Image guided localization of non-palpable breast lesions: a retrospective population-based cohort study

Julia Simanowski
MSc Health Sciences
University of Twente, faculty of Science and Technology
Enschede, July 2023
j.simanowski@student.utwente.nl

Supervised by:
A. Christenhusz MSc
Prof. Dr. J. van der Palen
Prof. Dr. S. Siesling

Abstract

Background

In 2020, in primary breast cancer 67% of all patients in the Netherlands received breast conserving surgery (BCS). Current standard-of-care for image-guided localization (IGL) of non-palpable breast cancer involves iodine seed, wire guidance, radio guided localization, ultrasound guidance, magnetic-marker and radiofrequency identification. However, comparative data regarding oncological safety, clear margins after surgery and number of re-excisions, is limited. Therefore, the aim of this retrospective population-based study is to compare IGL-techniques with respect to oncological safety in resection of non-palpable breast lesions.

Methods

All patients recorded by the Netherlands Cancer Registry, undergoing BCS with IGL between 2013 and 2022, were included in this study (n = 60.101). The status of resection margins (free, focally irradical, or more than focally irradical) was assessed according to the Dutch indications for re-excision. The correlation between image-guided localization and the status of tumor resection margins was assessed by a multinominal logistic regression analysis. The need for re-excision was assessed by logistic regression analysis. Both analyses were performed for invasive carcinoma and ductal carcinoma in situ (DCIS) separately. Iodine seed was taken as reference.

Results

There was a steady increase in the use of the iodine seed, magnetic-marker and radiofrequency identification (the latter two introduced in 2018), while wire-guided localization was decreasing. For patients with invasive carcinoma, there were no significant differences between the localization techniques regarding resection margin status. For patients with DCIS, the largest significant difference in the odds of a focally positive margin status was found between patients treated with magnetic-marker and iodine seed (OR = 1.94;1.13 – 3.34), while ultrasound guidance had the highest significant difference in the odds of a more than focally positive margin status compared to the iodine seed (OR = 1.80; 1.06 – 3.04). A significant difference in the odds of a re-excision was found between patients (both invasive carcinoma and DCIS) treated with wire guidance and iodine seed (OR = 1.37 and OR = 1.45 respectively).

Conclusion

With respect to resection margin status in treatment with image-guided localization, wire guided localization, ultrasound guided localization and the magnetic marker performed inferior to iodine seed for patients with DCIS. For patients with invasive carcinoma, no significant differences were revealed. Wire-guided localization has a higher occurrence of re-excisions compared to iodine seed for both patients with invasive carcinoma and patients with DCIS.

Introduction

The detection of malignant breast lesions is constantly being improved. The introduction of digital mammography [1,2] and the availability of the national screening program [3] in the Netherlands result in an increase in early detected breast tumors [4]. Of all Dutch patients diagnosed with breast cancer in 2021, 41% were diagnosed with stage I breast cancer [5]. Detection at an early stage increases the likelihood of these tumors not being palpable [6]. Non-palpable breast lesions mainly occur in patients with a small invasive tumor, patients with ductal carcinoma in situ (DCIS) or in patients who have responded well to neoadjuvant (chemo)therapy [4].

Treatment of patients with early stage breast cancer exists of a full breast amputation or breast conserving surgery (BCS), in some cases after prior neoadjuvant systemic therapy (chemo or hormone therapy) [7,8]. With BCS, the patient is subsequently treated with adjuvant radiotherapy, sometimes supplemented with systemic therapy. The demand for BCS is increasing: 67% of all breast cancer patients in the Netherlands received BCS in 2020 [9]. To successfully perform BCS in patients with a non-palpable breast tumor, there is the need for prior image-guided localization (IGL). The performance of IGL improves the oncological safety: an increase of the chance of obtaining clear margins while minimizing resection of healthy breast tissue to achieve optimal cosmetics and a decrease of the chance of needing a re-excision [10]. It results in higher patient satisfaction and the optimized use of healthcare resources [3].

Within IGL-techniques, wire guidance (WG) is still often seen as the gold standard world-wide [10]. A localizing wire is placed under ultrasound or mammography guidance. By following the wire, the surgeon reaches the location of the non-palpable tumor. It is safe, cost-effective and well-established. However, WG has a high risk of damage, is not easy to use, causes patient discomfort, limits scheduling flexibility and decreases operation room efficiency [3,11,12]. Therefore, the current-standard-of-care in the Netherlands for IGL of non-palpable breast cancer has been expanded with five other techniques:

1. The iodine seed (IS): the first type of radio guided localization. To mark the tumor, an iodine seed in a titanium capsule is implanted. With a gamma probe the seed will be detected to locate the tumor during surgery [13,14].
2. Radio guided occult lesion localization (ROLL): the second type of radio guided localization. A nuclear radiotracer (technetium) is injected to mark the tumor. With a gamma probe the tracer will be detected to locate the tumor during surgery [15]. In comparison to IS, ROLL is less flexible in the timing of the surgery due to the faster decay of technetium [14].
3. Ultrasound guidance (UG): the ultrasound is used intraoperative to locate and measure the tumor in surgery [12,16]. For this technique, no pre-operative invasive procedure is needed to mark the tumor.
4. The magnetic marker (MM): two types of magnetic seeds are used for IGL in the Netherlands; Sirius Pintuition [17] and Magseed [18]. These two types are based on a different technical principle. The seed of Pintuition has a magnetic core creating a magnetic field. The probe detects this magnetic signal to locate the tumor during surgery. The technology of Magseed works the other way around. The probe creates a magnetic field, which is reflected by the seed. The reflected signal will be detected by the probe to locate the tumor during surgery.
5. Radiofrequency identification (RFID): through the implantation of a RFID tag the tumor is marked. The tag transmits a radio wave signal which can be detected using firstly a handheld loop probe and secondly a surgical pencil probe [19].

The imaging modality of choice in the placement of the marker in WG, IS, ROLL, MM and RFID is ultrasound guidance. In most cases, the ultrasound can accurately identify the breast tumor. The use of ultrasound is preferred because it includes real-time imaging during deployment. Additionally, it does not include radiation and is more comfortable for the patient. If placement under ultrasound guidance is not feasible, a mammography will be used. This can be the case in patients with extensive DCIS or when the target is not visible on ultrasound. Mammography guidance is more time-consuming and less comfortable for the patient due to breast compression. In very few cases placement under MR guidance may be necessary [20].

Several studies have been performed to compare and examine the differences between the IGL-techniques. The majority of these studies show that there is no significant difference in achieving clear resection margins or the number of re-excisions needed between the IGL-techniques [2,3,15]. However, the introduction of new techniques does bring benefits. The possibility to place the marker prior to the day of surgery results in higher flexibility in hospital planning, higher operating room efficiency and higher flexibility in resource allocation. For surgery planning, there is less or no reliance on radiology scheduling. Secondly, the new techniques allow both the radiologist and the surgeon to work in total decision-making autonomy. There is no fixed protocol, as with WG, of how to place or follow the wire. Thirdly, it improves the patient's comfort, and thereby the quality of life. No patient compliance is required to keep the marker in the correct position [3,10,11].

However, there are disadvantages to using these a technique different from WG. In general the costs of using these new techniques are higher. For the techniques IS and ROLL, the presence of radioactivity must be taken into account. This requires the application of permits, and the need for radiation safety procedures. The use of MM may require replacement of medical instruments to avoid magnetic attraction between the marker or probe and the instruments used [10].

However, no population-based comparison studies of all six techniques have yet been performed. In this study nation-wide data registered by a national authority will be used. The aim of this retrospective population-based cohort study is to compare IGL-techniques with respect to oncological safety. Additionally, patient specific outcomes such as complications and hospitalization duration will be examined.

Methods

Data acquisition

In this study, a retrospective population-based cohort study has been performed to evaluate imaging-guided innovations for localization of non-palpable malignant breast lesions. All data were obtained from the Netherlands Cancer Registry (NCR), a population-based registry covering all newly diagnosed malignancies in the Netherlands as notified by the automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnoses. Data managers from the Netherlands Comprehensive Cancer Organisation (IKNL), which host the NCR, extract data directly from the patient's files in all hospitals from the Netherlands.

Patient and tumor characteristics

All patients undergoing BCS with IGL between 2013 and 2022 recorded by the NCR were included in this study (n = 60129). Male patients (n = 10), patients treated in an unknown hospital (n = 1) and patients registered with hydro-marker as IGL-technique are excluded (n = 17). The hydro-maker was not included in this study due to a small study population.

Data variables included the IGL-technique, the patient characteristics age at diagnosis, estrogen receptor status, progesterone receptor status, HER2 status and menopausal status, the tumor characteristics tumor type, differentiation rate, multifocality, lateralization, tumor size and tumor stage, resection margins, number of re-excisions, and the patient specific outcomes hospitalization duration and complications.

The continuous variables age at diagnosis, tumor size and hospitalization duration are checked for outliers using boxplot. As a result, patients with a hospitalization of 50 days or more were considered an outlier and were therefore reported as missing (n = 10). The variable HER2 status has been recoded to negative, positive, or missing.

Outcome variables

Resection margin status

The overall resection margin status was reported as free, focally irradical, or more than focally irradical, according to the Dutch Guideline for Breast Cancer Treatment [7]. A free resection margin is defined as no tumor reaching the ink. Focally irradical is defined as tumor (either invasive or DCIS) reaching in the ink in a small area (≤ 4 mm). When the tumor (either invasive or DCIS) reaches the ink in a larger area or multiple smaller areas, it is defined as more than focally irradical.

The performance of a re-excision

The performance of a re-excision is examined as a binary variable: yes or no. Neither the number of re-excisions, nor the type of re-excision has been considered in the statistical analyses of this outcome variable. The number of patients with no, one or more than one re-excision are shown in Table 1, with the corresponding percentage.

Complications
In this study complications that occurred during hospitalization or within 30 days after surgery are taken in into account. When multiple complications occur, the worst is recorded. Complications also include complications caused by plastic reconstruction. Complications are divided into four different categories: complication requiring surgical, endoscopic, or radiological intervention, life-threatening complications, mortality, and other grade 3 complications of unknown type.

Data regarding complications will be included in this study from 2019. As of this year, the registrations are complete. It is assumed that the failure to register a complication is equivalent to the absence of a complication. Only the complications requiring surgical, endoscopic, or radiological intervention have been taken into account in the statistical analysis. The other types of complications are disregarded due to a small study population. These types hardly or never occur within this population.

Hospitalization
Hospitalization duration (in days) has been calculated through the difference between date of incidence and date of first surgical procedure and the date of discharge of first surgical procedure.

Statistical analysis
Descriptive research has been carried out beforehand to determine the extent to which the various techniques are used in the Netherlands. This was also looked at specifically for each hospital. Among other things, trends in the use of the techniques to trace information about possible transfers have been examined.

All statistical analyses are stratified by type of carcinoma: invasive or DCIS. The group of patients with invasive carcinoma includes all patients who only have an invasive component or an invasive component combined with a DCIS component. The group DCIS includes all patients who only have a DCIS component.

To prevent omission of patients with missing values from the final statistical analysis, the variables differentiation rate, multifocality and tumor size were imputed by a multiple imputation by chained equations (MICE) for the whole study population. This imputation is performed separately for patients with invasive carcinoma and DCIS. HER2, estrogen receptor, and progesterone receptor status were only chained imputed for patients with invasive carcinoma. All chained imputations were performed with age at diagnosis and lateralization as additional independent variables. To fit the model used in the imputation, one patient with an undifferentiated tumor was excluded.

For patients with invasive carcinoma, the missing values in the variable menopausal status are recoded as follows: patients with age at diagnosis <50 are registered as premenopausal and patients with age at diagnosis ≥50 are registered as postmenopausal. This cut-off point corresponds to the median menopausal age in the Netherlands [21].

To evaluate whether categorical variables were significantly different between the six IGL-techniques, Chi-square test were performed; and to evaluate whether the means of the numerical variables were significantly different, analysis of variance (ANOVA) tests were performed.

A univariate and multivariate multinominal logistic regression analysis was performed to test for associations between the IGL-technique, and the outcome measure resection margin status (reference value free margin). Univariate and multivariate logistic regression analyses were performed to test for associations between the IGL-technique, and the outcome measures need for a re-excision and occurrence of a complication requiring surgical, endoscopic, or radiological intervention. Clinic-pathological variables that were significant in a univariate analysis were included in the multivariate model. Additionally, to include the differences in the policy of various hospitals, a correction for the treating hospital has been performed. The reference IGL-value is the iodine seed (IS).

Reviewing random patients through samples has led to uncertainty about the correctness of values regarding tumor resection margins and re-excisions of patients with one or more re-excisions without irradical margins in both the invasive and DCIS component. Therefore, it was decided to exclude these patients (n = 111) from the analyses regarding tumor resection margins and re-excisions.

In general, patients treated with BCS go home the same day. To see if there is a significant difference between patients treated with different IGL-techniques that deviate from this situation (that is a hospitalization duration of one full day or more), an ANOVA was performed.

A Kruskal-Wallis test was performed to determine whether there is a statistically significant difference between the medians of the outcome variable hospitalization duration within the IGL-techniques. When the outcome of this test was significant, cross-comparisons with Mann-Whitney U tests with Holm-Bonferroni correction were performed to examine how the mean hospitalization duration differs between the IGL-techniques.

Two sided p values < 0.05 were considered significant. All analysis were performed with StataSE 17.

Results

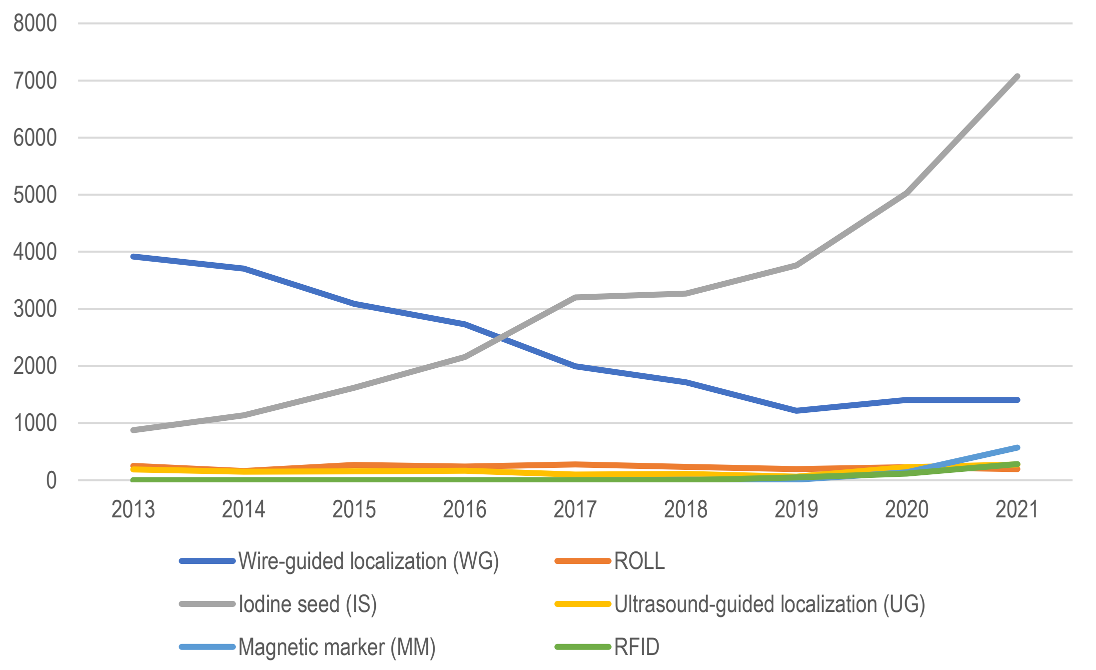
Use of IGL-techniques

The use of WG as the IGL-technique decreased each year in the time frame of this study. This while the use of IS increased. The use of MM and RFID, both introduced in 2018, is in this time frame on the rise. Figure 1 provides a visualization of the number of cases per IGL-technique.

The decrease in the use of WG is also seen in the number of hospitals which have WG as preferred IGL-technique in 2022. This is only in 8 hospitals. Most hospitals in the Netherlands have IS as preferred IGL-technique (n = 51). ROLL is the preferred technique in one hospital, while UG is in no hospital the preferred technique.

After the introduction of MM and RFID in 2018, nine hospitals switched to one of the two techniques. Seven hospitals are using MM as the preferred technique in 2022. At all these hospitals, 2021 was the year in which MM was the most used technique for the first time. RFID, on the other hand, has seen a smaller increase in use. RFID is seen as the preferred technique in 2022 in only two hospitals. While one of these hospitals switched to this technique as preferred technique in 2019, the other hospital has made this switch in 2021. The switch to MM or RFID as preferred technique has only been made by hospitals using WG as the preferred method. Hospitals using IS did not make the choice to switch to one of these techniques. However, in most hospitals where WG is not the preferred method, there is still several patients treated with WG.

Figure 1 Annual number of cases per localization technique*



* The year 2022 is not shown due to incompleteness of the data

Patient characteristics

Overall, 60101 female patients with BCS reported between 2013 and 2022 were included in this study. The majority of the population had invasive carcinoma (with or without a DCIS component) (79,4%). Age at diagnosis was on average was 62.0 (± 9.8). Six different IGL-techniques were used: IS (54.4%), WG (36.1%), ROLL (3.6%), UG (2.6%), MM (2.2%) and RFID (1.1%). The differences in patient and tumor characteristics between patients with invasive carcinoma and DCIS can be seen in Table 1.

Table 1 Baseline characteristics of all patients treated with BSC with IGL in 2013-2022 (n = 60101)

Characteristic		Total (n = 60101)	Invasive carcinoma (n = 47748)	DCIS (n = 12353)	p-value
IGL-Technique, no(%)	Iodine seed (IS)	21693 (36.1)	16352 (34.2)	5341 (43.2)	<0.001
	Wire-guided localization (WG)	2167 (3.6)	1663 (3.5)	504 (4.1)	
	ROLL	32690 (54.4)	26626 (55.8)	6064 (49.1)	
	Ultrasound-guided localization (UG)	1585 (2.6)	1373 (2.9)	212 (1.7)	
	Magnetic marker (MM)	1307 (2.2)	1184 (2.5)	123 (1.0)	
	RFID	659 (1.1)	550 (1.2)	109 (0.9)	
Age at diagnosis, mean (std)		61.99 (9.8)	62.36 (9.89)	60.55 (9.27)	<0.001
Tumor type, no(%)	Ductal carcinoma	48860 (81.3)	37834 (79.2)	11026 (89.3)	<0.001
	Lobular carcinoma	5019 (8.4)	5002 (10.5)	17 (0.1)	
	Ductal and lobular carcinoma	1568 (2.6)	1219 (2.6)	349 (2.8)	
	Other	4654 (7.7)	3693 (7.7)	961 (7.8)	
Multifocality, no(%)	No	55287 (92.2)	43420 (91.1)	11867 (96.5)	<0.001
	Yes	4650 (7.8)	4222 (8.9)	428 (3.5)	
	Missing	164			
Differentiation rate, no(%)	Good	17831 (30.6)	15768 (34.1)	2063 (17.3)	<0.001
	Moderate	27717 (47.6)	23034 (49.8)	4683 (39.3)	
	Bad	12638 (21.7)	7477 (16.2)	5161 (43.3)	
	Missing	1915			
Lateralization, no(%)	Left	30778 (51.2)	24398 (51.1)	6380 (51.7)	0.273
	Right	29321 (48.8)	23349 (48.9)	5972 (48.3)	
	Missing	2			
Tumor size, no(%)	< 2 cm	47030 (84.9)	40880 (88.7)	6150 (65.9)	<0.001
	2 – 5 cm	7922 (14.3)	5068 (11.0)	2854 (30.6)	
	> 5 cm	472 (0.9)	147 (0.3)	325 (3.5)	
	Missing	4677			
Discrepancy between cT and pT, no(%)	No	49196 (81.9)	37395 (78.3)	11801 (95.5)	<0.001
	Yes	10904 (18.1)	10353 (21.7)	551 (4.5)	
	Missing	1			
HER2 status, no(%)	Negative		42480 (90.9)		
	Positive		4252 (9.1)		
	Missing		1016		
Estrogen receptor (ER) status, no(%)	Negative		4939 (10.4)		
	Positive		42394 (89.6)		
	Missing		415		
Progesterone receptor (PR) status, no(%)	Negative		12324 (26.1)		
	Positive		34971 (73.9)		
	Missing		453		
Menopausal status, no(%)	Premenopausal		2076 (7.9)		
	Postmenopausal		22903 (87.3)		

	Perimenopausal		1257 (4.8)		
	Missing		21512		
Re-excision, no(%)	None	55801 (92.9)	45006 (94.3)	10795 (87.4)	<0.001
	1	3917 (6.5)	2515 (5.3)	1402 (11.3)	
	>1	383 (0.6)	227 (0.5)	156 (1.3)	

Resection margin status

After excluding 111 patients (all classified in the group with invasive carcinoma) with a free margin in both the invasive and the DCIS component, the resection margin status was examined for 59990 patients. In patients with invasive carcinoma 2681 patients (5.63%) had a focally irradical resection status. A more than focally irradical resection status was found in 1272 patients with invasive carcinoma (2.67%). In patients with DCIS 1428 patients (11.56%) had a focally irradical status and 580 (4.70%) patients had a more than focally irradical resection status.

Invasive carcinoma

Univariate analyses show the following variables being significantly associated with the tumor resection margin status: IGL-technique, age at diagnosis, tumor subtype, multifocality, differentiation rate, size of the tumor, discrepancy between cT and pT, HER2 status, ER status, PR status and menopausal status.

The multivariate analysis shows no significant association of an IGL-technique with an increased risk of a focally irradical and a more than focally irradical margin status. Table 2 provides an overview of the IGL-techniques related to irradical tumor resection margin statuses in patients with invasive carcinoma. However, the analysis shows a significant association of the following variables with an increased risk of a focally irradical margin status in patients with an invasive carcinoma: age at diagnosis <50, lobular and combined ductal and lobular subtype, multifocality, discrepancy between cT and pT, and positive ER status. Good differentiation rate, tumor size <2 cm, and a positive HER2 status were significantly associated with a decreased risk of a focally irradical margin status. A significant association with an increased risk of a more than focally irradical margin status was found in the following variables: multifocality, discrepancy between cT and pT, and positive ER status. Age at diagnosis >60, a ductal subtype, good differentiation rate, tumor size <2 cm and a positive HER2 status were significantly associated with a decreased risk of a focally irradical margin status.

DCIS

Univariate analyses show a significant association with the tumor resection margin status in the following variables: IGL-technique, tumor subtype, multifocality, differentiation rate, size of the tumor, and discrepancy between cT and pT.

The multivariate analysis shows a significant association with an increased risk of a focally irradical margin status in patients treated with IGL-techniques WG and MM. A significant association with an increased risk of a more than focally irradical margin status was found in patients treated with IGL-techniques WG and UG. Table 2 provides an overview of the IGL-techniques related to irradical tumor resection margin statuses in patients with DCIS. Additionally, a significant association with an increased risk of a focally irradical margin status was found in the following variables: multifocality, bad differentiation rate, and discrepancy between cT and pT. Subtypes categorized as other, good and moderate differentiation rate, and tumor size <2 cm were significantly associated with a decreased risk of a focally irradical margin status. Significant associations with an increased risk of a more than focally irradical margin status were found in the following variables: lobular subtype, multifocality, bad differentiation rate, and discrepancy between cT and pT. Good and moderate differentiation rate and tumor size <2 cm were significantly associated with a decreased risk of a more than focally irradical margin status.

Table 2 Univariate and multivariate analysis comparing the IGL-techniques with respect to tumor resection margin status (no(%))

Invasive carcinoma (n = 47637)								
IGL-technique	**Total**	**Margin free (n = 43684)**	**Margin focally irradical (n = 2681)**	**OR, univariate analysis**	**OR, multivariate analysis**	**Margin more than focally irradical (n = 1272)**	**OR, univariate analysis**	**OR, multivariate analysis**
Iodine seed (IS)	26567	24372 (91.7)	1492 (5.6)	1.0 (ref)	1.0 (ref)	703 (2.7)	1.0 (ref)	1.0 (ref)
Wire-guided localization (WG)	16310	14992 (91.9)	908 (5.6)	0.99 (0.91 – 1.08)	1.05 (0.94 – 1.19)	410 (2.5)	0.95 (0.84 – 1.07)	1.02 0.86 – 1.23
ROLL	1660	1478 (89.0)	111 (6.7)	**1.23 (1.00 – 1.50)**	1.11 (0.78 – 1.58)	71 (4.3)	**1.67 (1.30 – 2.14)**	1.36 (0.85 – 2.17)
Ultrasound-guided localization (UG)	1370	1250 (91.2)	78 (5.7)	1.02 (0.81 – 1.29)	0.85 (0.65 – 1.10)	42 (3.1)	1.16 (0.85 – 1.60)	0.86 (0.60 – 1.24)
Magnetic marker (MM)	1183	1084 (91.6)	70 (5.9)	1.05 (0.82 – 1.35)	1.11 (0.82 – 1.51)	29 (2.5)	0.93 (0.64 – 1.35)	0.92 (0.58 – 1.46)
RFID	547	508 (92.9)	22 (4.0)	0.71 (0.46 – 1.09)	0.98 (0.58 – 1.68)	17 (3.1)	1.16 (0.71 – 1.89)	1.20 (0.63 – 2.30)
DCIS (n = 12353)								
IGL-technique	**Total**	**Margin free (n = 10345)**	**Margin focally irradical (n = 1428)**	**OR, univariate analysis**	**OR, multivariate analysis**	**Margin more than focally irradical (n = 580)**	**OR, univariate analysis**	**OR, multivariate analysis**
Iodine seed (IS)	6064	5107 (84.2)	677 (11.2)	1.0 (ref)	1.0 (ref)	280 (4.6)	1.0 (ref)	1.0 (ref)
Wire-guided localization (WG)	5341	4356 (81.6)	650 (12.2)	**1.13 (1.00 – 1.26)**	**1.18 (1.01 – 1.39)**	335 (6.3)	**1.40 (1.19 – 1.65)**	**1.46 (1.16 – 1.83)**
ROLL	504	420 (83.3)	54 (10.7)	0.97 (0.72 – 1.30)	0.95 (0.59 – 1.56)	30 (6.0)	1.30 (0.88 – 1.92)	1.10 (0.60 – 2.00)
Ultrasound-guided localization (UG)	212	172 (81.1)	18 (8.5)	0.79 (0.48 – 1.29)	0.76 (0.45 – 1.29)	22 (10.4)	**2.33 (1.47 – 3.69)**	**1.80 (1.06 – 3.04)**
Magnetic marker (MM)	123	96 (78.1)	22 (17.9)	**1.73 (1.08 – 2.77)**	**1.94 (1.13 – 3.34)**	5 (4.1)	0.95 (0.38 – 2.35)	0.85 (0.32 – 2.25)
RFID	109	94 (86.2)	7 (6.4)	0.56 (0.26 – 1.22)	0.87 (0.35 – 2.14)	8 (7.3)	1.55 (0.75 – 3.23)	1.19 (0.49 – 2.89)

Re-excision

The performance of one or more re-excisions was needed in 2631 patients with invasive carcinoma (5.52%). Of them, 2417 patients (91.87%) needed one re-excision. More than one re-excision was performed in 214 patients (8.13%). Of these patients in need of one or more re-excisions 33.9% had a free margin status, 22.7% a focally irradical margin status and 43.4% a more than focally irradical margin status. Of these patients with invasive carcinoma in need for one of more re-excisions but with a free margin status, 88.7% had a (more) than focally irradical margin status in a simultaneously existing DCIS component, which have not been considered in this study.

In patients with DCIS 1558 patients (12.62%) needed one or more re-excisions. One re-excision was needed in 1402 patients (89.99%). Two or more re-excisions were performed in 156 patients (10.01%). In patients with DCIS needing one or more re-excisions 11.0% had a free margin status, 49.7% a focally irradical margin status and 39.3% a more than focally irradical margin status.

Invasive carcinoma

Univariate multinominal analyses show the following variables being significantly associated with the need for a re-excision: IGL-technique, age at diagnosis, tumor subtype, multifocality, differentiation rate, size of the tumor, discrepancy between cT and pT, and menopausal status.

The multivariate multinominal analysis shows a significant association of IGL-technique WG with an increased risk of the need for a re-excision. Table 3 provides an overview of the IGL-techniques related to the occurrence of re-excisions in patients with invasive carcinoma. Additionally, the following variables were also associated with an increased risk of the need of a re-excision: multifocality and discrepancy between cT and pT. Age at diagnosis >60, a ductal subtype, moderate differentiation rate and tumor size <2 cm were significantly associated with a decreased risk of the need for a re-excision.

DCIS

Univariate multinominal analyses show a significant association with the need for a re-excision in the following variables: IGL-technique, age at diagnosis, tumor subtype, multifocality, differentiation rate, size of the tumor, and discrepancy between cT and pT.

The multivariate multinominal analysis shows a significant association of IGL-technique WG with an increased risk of the need for a re-excision. Table 3 provides an overview of the IGL-techniques related to the occurrence of re-excisions in patients with DCIS. Additionally, the following variables were also associated with an increased risk of the need of a re-excision: lobular and combined ductal and lobular subtype, multifocality, bad differentiation rate, and tumor size >2 cm. Age at diagnosis >60 and good and moderate differentiation rate were significantly associated with a decreased risk of the need for a re-excision.

Table 3 Univariate and multivariate analysis comparing the IGL-techniques with respect to the occurrence of re-excisions (no(%))

Invasive carcinoma					
IGL-technique	**Total (n = 47637)**	**No re-excision (n = 45006)**	**Re-excision (n = 2631)**	**OR, univariate analysis**	**OR, multivariate analysis**
Iodine seed (IS)	26567	25151 (94.7)	1416 (5.3)	1.0 (ref)	1.0 (ref)
Wire-guided localization (WG)	16310	15342 (94.1)	968 (5.9)	**1.12 (1.03 – 1.22)**	**1.37 (1.21 – 1.54)**
ROLL	1660	1557 (93.8)	103 (6.2)	1.18 (0.96 – 1.44)	1.16 (0.82 – 1.64)
Ultrasound-guided localization (UG)	1370	1300 (94.9)	70 (5.1)	0.96 (0.75 – 1.22)	0.88 (0.67 – 1.16)
Magnetic marker (MM)	1183	1135 (95.9)	48 (4.1)	0.75 (0.56 – 1.01)	0.88 (0.62 – 1.24)
RFID	547	521 (95.3)	26 (4.8)	0.89 (0.60 – 1.32)	0.84 (0.52 – 1.37)
DCIS					
IGL-technique	**Total (n = 12353)**	**No re-excision (n = 10795)**	**Re-excision (n = 1558)**	**OR, univariate analysis**	**OR, multivariate analysis**
Iodine seed (IS)	6064	5380 (88.7)	684 (11.3)	1.0 (ref)	1.0 (ref)
Wire-guided localization (WG)	5341	4591 (86.0)	750 (14.0)	**1.28 (1.15 – 1.44)**	**1.45 (1.24 – 1.70)**
ROLL	504	435 (86.3)	69 (13.7)	1.25 (0.96 – 1.63)	1.24 (0.79 – 1.94)

Ultrasound-guided localization (UG)	212	182 (85.9)	30 (14.1)	1.30 (0.87 – 1.92)	1.22 (0.79 – 1.90)
Magnetic marker (MM)	123	108 (87.8)	15 (12.2)	1.09 (0.63 – 1.89)	1.30 (0.70 – 2.42)
RFID	109	99 (90.8)	10 (9.2)	0.79 (0.41 – 1.53)	1.11 (0.51 – 2.42)

Complications

In 482 patients with invasive carcinoma a complication requiring surgical, endoscopic, or radiological intervention has occurred. This type of complication occurred in 69 patients with DCIS. Life-threatening complications were only seen in patients with invasive carcinoma treated with IS (n = 6). In the entire population, there were two patients who experienced a grade 3 complication and three patients who experienced a complication resulting in mortality.

Univariate multinominal analyses show the following variables being significantly associated with the occurrence of a complication requiring surgical, endoscopic, or radiological intervention: IGL-technique, tumor subtype, multifocality, differentiation rate, size of the tumor, and discrepancy between cT and pT.

The multivariate multinominal analysis shows a significant association of IGL-technique ROLL with a decreased risk of the occurrence of a complication requiring surgical, endoscopic or radiological intervention. Table 4 provides an overview of the IGL-techniques related to the occurrence of complications. Additionally, a good differentiation rate was also associated with an decreased risk of the occurrence of this type of complication. Multifocality and a tumor size of 2-5 cm were significant associated with an increased risk of the occurrence of a complication requiring surgical, endoscopic, or radiological intervention.

A chi-squared test shows no significant association between the IGL-technique and the occurrence of complications requiring surgical, endoscopic, or radiological intervention in patients with DCIS (p = 0.358).

Table 4 Univariate and multivariate analysis comparing the IGL-techniques with respect to the occurrence of complications (no(%))

Invasive carcinoma					
IGL-technique	**Total** **(n = 24166)**	**No complication** **(n =23683)**	**Complication requiring surgical, endoscopic or radiological intervention** **(n = 474)**	**OR, univariate analysis**	**OR, multivariate analysis**
Iodine seed (IS)	17281	16929 (98.0)	344 (2.0)	1.0 (ref)	1.0 (ref)
Wire-guided localization (WG)	3855	3788 (98.3)	67 (1.7)	0.87 (0.67 – 1.13)	0.59 (0.32 – 1.08)
ROLL	640	638 (99.7)	2 (0.3)	**0.15** **(0.04 – 0.62)**	**0.08** **(0.01 – 0.43)**
Ultrasound-guided localization (UG)	664	649 (97.7)	14 (2.1)	1.06 (0.62 – 1.82)	0.60 (0.32 – 1.13)
Magnetic marker (MM)	1176	1141 (97.0)	35 (3.0)	**1.51** **(1.06 – 2.15)**	0.93 (0.45 – 1.88)
RFID	550	538 (97.8)	12 (2.2)	1.10 (0.61 – 1.96)	0.47 (0.11 – 1.93)
DCIS					

IGL-technique	Total (n = 4359)	No complication (n = 4288)	Complication requiring surgical, endoscopic or radiological intervention (n = 69)
Iodine seed (IS)	3180	3131 (98.5)	49 (1.5)
Wire-guided localization (WG)	788	774 (98.2)	12 (1.5)
ROLL	104	103 (99.0)	1 (1.0)
Ultrasound-guided localization (UG)	55	54 (98.2)	1 (1.8)
Magnetic marker (MM)	123	118 (95.9)	5 (4.1)
RFID	109	108 (99.1)	1 (0.9)

Hospitalization duration

The duration of the hospitalization was reported for a total of 40362 patients. Of these patients, 17491 of the 30433 patients with invasive carcinoma (57.5%) went home the same day. In patients with DCIS this is 17491 of the 9762 patients (64.8%). In patients with invasive carcinoma who stayed longer in hospital, a significant difference was found between the average hospitalization duration of the different IGL-techniques. The mean hospitalization durations of patients who stayed a minimum of one full day, are stated in table 5.

The patients with a hospitalization duration of 50 days or higher, and thus excluded from the analysis (n = 16) were treated with IS (n=10), WG (n= 4) or ROLL (n = 2) as IGL-technique.

Table 5 Descriptive statistics of the hospitalization duration of minimal one full day

	Invasive carcinoma			DCIS		
		Average (std.)	p-value		Average (std.)	p-value
Total	12942	1.24 (2.2)		3440	1.46 (8.4)	
IGL-technique						
Iodine seed (IS)	5790	1.24 (2.5)	0.001	1503	1.72 (12.2)	0.965
Wire-guided localization (WG)	6327	1.20 (1.5)		1754	1.27 (3.2)	
ROLL	451	1.68 (4.7)		115	1.20 (0.7)	
Ultrasound-guided localization (UG)	357	1.43 (2.5)		60	1.17 (0.7)	
Magnetic marker (MM)	8	1.38 (0.5)		0		
RFID	9	1.00 (0.00)		8	1.00 (0.00)	

A Kruskall-Wallis test indicated a statistically significant difference between the hospitalization (in days) by the different IGL-techniques in patients with invasive carcinoma ($p < 0.001$). There was also a statistically significant difference between the hospitalization (in days) by the different IGL-techniques in patients with DCIS ($p < 0.001$).

In patients with invasive carcinoma IGL-technique IS results in a significant lower hospitalization duration than WG (- 6.2 days), while there is a significant higher hospitalization compared to ROLL (+ 5.1 days). The largest significant difference was found between WG and ROLL, where WG has a mean +7.6 days longer hospitalization than ROLL. In patients with DCIS IS also results in a significant higher hospitalization than ROLL (+ 4.9 days). In addition to this difference, a significant difference was also found between WG and ROLL, where WG has a mean +4.4 days longer hospitalization than ROLL. Table 6 shows all mean differences in hospitalization between the IGL-techniques.

Table 6 Mann-Whitney U tests comparing the IGL-techniques with respect to the mean hospitalization duration

Invasive carcinoma (n = 30433)					
Col mean – row mean	Iodine seed (IS)	Wire-guided localization (WG)	ROLL	Ultrasound-guided localization (UG)	Magnetic marker (MM)
Wire-guided localization (WG)	**-6.237 0.000**				
ROLL	**5.149 0.000**	**7.626 0.000**			
Ultrasound-guided localization (UG)	-0.197 0.844	1.890 0.176	**-3.552 0.004**		
Magnetic marker (MM)	**3.397 0.006**	**3.846 0.001**	2.434 0.075	**3.315 0.007**	
RFID	**3.038 0.017**	**3.496 0.005**	2.051 0.161	**2.967 0.018**	-0.350 1.000
DCIS (n = 9762)					
Col mean – row mean	Iodine seed (IS)	Wire-guided localization (WG)	ROLL	Ultrasound-guided localization (UG)	Magnetic marker (MM)
Wire-guided localization (WG)	1.124 1.000				
ROLL	**4.857 0.000**	**4.446 0.000**			
Ultrasound-guided localization (UG)	0.955 1.000	0.652 1.000	-2.025 0.558		
Magnetic marker (MM)	1.501 1.000	1.467 1.000	1.134 1.000	1.371 1.000	
RFID	-0.410 0.6820	-0.521 1.000	-1.592 1.000	-0.708 1.000	-1.572 1.000

Discussion

With respect to oncological safety in treatment with IGL, WG performed inferior to IS in patients with invasive carcinoma. The odds that a re-excision is necessary are higher. For patients with DCIS, this inferior performance of IGL-techniques has been found in WG, UG and MM. While WG and MM provide higher odds for obtaining focally irradical margins, treatment with WG and UG increase the odds for obtaining more than focally irradical margins. In addition, WG also causes a higher odd for needing a re-excision.

In the context of patient specific outcomes, the IGL only influences only the occurrence of complications in patients with invasive carcinoma. Treatment with ROLL causes lower odds for developing complications. For hospitalization in invasive carcinoma, the biggest differences were the inferior performances of WG compared to ROLL and IS. For DCIS, WG and IS performed inferior to ROLL.

The findings in this study are preliminary results. In follow-up research, the patient's reported margins will be examined more closely. Especially of the 111 excluded patients due to uncertainty about the correctness. Random checks have shown that in several patients the reported data does not match the comprehensive pathology reports. This is caused, among other things, by incorrect localization of the tumor during the first surgery, or by relating independent surgical interventions.

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Thus, WG has been found significantly associated with a focally irradical and a more than focally irradical margin status in patients with DCIS. However, in most studies there appears to be no significant association between WG and a positive resection margin compared to radio guided localization (IS or ROLL) [2,3,15]. Additionally to WG, UG has been found significantly associated with a more than focally irradical margin status in patients with DCIS. The use of an ultrasound in patients with DCIS is complicated. DCIS is often undetectable by ultrasound [22,23], and thus this could explain the significant association with an increased chance of focally irradical margins in DCIS. On the other hand, there is a trend of a reduced chance of positive resection margins in the IGL-technique UG in invasive carcinoma. The use of ultrasound makes is possible to obtain a real-time visualization of the tumor, which can lead to greater precision [24,25].

It is interesting to see how MM influences the resection margin status. While there is a significant association with the margin being focally irradical in patients with DCIS, there is a trend towards a reduced chance of a more than focally irradical margin status. This difference can also be seen in the trends around resection margin status in patients with invasive carcinoma.

However, the results of MM may be affected. The influence that merging the two different types of magnetic markers in this study could have on the outcomes, should be considered. Due to the large differences in the technical principle used, the individual performance of the Pintuition or Magseed marker may differ from the average performance. The two markers are not registered separately within the NCR. For follow-up research, it is recommended to make this distinction if the population size allows it.

In the Netherlands, re-excision is indicated at a more than focally irradical margin status [26]. Due to the found significant association in DCIS patients as stated above and the slight trend in the increased risk of a more than focally irradical margin status in patients with invasive carcinoma, it is quite logical that WG has a significant association with the need for a re-excision in both groups. This finding is supported by a few studies [27]. However, in most cases there is only a trend and the association is not significant [2,3]

The higher chance of a more than focally irradical margin status and the need for re-excision in patients with DCIS compared to patients with invasive carcinoma could be explained through the high number of patients with a bad differentiation rate. For both outcome measures, this study shows that patients with bad differentiated DCIS have a significant higher chance of occurrence than patients with bad differentiated invasive carcinoma. This is consistent with other studies that proved the influence of differentiation rate in patients with DCIS [28–30].

It has been established that patients treated with WG more often must deal with irradical margins and thus re-excisions. Although the material cost of WG is lower than that of IS or any other new technique, the costs for the hospital will be higher when using WG. Having to perform re-excisions more often results in a large cost item. A single re-excision costs approximately €7000.00 in the Netherlands [31]. Additionally, the significant higher hospitalization duration will increase the cost even further.

The strengths of this study are the cohort consisting of a national population. In addition, the data was supplied by IKNL, which ensures that data is registered based on national protocols directly from the patients file. However, due to the presence of missing data, imputations and recoded data were used for the analyses. As a result, results for tumor size, multifocality, differentiation rate, HER2 status, PR status, ER status and menopausal status may be underestimated or overestimated. The patient characteristic body mass index (BMI) has not been considered in this study. A higher BMI could be caused by a larger cup size. In practice, it has been found that in some cases a larger cup size can make it more difficult to localize and remove a tumor positioned deep within the breast. However, there is no scientific evidence for this.

Many studies are currently being conducted in the field of breast cancer diagnosis. This is done in the field of new techniques and risk stratification, but also in relation to population screening: age selection and screening frequency [32]. The number of small, non-palpable tumors is therefore likely to increase in the future. The knowledge gained in this study about the influence of the different localization techniques, but also the contribution made by patient and tumor characteristics, allows a more complete risk profile to be outlined per patient.

Additionally, an ongoing study is investigating whether low grade DCIS patients can be treated with active surveillance instead of standard treatment. Based on the results of this study, it is advised to pay extra attention to patients with multifocal tumors and/or tumors larger than 2 cm when making this decision. These two tumor characteristics increase the risk of irradical margins and re-excisions in patients with low-grade DCIS.

Conclusion

In this study, IS has proved to be superior to WG in the obtained oncological safety during BCS with IGL. The use of IS results in a lower number of patients with irradical margins, and thus re-excisions. With respect to patient specific outcomes ROLL is superior to WG. The use of this technique results in less complications and a shorter hospitalization duration. Therefore, IS and ROLL but also the other new techniques that have been introduced in Dutch hospitals are recommended as an effective alternative to WG in localizing non-palpable breast lesions.

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