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Original Article

Nationwide registry study on trends in localization techniques and reoperation rates in non-palpable ductal carcinoma *in situ* and invasive breast cancer

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Abstract

Background: There is a transition from wire-guided localization (WGL) of non-palpable breast cancer to other localization techniques. Multiple prospective studies have sought to establish superior clinical outcomes for radioactive-seed localization (RSL), but consistent and congruent evidence is missing.

Methods: In this study, female patients with breast cancer operated with breast-conserving surgery after tumour localization of a non-palpable breast cancer or ductal carcinoma *in situ* (DCIS) were included. The cohort was identified from the nationwide Netherlands Breast Cancer Audit conducted between 2013 and 2018. Trends in localization techniques were analysed. Univariable and multivariable analyses were performed to assess the association between the localization technique and the probability of a reoperation.

Results: A total of 28 370 patients were included in the study cohort. The use of RSL increased from 15.7 to 61.1 per cent during the study years, while WGL decreased from 75.4 to 31.6 per cent. The localization technique used (RSL *versus* WGL) was not significantly associated with the odds of a reoperation, regardless of whether the lesion was DCIS (odds ratio 0.96 (95 per cent c.i. 0.89 to 1.03; $P = 0.281$)) or invasive breast cancer (OR 1.02 (95 per cent c.i. 0.96 to 1.10; $P = 0.518$)).

Conclusion: RSL is rapidly replacing WGL as the preoperative localization technique in breast surgery. This large nationwide registry study found no association between the type of localization technique and the odds of having a reoperation, thus confirming the results of previous prospective cohort studies.

Lay summary

Localization techniques are used to help surgeons find the tumour location during breast-cancer surgery. The use of wire-guided localization is being replaced by newer marker-based techniques, such as radioactive-seed localization (RSL). Several clinical studies have sought to establish a clinical outcome benefit (for example, fewer reoperations) of the newer techniques, but consensus is lacking. This study aimed to reassess whether there is a clinical outcome benefit of using RSL in a very large (28 370 patients) nationwide study cohort. No association between the localization technique used and reoperation was found. This implies that from a clinical viewpoint there is no reason to select one localization technique over another.

Introduction

The introduction of mammographic screening programmes has led to an increase in diagnosis of non-palpable breast cancer. Breast-conserving surgery (BCS) is the preferred treatment for these cancers[1]. In BCS, achieving cancer-free resection margins is of vital importance, as positive margins are associated with a two-fold increase in local recurrence risk[2]. Surgery of non-

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palpable breast cancer can be challenging, and a radical resection requires preoperative localization of the tumour.

Wire-guided localization (WGL) has been the standard for tumour localization since its first description in the 1970s[3]. In WGL, a metal anchor wire is placed in the tumour, typically on the day of surgery. During surgery, the surgeon follows the wire from the skin to the tumour and resects the tissue surrounding the tip. Using WGL, 37 per cent of patients with ductal carcinoma *in situ* (DCIS) and 13 per cent of patients with invasive breast cancer require a reoperation due to positive resection margins[4]. WGL has several procedural disadvantages, such as limited guidance towards the lesion, undesirable incision locations, more extensive dissection and resection of healthy tissue[5]. WGL also carries logistic challenges, as patients need to visit the radiology department for wire placement on the day of surgery with potential for delays[5,6]. It is also stressful for patients to undergo two procedures the same day, and to have a wire protruding from their breast while awake[7].

Radioactive guided technologies such as radioactive occult-lesion localization (ROLL) and radioactive-seed localization (RSL) have been introduced as alternatives to WGL. In RSL, a tiny radioactive iodine-125 seed is implanted before surgery in or near the tumour and the area is identified during surgery by a handheld gamma probe detector[6,8,9]. RSL allows for surgical flexibility as surgeons can assess their approach independently from the radiologist. It separates radiology and surgery schedules as the seed can be placed in well in advance of surgery, thus facilitating logistics[10]. Working with RSL is also scored as easier than WGL by surgeons[11]. Most importantly it eliminates the need for two stressful procedures on the day of surgery[7] and is associated with decreased patient pain perception[11,12].

It has been hypothesized that the use of RSL leads to superior clinical outcomes when compared with WGL, such as lower rates of positive margins and reoperation[6]. Most prospective studies to date have, however, failed to provide conclusive evidence of the superiority of RSL. A Cochrane systematic review of literature, including a relatively small data set of 1273 patients, concluded that there is no clear evidence to support one guided technique over another[13].

The objective of the present study was to describe trends in the use of different localization techniques in patients with non-palpable DCIS and invasive breast cancer between 2013 and 2018 using a large population-based registry, and to assess the relationship between the localization technique used and the probability of reoperation.

Methods

All patients operated for breast cancer in the Netherlands are registered in the Netherlands Breast Cancer Audit (NBCA), which is a multidisciplinary population-based nationwide registry of diagnostic and treatment modalities and outcome indicators. Patients diagnosed with DCIS or invasive breast cancer and registered in the NBCA registry between October 2012 and September 2018 were eligible for inclusion in the study cohort. Exclusion criteria were patients with palpable lesions, neo-adjuvant therapy, not having BCS, incomplete data on tumour histology, grade and receptor status, missing margin status or unknown localization technique. Localization techniques were recorded as WGL, ROLL, RSL and other. The latter included ultrasound guidance and techniques that were not further specified.

Variables

Age was defined as age at diagnosis. Year was defined as the calendar year of diagnosis. MRI performed was defined as having at least one preoperative MRI scan. Tumour grade was defined as DCIS grade or following the Bloom–Richardson grading system for invasive breast cancer. Margin status was defined as 'negative' (no ink on tumour); 'focally positive' (a single focus of invasive tumour or DCIS component on inked margin over a length of 4 mm or less) or 'more than focally positive' (more than a single focus of invasive tumour or DCIS component on inked margin over a (combined) length of more than 4 mm). All Dutch pathologists report margin status using this definition.

Reoperation was defined as a second surgical procedure for the same area, which could be a reresection or mastectomy. According to Dutch guidelines, for patients with pure DCIS a reoperation is indicated for any positive margin. For patients with invasive breast cancer, a reoperation is recommended only for those with a more than focally positive margin. These guidelines remained the same during the inclusion period. Whether a reoperation is actually performed is left to the discretion of the multidisciplinary team and could depend on factors beyond margin status.

Statistics

Included patients were subdivided into a cohort of pure DCIS and a cohort with at least one invasive component. Variables included in the analyses for DCIS were age, incidence year, whether an MRI was performed, tumour grade and the type of localization technique. For invasive breast cancer the authors additionally included histological subtype, hormone receptor status, tumour stage, nodal status and the presence of DCIS.

Descriptive statistics are provided for all patients and presented as number of patients per localization procedure and per parameter. Univariable and multivariable logistic regression analyses were performed to determine the association of the localization technique, patient and tumour characteristics with the probability of reoperation. As the frequency of ROLL and other localization techniques was low they were excluded from these analyses. For the univariable analyses, patient, tumour and treatment characteristics were compared between groups using Pearson's $\chi 2$ test for categorical data. For the multivariable analyses, stepwise regression with backwards selection was used to identify the co-variables that were independently associated with a reoperation. Odds ratios and 95 per cent confidence intervals determined for each variable were compared with those of the reference group. A two-sided $P < 0.050$ was considered statistically significant. Data analyses were performed using SPSS®, version 25 (SPSS Inc., Chicago, Illinois, USA).

Results

In total, 97 111 patients were considered for inclusion. *Fig. 1* shows the flow chart of the available data. A total of 28 370 patients were operated with BCS for a non-palpable tumour and thus included in the study cohort. Of these, 7430 were treated for pure DCIS and 20 940 for invasive breast cancer (with or without a DCIS component). *Tables 1* and *2* show the patient characteristics for each of the localization techniques for DCIS (7430 patients; *Table 1*) and invasive breast cancer (20 940 patients; *Table 2*).

The number of patients with pure DCIS treated with BCS remained stable during the study period, with a mean of 1239 new patients per year (*Table 1*). Of all DCIS diagnoses 80.2 per

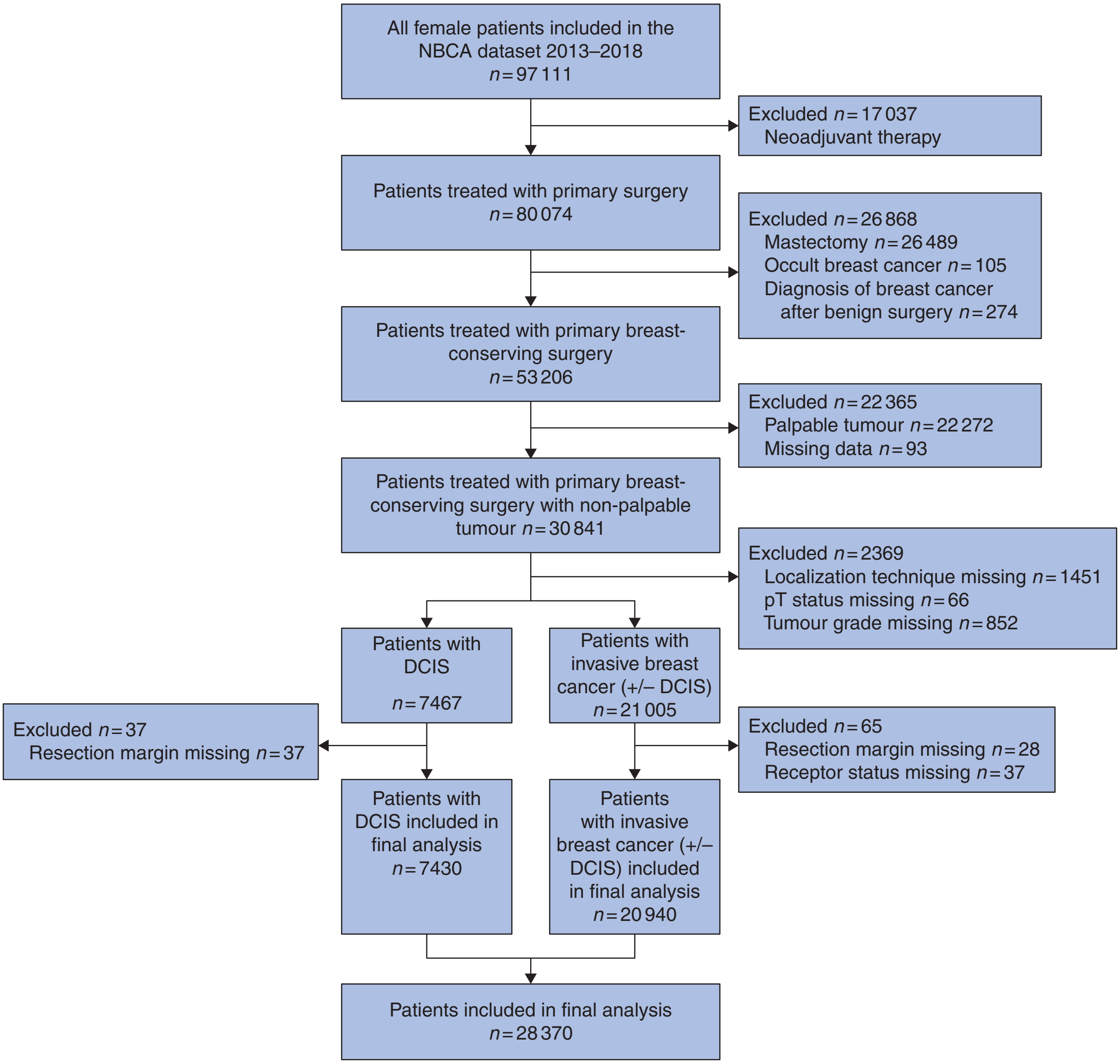

Fig. 1 Flow chart of record selection and exclusion.

NBCA, Netherlands Breast Cancer Audit; DCIS, ductal carcinoma *in situ*.

cent were screen-detected and the majority were grade 2 or 3 (6099 patients; 82.1 per cent). The first operation of pure DCIS resulted in an involved margin (focally or more than focally positive) in 17.8 per cent of procedures, leading to a reoperation in 13.7 per cent of procedures.

The number of patients treated with BCS for invasive breast cancer also remained stable during the study period, with a mean of 3490 new patients per year (*Table 2*). Of these, 77.3 per cent were screen-detected. Nearly half of the tumours were grade 2 (10 012 patients; 47.8 per cent), followed by grade 1 (8160 patients; 39.0 per cent). Nodal involvement was present in 17.7 per cent of patients. After BCS, focally involved margins were found in 8.9 per cent of procedures, and more than focally involved margins in 3.9 per cent. A reoperation was performed in 5.7 per cent of patients (1197 patients).

Figure 2 shows trends in the use of the different localization techniques throughout the study period for all patients. The total number of procedures per year was a mean of 4728 (range 4067–5015). The proportion of patients having WGL decreased from 75.4 per cent in 2013 to 31.6 per cent in 2018. In the same period, the proportion undergoing RSL increased from 15.7 to 61.1 per cent. The use of ROLL and other techniques, including ultrasound localization, has remained stable throughout the study period.

Tables 3 and *4* show the results of univariable and multivariable logistic regression analyses of likelihood for reoperation in patients with DCIS (*Table 3*) and invasive breast cancer (*Table 4*). In DCIS, the likelihood to undergo a reoperation did not differ significantly between the RSL or WGL groups (odds ratio 0.96 (95 per cent c.i. 0.89 to 1.03)). All other variables (age, year, MRI and tumour grade) showed statistically significant association with the likelihood of a reoperation.

Similarly, in patients with invasive breast cancer, no statistically significant difference in the likelihood to undergo a reoperation was shown between patients with RSL or WGL (odds ratio 1.02 (95 per cent c.i. 0.96 to 1.10)). Again, all other variables analysed

Table 1 Characteristics of patients with ductal carcinoma *in situ*

Characteristic	WGL	RSL	ROLL	Other	Total
Patients	4165 (56.1)	2685 (36.1)	379 (5.1)	201 (2.7)	7430 (100)
Age (years)*	61.2 (25–87)	60.7 (33–86)	60.6 (41–89)	61.7 (35–88)	61.0 (25–89)
Age group					
<50 years	223 (5.4)	142 (5.3)	24 (6.3)	20 (10.0)	409 (5.5)
50–75 years	3740 (89.8)	2423 (90.2)	346 (91.3)	159 (79.1)	6668 (89.7)
>75 years	202 (4.8)	120 (4.5)	9 (2.4)	22 (10.9)	353 (4.8)
Year					
2013	810 (19.4)	170 (6.3)	76 (20.1)	42 (20.9)	1098 (14.8)
2014	891 (21.4)	243 (9.1)	55 (14.5)	36 (17.9)	1225 (16.5)
2015	833 (20.0)	405 (15.1)	71 (18.7)	26 (12.9)	1335 (18.0)
2016	704 (16.9)	522 (19.4)	64 (16.9)	40 (19.9)	1330 (17.9)
2017	543 (13.0)	664 (24.7)	67 (17.7)	27 (13.4)	1301 (17.5)
2018	384 (9.2)	681 (25.4)	46 (12.1)	30 (14.9)	1141 (15.4)
Screen-detected					
Yes	3373 (81.0)	2165 (80.6)	313 (82.6)	107 (53.2)	5958 (80.2)
No	792 (19.0)	520 (19.4)	66 (17.4)	94 (46.8)	1472 (19.8)
MRI					
No	3391 (81.4)	2008 (74.8)	328 (86.5)	151 (75.1)	5878 (79.1)
Yes	774 (18.6)	677 (25.2)	51 (13.5)	50 (24.9)	1552 (20.9)
DCIS grade					
1	736 (17.7)	467 (17.4)	86 (22.7)	43 (21.4)	1332 (17.9)
2	1710 (41.1)	988 (36.8)	166 (43.8)	87 (43.3)	2951 (39.7)
3	1719 (41.3)	1230 (45.8)	127 (33.5)	71 (35.3)	3148 (42.4)
Margin status					
Negative	3388 (81.3)	2250 (83.8)	316 (83.4)	160 (79.6)	6114 (82.3)
Focally positive	507 (12.2)	295 (11.0)	36 (9.5)	21 (10.4)	859 (11.6)
More than focally positive	270 (6.5)	140 (5.2)	27 (7.1)	20 (10.0)	457 (6.2)
Reoperation					
Yes	588 (14.1)	345 (12.8)	48 (12.7)	36 (82.1)	1017 (13.7)
No	3577 (85.9)	2340 (87.2)	331 (87.3)	165 (17.9)	6413 (86.3)

Values in parentheses are percentages unless indicated otherwise; *values are mean (range). WGL, wire-guided localization; RSL, radioactive-seed localization; ROLL, radioactive occult-lesion localization; DCIS, ductal carcinoma *in situ*.

(age, year, MRI, tumour grade, histological subtype, presence of a DCIS component, receptor status and nodal stage) showed a statistically significant association with the likelihood of a reoperation.

Discussion

The primary objective of this large population-based registry study covering 28 370 patients was to assess whether there was a significant association between the localization technique used and the reoperation rate in patients with non-palpable breast cancer and DCIS treated with BCS. No statistically significant association was observed between localization technique and the odds of a reoperation, neither in patients with pure DCIS (7430 patients) nor in patients with invasive breast cancer (20 940 patients).

These findings are in line with several prospective series published comparing novel localization techniques with WGL on outcome parameters such as margin status or reoperation rates, for example by Lovrics and colleagues[11], Langhans and colleagues[10] and Bloomquist and colleagues[12]. Gray and co-workers[6] were the only group to publish improved margin status with RSL compared with WGL in a randomized series of 97 patients. The present study therefore reaffirms the conclusions drawn by Chan and colleagues in their Cochrane review of literature[13]. Based upon available prospective evidence and the present large retrospective analysis, there are no clinical outcomes that support the use of one localization technique over another.

Interestingly, and regardless of evidence of clinical superiority, the secondary analysis on trends in use of different localization techniques shows that the RSL technique increased at the expense of WGL. The proportion of patients undergoing RSL increased roughly linearly from 15.7 per cent in 2013 to 61.1 per cent in 2018, whilst the proportion of use of WGL decreased from 75.4 to 31.6 per cent during the same period. Other techniques, such as ROLL and ultrasound localization, remained at stable and low proportions. This indicates that breast surgeons prefer RSL over other techniques. Furthermore, available literature indicates that RSL has also gained traction outside the studied population[5,14,15], although exact data are lacking.

The fact that RSL is rapidly replacing WGL without evidence of clinical superiority implies that secondary benefits of using radioactive seeds are driving the transition away from wires. Indeed, many of the published comparative literature on localization techniques conclude that, although clinical superiority was not established, RSL was found to provide major logistic advantages[10], being easier to perform, and associated with reduced operative times[11] and a reduction in resected volumes. Additionally, RSL can be combined easily with neoadjuvant systemic therapy as the seed functions both as a long-term MRI-visible tissue marker and a subsequent surgical localization marker.

Nevertheless, the use of radioactive seeds can be challenging, with strict regulation and the need to record carefully the chain of custody of each seed. Consequently, over the past years several techniques that provide the benefits of seed-based localization without the challenges of nuclear regulations have been brought to the market. Magnetic seeds[16,17], radiofrequency identification tags[18] and microimpulse radar[19] are relatively new and currently under evaluation in several clinical trials. Multiple studies have compared these alternatives to WGL and found similar results as when comparing RSL with WGL. For example, Lee and colleagues[20] found no difference in clinical outcomes, and suggest that physicians may consider more nuanced futures of localization systems when switching to wire-free alternatives.

Table 2 Characteristics of patients with invasive breast cancer

Characteristic	WGL	RSL	ROLL	Other	Total
Patients	11 271 (53.8)	7984 (38.1)	891 (4.3)	794 (3.8)	20 940 (100)
Age (years)*	63.6 (25–100)	63.6 (28–99)	63.6 (35–93)	63.6 (29–90)	63.6 (25–100)
Age groups					
<50 years	399 (3.5)	283 (3.5)	33 (3.7)	40 (5.0)	755 (3.6)
50–75 years	10 397 (92.2)	7342 (92.0)	816 (91.6)	689 (86.8)	19 244 (91.9)
>75 years	475 (4.2)	359 (4.5)	42 (4.7)	65 (8.2)	941 (4.5)
Year					
2013	2258 (20.0)	466 (5.8)	145 (16.3)	100 (12.6)	2969 (14.2)
2014	2552 (22.6)	721 (9.0)	109 (12.2)	146 (18.4)	3528 (16.8)
2015	2135 (18.9)	1107 (13.9)	156 (17.5)	152 (19.1)	3550 (17.0)
2016	1777 (15.8)	1418 (17.2)	146 (16.4)	173 (21.8)	3514 (16.8)
2017	1415 (12.6)	2010 (25.2)	185 (20.8)	104 (13.1)	3714 (17.7)
2018	1134 (10.1)	2262 (28.3)	150 (16.8)	119 (15.0)	3665 (17.5)
Screen-detected					
Yes	8808 (78.1)	6130 (76.8)	717 (80.5)	532 (67.0)	16 187 (77.3)
No	2463 (21.9)	1854 (23.2)	174 (19.5)	262 (33.0)	4753 (22.7)
MRI					
Yes	2730 (24.2)	2570 (32.2)	218 (24.5)	209 (26.3)	5727 (27.3)
No	8541 (75.8)	5414 (67.8)	673 (75.5)	585 (73.7)	15 213 (72.7)
1	4391 (39.0)	3173 (39.7)	315 (35.4)	281 (35.4)	8160 (39.0)
2	5367 (47.6)	3827 (47.9)	449 (50.4)	369 (46.5)	10 012 (47.8)
3	1513 (13.4)	984 (12.3)	127 (14.3)	144 (18.1)	2768 (13.2)
pT stage					
pT1a	1139 (10.1)	750 (8.4)	64 (7.2)	63 (7.9)	2016 (9.6)
pT1b	4108 (36.4)	3042 (38.1)	312 (35.0)	253 (31.9)	7715 (36.8)
pT1c	5282 (46.9)	3630 (45.5)	443 (49.7)	394 (49.6)	9749 (46.6)
pT2	721 (6.4)	540 (6.8)	70 (7.9)	76 (9.6)	1407 (6.7)
pT3/T4	21 (0.2)	22 (0.3)	2 (0.2)	8 (1.0)	53 (0.3)
Histological Subtype					
Ductal	9661 (85.7)	6714 (84.1)	769 (86.3)	674 (84.9)	17 818 (85.1)
Lobular	1043 (9.3)	829 (10.4)	98 (11.0)	80 (10.1)	2050 (9.8)
Other	567 (5.0)	441 (5.5)	24 (2.7)	40 (5.0)	1072 (5.1)
DCIS Component					
Invasive only	5449 (48.3)	3767 (47.2)	359 (40.3)	384 (48.4)	9959 (47.6)
Invasive + DCIS	5822 (51.7)	4217 (52.8)	532 (59.7)	410 (51.6)	10 981 (52.4)
Receptor status					
Triple negative	714 (6.3)	408 (5.1)	51 (5.7)	53 (6.7)	1226 (5.9)
HR+, HER2−	9731 (86.3)	7050 (88.3)	793 (89.0)	690 (86.9)	18 264 (87.2)
HR−, HER2+	215 (1.9)	110 (1.4)	10 (1.1)	13 (1.6)	348 (1.7)
HR+, HER2+	611 (5.4)	416 (5.2)	37 (4.2)	38 (4.8)	1102 (5.3)
pN stage					
pNx	257 (2.3)	418 (5.2)	19 (2.1)	33 (4.2)	727 (3.5)
pN0	8997 (79.8)	6219 (77.9)	702 (78.8)	579 (72.9)	16 497 (78.8)
pN0(i+)	391 (3.5)	264 (3.3)	34 (3.8)	31 (3.9)	720 (3.4)
pN1mi	533 (4.7)	393 (4.9)	57 (6.4)	47 (5.9)	1030 (4.9)
pN1	982 (8.7)	634 (7.9)	70 (7.9)	90 (11.3)	1776 (8.5)
pN2/3	111 (1.0)	56 (0.7)	9 (1.0)	14 (1.8)	190 (0.9)
Margin status†					
Negative	9822 (87.1)	6983 (87.5)	772 (86.6)	676 (85.1)	18 253 (87.2)
Focally positive	1023 (9.1)	690 (8.6)	68 (7.6)	82 (10.3)	1863 (8.9)
More than focally positive	426 (3.8)	311 (3.9)	51 (5.7)	36 (4.5)	824 (3.9)
Reoperation					
Yes	635 (5.6)	451 (5.6)	56 (6.3)	55 (6.9)	1197 (5.7)
No	10 636 (94.4)	7355 (94.4)	835 (93.7)	739 (93.1)	19 743 (94.3)

Values in parentheses are percentages unless indicated otherwise. WGL, wire-guided localization; RSL, radioactive-seed localization; ROLL, radioactive occult-lesion localization; DCIS, ductal carcinoma *in situ*; HR, hormone receptor. *Values are mean (range). †Margin status was reported separately for invasive and *in situ* component. Margin status was determined as (focally) positive if either one of these variables was positive.

Srour and co-workers[19] found that wire-free localization systems lead to reduced perioperative time with similar positive-margin rate and reoperation rates.

The present study again confirms that localization techniques alone cannot be expected to reduce reoperations or positive-margin rates. A future surgical treatment paradigm in which primary localization is complemented by some form of margin-assessment tool could be foreseen. The use of directly postoperative margin-assessment tools, such as frozen-section analysis, have been investigated for diagnostic accuracy but have, as yet, failed to achieve widespread adoption[21]. Emerging technologies for real-time intraoperative margin assessment with the potential to improve margins are under investigation but not yet commercially available[22].

The current study regression analyses further showed that in the group of DCIS lesions a higher tumour grade was significantly associated with increased odds of having a reoperation. This is inconsistent with the findings from Houvenaeghel and colleagues[23], who found no significant difference between DCIS grade and reoperation rates in a multivariable analysis of a retrospective cohort of 1161 patients with DCIS. This contradictory finding may be explained by the fact that Houvenaeghel and colleagues incorporated DCIS size in their multivariable analyses,

Table 3 Univariable and multivariable logistic regression analyses for reoperation among patients with ductal carcinoma *in situ* after wire-guided localization or radioactive-seed localization (6850 cases, of which 933 are reoperations)

	Univariable		Multivariable	
	Odds ratio	P	Odds ratio	P
Age (years)				
<50	Ref	0.083	Ref	0.049
50–75	0.73 (0.55, 0.96)		0.70 (0.53, 0.93)	
>75	0.73 (0.48, 1.10)		0.73 (0.47, 1.11)	
Year				
2013	Ref	0.003	Ref	0.003
2014	0.81 (0.64, 1.02)		0.79 (0.62, 1.00)	
2015	0.74 (0.58, 0.93)		0.72 (0.56, 0.91)	
2016	0.73 (0.57, 0.92)		0.72 (0.56, 0.91)	
2017	0.60 (0.47, 0.77)		0.59 (0.46, 0.76)	
2018	0.80 (0.63, 1.01)		0.79 (0.62, 1.02)	
MRI				
No	Ref	<0.001	Ref	0.011
Yes	1.35 (1.15, 1.68)		1.24 (1.05, 1.46)	
DCIS grade				
1	Ref	<0.001	Ref	<0.001
2	1.80 (1.40, 2.30)		1.79 (1.40, 2.30)	
3	2.84 (2.24, 3.61)		2.85 (2.34, 3.63)	
Localization technique				
WGL	Ref	0.135	Ref	0.281
RSL	0.95 (0.88, 1.02)		0.96 (0.89, 1.03)	

Values in parentheses are 95 per cent confidence intervals. Ref, reference value; DCIS, ductal carcinoma *in situ*; WGL, wire-guided localization; RSL, radioactive-seed localization.

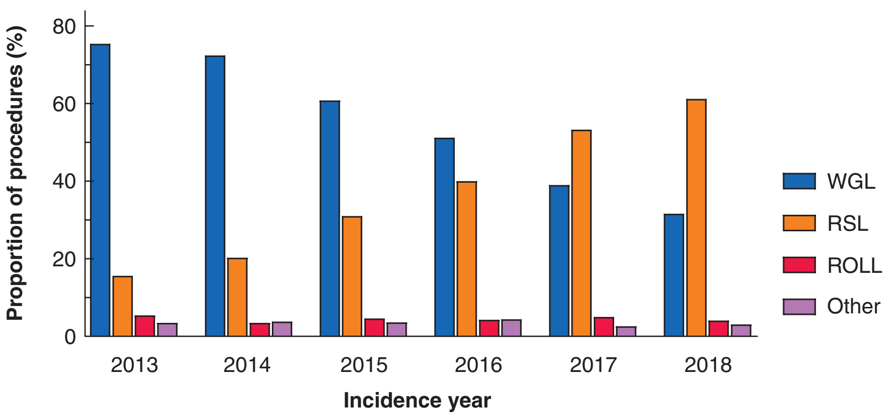

Fig. 2 Localization procedures *versus* inclusion year over the study period 2013–2018.

Procedures for ductal carcinoma *in situ* and invasive breast cancer are combined in this figure (28 370 patients). WGL, wire-guided localization; RSL, radioactive-seed localization; ROLL, radioactive occult-lesion localization.

which could not be done in the present study due to missing data on this variable. In the group of invasive breast cancer, there was a significant reduction in the odds of requiring a reoperation for smaller tumours, a finding in line with literature[23].

For both pure DCIS and invasive cancer, preoperative breast MRI was found to be significantly associated the need of a reoperation. Previous studies have found that patients undergoing preoperative breast MRI for pure DCIS were more likely to have a mastectomy, either as first surgical treatment or following BCS in the event of positive margins[24]. Preoperative MRI increases the mastectomy rate, but does not decrease the number of positive surgical margins after BCS[25]. Moreover, a meta-analysis from 2013 concluded that MRI significantly increased mastectomy rates[26].

Interestingly, there was a discrepancy both for pure DCIS and invasive breast cancer between the expected and the actual reoperation rate based on the finding of positive margins (pure DCIS 17.8 per cent with any positive margins *versus* 13.7 per cent reoperations; invasive breast cancer 3.9 per cent more than focally positive margins *versus* 5.7 per cent reoperations). Although this element was not specifically analysed in the current study, the discrepancy could be hypothesized to be a result of careful consideration by the multidisciplinary team, in which patient preference and histological data also contribute and sometimes have a decisive role in determining whether a reoperation is required.

The present study is limited due to its retrospective character. Although multivariable analyses were performed, there could always be residual confounding. There were no data on the use of multiple wires or seeds (bracketing). Additionally, there were no data on the proportion of reoperations that were performed following a positive diagnostic excisional biopsy. The utilization of excisional biopsies in the Netherlands is, however, extremely

Table 4 Univariable and multivariable logistic regression analyses for reoperation among patients with invasive breast cancer after radioactive-seed localization or wire-guided localization (19 255 cases, of which 1086 are reoperations)

	Univariable		Multivariable	
	Odds ratio	P	Odds ratio	P
Age (years)				
< 50	Ref	<0.001	Ref	<0.001
50–75	0.44 (0.34, 0.56)		0.55 (0.43, 0.72)	
> 75	0.33 (0.22, 0.50)		0.41 (0.27, 0.64)	
Year				
2013	Ref	0.010	Ref	0.019
2014	0.89 (0.73, 1.10)		0.89 (0.72, 1.10)	
2015	0.84 (0.68, 1.04)		0.84 (0.67, 1.04)	
2016	0.76 (0.61, 0.94)		0.74 (0.59, 0.93)	
2017	0.70 (0.56, –0.86)		0.69 (0.55, 0.87)	
2018	0.75 (0.61, 0.93)		0.75 (0.59, 0.94)	
MRI				
No	Ref	<0.001	Ref	<0.001
Yes	1.78 (1.57, 2.02)		1.47 (1.28, 1.69)	
Histological subtype				
Ductal	Ref	<0.001	Ref	<0.001
Lobular	1.72 (1.45, 2.05)		2.16 (1.75, 2.66)	
Other/unknown	0.79 (0.58, 1.08)		1.06 (0.77, 1.47)	
DCIS component				
Invasive only	Ref	<0.001	Ref	<0.001
Invasive + DCIS	2.20 (1.93, 2.52)		2.60 (2.24, 3.01)	
Tumour stage				
pT1a	Ref	<0.001	Ref	<0.001
pT1b	0.41 (0.34, 0.51)		0.46 (0.37, 0.56)	
pT1c	0.59 (0.49, 0.71)		0.53 (0.44, 0.65)	
pT2	1.70 (1.35, 2.13)		1.2 (0.96, 1.58)	
pT3/4	18.1 (9.56, 34.3)		14.1 (7.19, 27.6)	
Receptor status				
Triple negative	Ref	<0.001	Ref	<0.001
HR+, HER2−	0.85 (0.66, 1.09)		0.97 (0.74, 1.28)	
HR−, HER2+	2.5 (1.67, 3.68)		2.02 (1.34, 3.03)	
HR+, HER2+	1.24 (0.88, 1.73)		1.08 (0.76, 1.53)	
pN stage				
pNx	Ref	<0.001	Ref	<0.001
pN0	0.69 (0.50, 0.94)		0.73 (0.53, 1.01)	
pN0(i+)	1.21 (0.80, 1.83)		0.98 (0.64, 1.52)	
pN1mi	1.20 (0.82, 1.76)		1.20 (0.80, 1.79)	
pN1	1.56 (1.11, 2.20)		1.34 (0.93, 1.92)	
pN2/3	4.56 (2.86, 7.25)		3.01 (1.82, 4.97)	
Grade				
1	Ref	<0.001	Ref	<0.001
2	1.77 (1.53, 2.05)		1.45 (1.24, 1.69)	
3	2.36 (1.96, 2.84)		1.78 (1.44, 2.20)	
Localization technique				
WGL	Ref	0.965	Ref	0.518
RSL	1.00 (0.94, 1.07)		1.02 (0.96, 1.10)	

Values in parentheses are 95 per cent confidence intervals. Ref, reference value; DCIS, ductal carcinoma *in situ*; WGL, wire-guided localization; RSL, radioactive-seed localization; HR, hormone receptor; MRI, Magnetic Resonance Imaging.

low[27] and thus this could be expected to have a very limited impact on the results. Furthermore, reoperation alone is not the only important indicator for a good localization technique and data on resection volumes and operative time were not available. Nonetheless, the current study is unique regarding the number of patients included with recent and complete data representing current practice.

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