cm^3, p= 0.607). The number of patients enrolled in this trial approaches the number of patients in the ROLL trial. However, an inhomogeneous population was studied as patients with both invasive carcinoma (82%) and DCIS (18%) were enrolled. Our group recently performed a systematic review regarding the accuracy of RSL in which we also concluded that RSL is comparable to WGL in terms of complete resection and re-excision rate.[7] We feel that RSL has the potential to replace the current standard technique (i.e. WGL) for the management of non-palpable breast cancers in the Netherlands, since it is likely to be time and therefore cost saving compared to WGL. Since the situation in the Netherlands is differs from that in the US, we propose controlled implementation of RSL in our country in order to estimate (cost-)effectiveness, learning curve effects and complications. A multicentre registration study keeping track of all consecutive RSL procedures in terms of margin status, excised tissue volumes, localisation and operating time and complications, should at least be performed to evaluate if RSL indeed lives up to its expectations.

In our opinion, the work described in this thesis once more depicts the importance of multidisciplinary teamwork when it comes to the treatment of (non-palpable) breast cancer. Whichever localisation method is chosen, the quality of the team as a whole determines the outcome. Optimal localisation can only be accomplished when the radiologist, the surgeon and nuclear medicine physician are well trained, dedicated and collaborating. During the treatment process of patients with breast cancer, decision making skills (i.e. choosing the most optimal treatment procedure) are at least as important as the technical skills of the separate team members.

In this era of personalised medicine it may be apparent that there is no optimal localisation technique for the total non-palpable breast cancer population. A certain localisation technique could be more suitable and provide better results for a specific patient group than another. If so, the method used for localisation should be determined within a multidisciplinary setting for each patient individually based on patient and tumour characteristics, but always guided by scientific evidence.

Due to the enormous amount of scientific work in the field of breast cancer, novel developments rapidly evolve. A breast cancer management team should consist of physicians who are familiar with the most recent guidelines and literature and who are willing to work in a multidisciplinary way. Similar to the localisation procedure, total breast cancer management can only be successful when all involved physicians work in this way.

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CHAPTER 10

Summary

In the Netherlands more than 13.000 women are annualy diagnosed with breast cancer and this number is expected to keep rising. Nowadays the majority of the carcinomas are detected in an early stage due to the introduction of screening programmes. Early stage carcinomas are small and not yet (clinically) metastasised, facilitating adequate treatment and cure. Most of the early stage carcinomas can be treated with breast conserving treatment (BCT) and sentinel node biopsy (SNB) followed by whole breast irradiation. A substantial proportion of the early stage cancers is non-palpable, creating the need for accurate preoperative localisation tools. Although various promising alternatives have emerged, wire guided localisation is still the technique of choice for many breast cancer surgeons.

The axillary nodal status in patients with early stage breast cancer is the single most important prognostic tool and guides treatment options and adjuvant therapies. SNB is a valuable and widely used procedure for the assessment of the axillary lymph node status and has been refined during the past decade. Nevertheless, there remain certain areas of controversy in the techniques used for sentinel lymph node mapping. For example, there is no consensus on the optimal injection site of the dual tracer. Another subject of discussion is the assessment of extra-axillary sentinel nodes; until now the clinical relevance of routine biopsy of internal mammary sentinel nodes has not yet been proven.

The studies presented in this thesis focus upon various features of early stage breast cancer management. In chapter 2 a review of the currently available techniques for localisation of non-palpable breast cancer is provided. Studies assessing the golden standard (WGL), ultrasound guided surgery, ROLL and RSL were selected and subjected to a critical appraisal. Most studies concerning this subject included patients with both benign and malignant non-palpable lesions. In order to compare the effectiveness, advantages and shortcomings of these techniques in breast cancer only, patients with benign lesions were excluded. In total, 19 studies were appraised; 12 comparative studies and 7 cohort studies. Radioguided surgery seemed the most promising method of localisation, differences in results however did not reach statistical significance.

Since a well designed randomised controlled trial was required to assess the true effectiveness of radioguided surgery compared to WGL, the Dutch ROLL trial was set up in 2008. The aim of this trial was to determine if ROLL is superior to WGL in patients with invasive breast carcinoma requiring breast conserving surgery. The results of this trial are presented in chapter 3. The study showed similar complete tumour excision and re-excision rates for ROLL and WGL, being 86% vs. 88% and 12% vs. 10% respectively. In the ROLL group however, larger lumpectomy volumes were excised (71 cm^3 vs 64 cm^3). Assessment of the secondary endpoints including ease of the procedure for both physicians and patients, success rate of the sentinel node procedure and cosmetic outcome did not reveal any differences. Based upon these findings it was concluded that ROLL cannot replace WGL as the standard of care. The results of the ROLL trial came as a surprise since previous studies showed favourable results for ROLL and the surgeons found ROLL pleasant to work with. This outcome stresses the importance of performing randomised comparisons to properly evaluate new interventions in the field of surgery before implementing them.

In the study described in chapter 4, the cost-effectiveness of ROLL compared to WGL was evaluated. Direct medical costs and changes in quality of life measured over a 6 month period were taken into account. ROLL was found to be comparable to WGL with respect to both costs and quality of life effects and will therefore not lead to more cost-effective medical care. These results add to the clinical results and enforce the conclusion that ROLL cannot replace WGL as standard of care.

Chapter 5 describes 5 cases of localisation failure (<25% of the tumour in the surgical specimen) that were encountered in the ROLL group during the ROLL trial. Multidisciplinary evaluation of these cases pointed out that this was due to incorrect pre-operative localisation or dispersion of the radiotracer. In the WGL group incorrect placement of the wire occurred, but did not lead to a localisation failure. Since a mammography is performed to assess the precise site of the hookwire, the incorrect

placement was detected in an early stage allowing intervention. When using ROLL, localisation failures can be avoided by injection of the radiotracer mixed with contrast, followed by check mammography to ascertain correct placement of the radiotracer.

Extensive research concerning the sentinel node procedure has led to the refinement and consequently high success rates (95%) of this procedure. In chapter 6 the impact of site of dual tracer injection on the risk of unplanned axillary lymph node dissection is evaluated, focussing only on patients with non-palpable breast cancer. Here, patients with peri-areolar injection of the dual tracer were compared to patients with intra/peri-tumoral injection of the tracer. Intra/peri-tumoural injection of the dual tracer increases the risk for unsuccessful SNB procedure and unplanned ALND among patients with non-palpable breast cancer.

There is no consensus on the added diagnostic or prognostic value of retrieving sentinel lymph nodes from the internal mammary chain (IMC) when seen on pre-operative lymphoscintigraphy. Chapter 7 examined the impact of routinely performed IMC sentinel node biopsy on the systemic and locoregional treatment plan in 493 patients. Current guidelines (2012) were used to determine if the internal mammary sentinel node histology result influenced treatment. Systemic treatment was changed in none of the patients. Radiotherapy was altered in 11% of the patients that underwent excision of the internal mammary sentinel node. As there is no sufficient ground for adjustment of radiotherapy it is suggested not to perform biopsy of the IMC sentinel node routinely, but only in a selected patient group.

Histology parameters are essential for deciding upon adjuvant treatment following breast cancer surgery. Chapter 8 studies the impact of inter-observer variability on treatment strategy. Patients with clinically negative, non-palpable breast cancer were included. All patients underwent lumpectomy and sentinel node procedure. Both the lumpectomy specimen as well as the sentinel node specimen slides were subjected to evaluation by 2 pathologists. Firstly in a routine setting, followed by central review performed by a dedicated breast pathologist. In cases of discordance between routine and central review assessments, the impact on locoregional and systemic treatment strategy was determined using the current guidelines. The inter-observer variation would have impacted locoregional and/or systemic treatment strategies in 8% of the patients.

Chapter 9 describes the current situation and our future perspectives with regard to the localisation of non-palpable breast cancer.

CHAPTER 11

Summary in Dutch
Samenvatting in het Nederlands (voor niet ingewijden)

In Nederland wordt er elk jaar bij meer dan 14.000 vrouwen borstkanker vastgesteld en naar verwachting zal dit aantal de komende jaren blijven stijgen. In 1990 is het bevolkingsonderzoek borstkanker gestart. Dankzij de invoering hiervan wordt borstkanker veel vaker in een vroeg stadium al gedetecteerd. In dit vroege stadium is de kwaadaardige tumor (carcinoom) vaak nog klein van omvang en zijn er geen aanwijzingen voor uitzaaiingen. Hierdoor is de kans op een succesvolle behandeling en genezing groter. De meerderheid van patiënten waarbij sprake is van borstkanker in een vroeg stadium kan behandeld worden met borstsparende chirurgie; hierbij wordt het carcinoom en een ruim gedeelte gezond weefsel hier omheen verwijderd. Tijdens dezelfde operatie wordt met de zogenoemde schildwachtklier procedure bepaald of er eventuele uitzaaiingen naar de lymfeklieren zijn. De operatie wordt gevolgd door bestraling van de aangedane borst.

Een aanzienlijk deel van de vroeg stadium carcinomen is bij presentatie (nog) niet te voelen, dit maakt het voor de chirurg moeilijk te bepalen welk deel van de borst weggehaald moet worden. Hoewel er de afgelopen jaren verscheidene methoden zijn ontwikkeld om de chirurg te helpen bij het lokaliseren van het niet te voelen carcinoom tijdens de operatie, lijkt draadgeleide lokalisatie nog altijd de methode van voorkeur te zijn.

Het wel of niet aanwezig zijn van uitzaaiingen in de schildwachtklier is van groot belang voor de prognose van patiënten met borstkanker en speelt een belangrijke rol bij het bepalen van het therapeutisch beleid. Tijdens de schildwachtklier procedure wordt de eerste lymfeklier waarop de kwaadaardige tumor draineert (de schildwachtklier) opgespoord met een blauwe en/of radioactieve speurstof en onderzocht op kwaadaardige cellen. Dit is een betrouwbare en veel gebruikte procedure om de status van de overige lymfeklieren te beoordelen. Als men in Groningen de trein neemt, moet men altijd over station Zwolle om in de rest van Nederland te komen. De schildwachtklier kan men zien als station Zwolle; als daar dus geen kwaadaardige cellen in worden gevonden kan er vanuit gegaan worden dat er geen kwaadaardige cellen zijn doorgereisd naar de rest van het lichaam. Hoewel de schildwachtklier procedure over de afgelopen jaren verfijnd is bestaat er nog steeds discussie over bepaalde technische aspecten. Zo is er bijvoorbeeld geen consensus bereikt over de optimale injectie plek van de radioactieve en blauwe speurstof. Het biopteren van schildwachtklieren die buiten de oksel opkomen blijft ook onderwerp van discussie; tot nu toe is de klinische relevantie hiervan nog niet aangetoond.

In dit proefschrift wordt de behandeling van borstkanker in een vroeg stadium op verschillende manieren belicht. In hoofdstuk 2 hebben wij een literatuurstudie uitgevoerd waarin de hedendaags gebruikte methoden voor het lokaliseren van niet te voelen borstkanker worden beschreven en vergeleken. In de studies die wij hebben geëvalueerd werd gebruik gemaakt van draadgeleide lokalisatie, echogeleide lokalisatie en radioactief geleide lokalisatie. Bij draadgeleide lokalisatie wordt er voordat de operatie plaatsvindt door de radioloog een metalen draad in het carcinoom geplaatst. De chirurg gebruikt deze draad tijdens de operatie voor het lokaliseren van het carcinoom. Bij echogeleide lokalisatie wordt tijdens de operatie gebruik gemaakt van echo beelden om het carcinoom te lokaliseren. Bij radioactief geleide lokalisatie opereert de chirurg op geleide van een radioactieve bron welke vóór de operatie in het carcinoom is geplaatst. Bij de zogenaamde radioguided occult lesion localisation (ROLL) techniek wordt er radioactieve vloeistof in het carcinoom gespoten. Ook kan er een radioactief jodiumzaadje in het carcinoom geplaatst worden. In de meeste onderzoeken werden zowel patiënten met een kwaadaardige als een goedaardige (niet te voelen) tumor geïncludeerd. Om de effectiviteit, de voor- en nadelen van de verschillende methoden te vergelijken in uitsluitend patiënten met borstkanker, werden de patiënten met een goedaardig gezwel geëxcludeerd. In totaal werden er 19 studies geëvalueerd; 12 vergelijkende en 7 cohort studies. Onze studie laat zien dat radioactief geleide lokalisatie de meest veelbelovende methode van lokalisatie lijkt te zijn, maar dat er een goed opgezette gerandomiseerde studie nodig is om dergelijke bevindingen te bevestigen. Om die reden is in 2008 gestart met de ROLL studie; een onderzoek waarin de effectiviteit van draadgeleide lokalisatie is vergeleken met de ROLL techniek. Zoals eerder beschreven, wordt er bij de ROLL techniek preoperatief radioactieve vloeistof in de tumor gespoten. Met een geigerteller kan de chirurg

vervolgens tijdens de operatie bepalen waar de tumor gelokaliseerd is. Het doel van deze studie was te bepalen of de ROLL techniek superieur is aan draadgeleide lokalisatie bij borstsparende chirurgie voor patiënten met een invasief mammacarcinoom waarbij borstsparende chirurgie wordt toegepast. De resultaten van deze studie worden gepresenteerd in hoofdstuk 3. Er werd geen verschil gevonden in het percentage patiënten dat een succesvolle operatie (volledige verwijdering van het carcinoom) onderging. Wel werd er verschil gezien in de hoeveelheid weefsel dat verwijderd werd door de chirurg; dit was significant meer bij patiënten die zijn behandeld zijn met de ROLL techniek. Andere aspecten, zoals het gemak van de procedure voor zowel patiënt als arts en het uiteindelijke cosmetische resultaat, lieten geen verschil zien tussen ROLL en draadgeleide lokalisatie. Op basis van deze resultaten concluderen wij dat de ROLL techniek de draadgeleide lokalisatie niet kan vervangen als standaard lokalisatie procedure.

Het uitvoeren van goede opgezette vergelijkende studies is van groot belang bij het introduceren van nieuwe technieken. De ROLL studie is hier een goed voorbeeld van.

Op basis van kleine, niet gerandomiseerde studies kan men niet besluiten over te stappen op een nieuwe techniek. De resultaten van een goed opgezette vergelijkende studie moeten worden afgewacht voordat een dergelijke stap wordt gezet.
In hoofdstuk 4 wordt de ROLL techniek opnieuw vergeleken met de draadgeleide lokalisatie, maar nu op het gebied van de kosteneffectiviteit. Voor deze studie werden de directe medische kosten en de veranderingen in de kwaliteit van leven tot 6 maanden na de operatie aan elkaar gerelateerd. De ROLL techniek was vergelijkbaar met de draadgeleide lokalisatie wat betreft de kosten en kwaliteit van leven. Implementatie van de ROLL techniek zal daarom niet leiden tot kosten-effectievere medische zorg. Deze resultaten voegen toe aan de klinische resultaten en versterken dan ook de conclusie dat de ROLL techniek de draadlokalisatie niet kan vervangen.

In hoofdstuk 5 wordt een beschrijving gegeven van 5 casus uit de groep patiënten behandeld met ROLL, waarbij sprake was van een mislokalisatie (< 25% van de tumor aanwezig was in het chirurgisch verwijderde weefsel). Na evaluatie van deze casus bleek dat 4 van deze mislokalisaties veroorzaakt zijn door een verkeerde plaatsbepaling van de tumor door de radioloog vóór de operatie en 1 door ongewenste verspreiding van de geïnjecteerde radioactieve vloeistof in het borstweefsel, waardoor de chirurg tijdens de operatie af is gegaan op het verkeerde weefsel. Op basis van onze evaluatie stellen wij voor om bij gebruik van de ROLL techniek een mengsel van de radioactieve vloeistof met contrast middel in het carcinoom te spuiten in plaats van de radioactieve vloeistof alleen. Op die manier zou er met beeldvorming gecontroleerd kunnen worden of de vloeistof in het juist weefsel terecht is gekomen.

Uitgebreid onderzoek naar de schildwachtklier procedure heeft ertoe geleid dat deze procedure de afgelopen jaren sterk verbeterd is, met nu een succespercentage van 95%. Als deze procedure niet succesvol verloopt is het, om uitspraken te kunnen doen over eventuele uitzaaiingen naar de lymfklieren, noodzakelijk om een okselkliertoilet te verrichten. Bij een okselkliertoilet worden alle lymfeklieren in de oksel verwijderd. Omdat deze chirurgische procedure uitgebreider is dan de schildwachtklier procedure brengt het ook meer risico's met zich mee. In hoofdstuk 6 wordt bekeken in hoeverre de plaats van injectie van de blauwe en radioactieve speurstof van invloed is op de kans op een ongepland okselkliertoilet. Hierbij focussen we ons op patiënten met een niet te voelen mamma carcinoom. Een oppervlakkige injectie rond de tepel werd vergeleken met een diepere injectie in of rondom de tumor bij in totaal 314 patiënten
Op basis van dit onderzoek lijkt het zo te zijn dat bij patiënten met niet te voelen borstkanker de kans op het niet opsporen van de schildwachtklier en dus een ongepland okselkliertoilet verhoogd is bij diepere injectie in of rondom de tumor.
Op dit moment bestaat er nog geen consensus over de toegevoegde waarde van het verwijderen van schildwachtklieren die worden opgespoord buiten de oksel, zoals bij het borstbeen. In hoofdstuk 7 wordt het effect van het routinematig biopteren van schildwachtklieren bij het borstbeen op het postoperatieve behandelplan onderzocht in bijna 500 patiënten. Hierbij is gebruik gemaakt van de behandelrichtlijnen van het mammacarcinoom 2012. In geen enkele patiënt werd de systemische therapie (chemotherapie of hormoontherapie) aangepast op basis van de bevindingen bij het weefselonderzoek van de schildwachtklier bij het borstbeen. De radiotherapie

(bestraling) werd veranderd in 11% van de patiënten die een biopt van een schildwachtklier bij het borstbeen onderging. Omdat er geen gegrond bewijs is voor deze aanpassingen in het radiotherapeutische beleid lijkt het routinematig biopteren van schildwachtklieren bij het borstbeen niet zinvol en dient het voorbehouden te worden voor een geselecteerde populatie.
Na de operatie worden het verwijderde borstweefsel en de verwijderde lymfeklier(en) onderzocht door een patholoog. De keuze van behandeling na de operatie is afhankelijk van de uitslag van dit weefsel onderzoek. In hoofdstuk 8 worden de uitkomsten gepresenteerd van een studie waarin wij hebben gekeken naar de inter-observer variatie bij weefselonderzoek. De gegevens van de patiënten uit de ROLL studie werden hiervoor gebruikt. In eerste instantie werd het weefsel beoordeeld door de patholoog in het ziekenhuis waar de operatie was uitgevoerd. Vervolgens werd het nogmaals beoordeeld door een gespecialiseerde borstkanker patholoog. Op het moment dat er sprake was van discordante beoordelingen werd bekeken of dit de keuze van de postoperatieve behandeling (bijvoorbeeld aanvullend bestraling of chemotherapie) beïnvloed zou hebben. Wij vonden dat bij 8% van de 314 patiënten de inter-observer variatie geleid zou kunnen hebben tot een wijziging van de postoperatieve behandeling.

In hoofdstuk 9 bespreken wij de huidige situatie op het gebied van lokalisatie methoden voor het niet te voelen mamma carcinoom in Nederland. Tevens delen wij onze toekomstperspectieven op dit vlak en worden er enkele mogelijkheden voor verder onderzoek aangegeven.

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submitted

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Curriculum Vitae

Emily Louise Postma was born in Durban, South Africa on the 24th of December 1984. At the age of 2 she moved to Nijmegen with her parents where her father took up a surgical post at the UMCN St.Radboud. In 2003, after she finished her high school studies at the Stedelijk Gymnasium in Nijmegen she went on to study medicine at the University of Utrecht (2003-2010). During this period she participated in various commisions within her student sorority. During an internship at the department of surgery at St.Antonius hospital, Nieuwegein she developed her interest for surgery. She spent 3 months in Sweden performing research at the University of Linkoping (Prof. Soderholm) and did her final internship at the Department of Surgery at the University Medical Centre Utrecht. After graduating, she was given the opportunity to work as a PhD-student with Prof. van Hillegersberg, coordinating a large randomised controlled trial, comparing the effectiveness of two different methods of non-palpable breast cancer localisation. The results of her research are presented in this thesis. Besides her work, she enjoyes travelling and sports. She completed the Berlin Marathon in sept 2012 and this year hopes to complete the Alpes D'Huzes.
In December 2012 she took up a post working at Diakonessenhuis in Utrecht at the department of surgery.