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Original article

Resection margins and local recurrences of impalpable breast cancer: Comparison between radioguided occult lesion localization (ROLL) and radioactive seed localization (RSL)

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ABSTRACT

Objectives: The aim of this retrospective study is to compare surgical margins, reoperation rates and local recurrences after breast conserving surgery (BCS) using radioguided occult lesion localization (ROLL) or radioactive seed localization (RSL).
Materials and methods: We reviewed 744 consecutive patients with impalpable primary invasive breast cancer who underwent BCS at Helsinki University Hospital between 2010 and 2012. ROLL was used in our unit until October 31st, 2011; from November 1st we changed localization method to RSL.
Results: 318 patients underwent ROLL and 426 RSL. Patients in the RSL group had more often multifocal ($p = 0.013$) tumours. No statistically significant differences were found regarding tumour size, specimen weight, histology or grade of tumours or lymph node status. 42 (5.6%) patients were reoperated because of insufficient margins, 13 (4.1%) in the ROLL group and 29 (6.8%) in the RSL group. The reoperation rate was not different between the groups either in the univariable analysis ($p = 0.112$) or in the multivariable binary logistic regression analysis ($p = 0.204$). Risk factors for reoperations were multifocality of the tumour ($p < 0.001$), extensive intraductal component ($p < 0.001$), larger tumour size ($p = 0.011$), and smaller specimen weight ($p = 0.014$). The median follow-up time in the ROLL group was 81 (8–94) months and 64 (3–73) months in the RSL group. The five-year local recurrence-free survival (LRFS) estimates for ROLL and RSL groups were 98.0% and 99.4%, respectively (log-rank test, $p = 0.323$).
Conclusion: Reoperation rates and LRFS were comparable for ROLL and RSL in patients with impalpable breast cancer treated with BCS.

1. Introduction

The number of impalpable malignant breast tumours has increased due to improved imaging and screening programmes. Breast conserving surgery (BCS) in patients with impalpable tumours requires precise preoperative lesion localization to ensure adequate surgical margins. Furthermore, the aim in BCS is to achieve good aesthetic result by minimizing the amount of resected healthy breast tissue [1].

Wire-guided localization (WGL) has been the gold standard for surgical excision of impalpable breast lesions. There are, however, some downsides with WGL. It has rates of incomplete surgical excision ranging from 12% to 60% [2–5]. Furthermore, WGL is unpleasant for patient and scheduling of wire insertion and surgery can be challenging. Therefore, other localization methods have been introduced.

Radioguided occult lesion localization (ROLL) is a technique using albumin particles labelled with radioactive technetium (Tc-99 m), which is injected before surgery intra- or peritumorally under ultrasound (US) or stereotactic guidance. Intraoperatively a gamma probe is used to detect the radioactivity; the same probe is used for sentinel lymph node biopsy (SLNB).

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Abbreviations

BCS	Breast conserving surgery
WGL	Wire-guided localization
ROLL	Radioguided occult lesion localization
US	Ultrasound
SLNB	Sentinel lymph node biopsy
RSL	Radioactive seed localization
LR	Local recurrence
DCIS	Ductal carcinoma in situ
RT	Radiotherapy
CNB	Core needle biopsy
FNAC	Fine needle aspiration cytology
MRI	Magnetic resonance imaging
MDT	Multidisciplinary team
CT	Computed tomography scan
LRFS	local recurrence-free survival
EIC	Extensive intraductal component

Radioactive seed localization (RSL) technique is using iodine-125 –containing titanium seed, also inserted under US or stereotactic guidance into the center of the tumour. The tumour and the seed can be detected intraoperatively accurately using gamma probe likewise. RSL can be performed well ahead of surgery with flexible scheduling, since the half-life of iodine-125 is significantly longer compared to technetium-99 m (60 days vs. 6 h) [5].

There are several studies comparing ROLL or RSL to WGL [6–8] but only few comparing ROLL and RSL [9–11]. The aim of this retrospective study is to compare surgical margins, reoperation rates and local recurrences (LR) after BCS using ROLL and RSL.

2. Material and methods

1876 consecutive patients with primary invasive breast cancer or ductal carcinoma in situ (DCIS) who underwent BCS at Breast Surgery Unit of Helsinki University Hospital between the January 1st, 2010 and December 31st, 2012 were reviewed for this retrospective cohort study. None of the patients received neoadjuvant treatment.

We excluded patients who underwent a lumpectomy with neither adjuvant treatment nor axillary surgery due to comorbidities, patients who had been diagnosed by surgical biopsy and those whose breast cancer was found unexpectedly in reduction mammoplasty specimen. Furthermore, we excluded patients with palpable tumours, those who underwent other localization procedure than ROLL or RSL and patients with pure DCIS. In the remaining 744 patients, tumours were localized using either ROLL or RSL (Fig. 1).

ROLL was used in our unit until October 31st, 2011, since then we used RSL. During the ROLL era, WGL was used for large area of microcalcifications and for multifocal tumours. In addition, WGL was used in DCIS, when there was no need for SLNB. During the RSL era WGL was used only occasionally. In total, there were 93 patients with pure DCIS; 13 of them underwent ROLL and 30 RSL. Due to the small number of eligible DCIS cases, especially in the ROLL group, the analysis for pure DCIS cases was performed separately.

Patient, tumour, treatment and follow-up data was collected from electronic patient records. Synchronous bilateral cancer was regarded as two separate cases when assessing primary surgical outcome. Bilateral disease was excluded from the survival analysis.

2.1. Imaging

All patients underwent preoperative mammography and breast and axillary US. Core needle biopsy (CNB) was taken from breast lesion(s) and fine needle aspiration cytology (FNAC) from suspicious axillary lymph nodes. Patients who had an invasive lobular carcinoma diagnosed on CNB underwent magnetic resonance imaging (MRI).

2.2. Tumour localization technique

The image-guided localization was performed or supervised by experienced breast radiologists. Both ROLL and RSL were performed under US or stereotactic guidance, dependent upon the visibility of the tumour. In ROLL, a single peritumoural 100–120 MBq Tc-99 m nanocolloid injection was used and utilized for the SLNB. A lymphoscintigraphy with dual-head gamma camera was obtained 1.5–3 h after injection to exclude leakage and to identify the sentinel nodes. The RSL was performed within four weeks prior to surgery. Iodine-125-radiolabeled seeds (Oncura, RAPID Strand, Arlington Heights,Ill, USA) were used. The 4.5 by 0.8 mm titanium-encapsulated seed was placed inside an 18-gauge needle and aimed at the center of the tumour. A two-view mammography (craniocaudal and lateromedial) was performed to confirm correct placement of the seed.

During surgery, the seed or the nanocolloid was localized using a handheld gamma probe and the tumour area was excised. A specimen radiography was routinely performed to assess the radiological margins and in case of RSL, to confirm the presence of the seed. Specimen US was performed whenever needed, at the discretion of the breast radiologist.

2.3. Surgical technique

All breast and axillary operations were performed or supervised by experienced breast surgeons. Surgeon decided on the operation technique individually depending on the location and size of the tumour, as well as on the size and the glandular density of breast, in agreement with the patient. In this study, conventional BCS stands for resection of the tumour with adequate mobilization and closure of breast tissue. Oncoplastic BCS instead refers to other level 1 and level 2 oncoplastic procedures [12,13].

Patients with axillary lymph node metastasis in US guided FNAC underwent axillary lymph node dissection. SLNB was performed in remaining patients.

Reoperation due to inadequate margins was either a re-excision or a mastectomy and was dependent on breast size, glandular density and aesthetic result after the first operation, with patient's preference taken into account. The guidelines for adequate surgical margins changed at the beginning of the study period in 2010, the new recommendations were adopted in our unit gradually. Previously 5 mm microscopical histological margins were required for invasive cancer and 10 mm for DCIS. Consensus symposium in 2010 recommended that no ink on tumour is adequate for invasive cancer and 2 mm for DCIS [14]. At our unit, the recommended DCIS margins were applied for margins of the intraductal component in patients with invasive cancer.

2.4. Histopathological examination

Histopathological analyses from surgical specimens were performed by experienced breast pathologists. The breast and lymph node specimens were handled and examined as described in our earlier study [15].

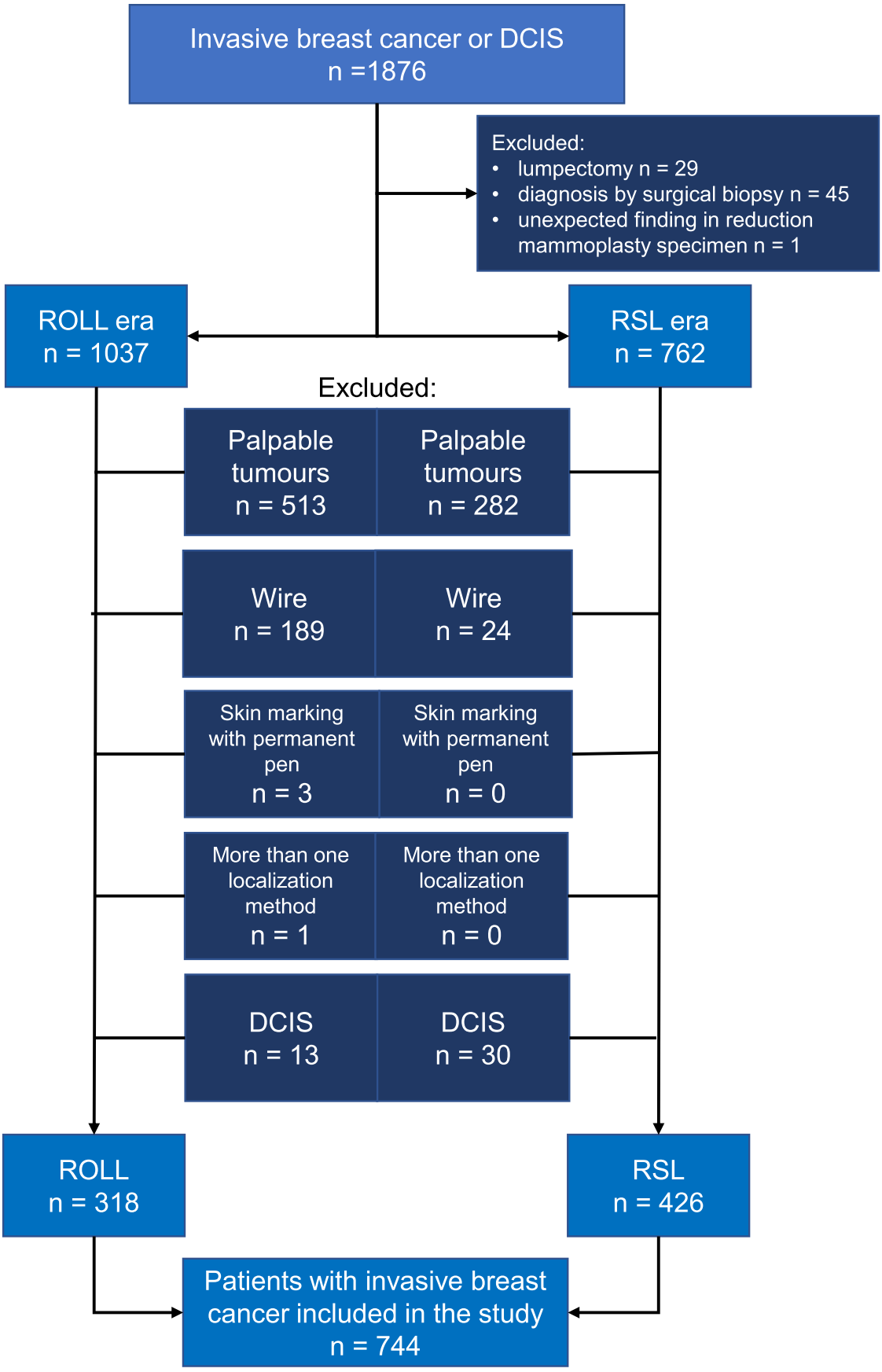

Fig. 1. Patient inclusion flowchart.

2.5. Adjuvant treatment

All cases were discussed at a multidisciplinary team (MDT) meeting after surgery in order to recommend adjuvant treatment. All patients received postoperative RT except those who underwent mastectomy as a second operation and those who were not fit for RT or refused RT. Patients who had distant metastases identified on postoperative whole body computed tomography scan (CT) did not receive RT either. Adjuvant chemotherapy and endocrine treatment were recommended according to the Finnish national evidence-based guidelines [16]. The RT and adjuvant systemic treatment protocols used at our institution are described in our earlier study [17].

2.6. Follow-up

The first clinical checkup took place within three weeks after the operation. After adjuvant treatment, the patients were followed-up at the Department of Oncology of Helsinki University Hospital for 5–10 years, according to the risk of recurrence. The follow-up consisted of visits at least at one, three and five years after the operation.

Mammography was performed annually, combined with US in women ≤45 years of age, in women with high density of breast in mammography or if needed as further diagnostic investigation. Annual breast MRI was performed in women with hereditary breast cancer. Additionally, MRI, whole body CT or bone isotope scan were performed whenever indicated for instance due to symptoms which might indicate local or distant recurrence.

In addition, all patients had an access to an outpatient clinic whenever there were concerns regarding symptoms related to side effects of treatments or potential recurrence.

After the first 5–10 years, the follow-up continued at primary health care, according to regional guidelines.

2.7. Statistical analyses

Statistical analyses were performed using IBM™ SPSS™ Statistics version 22 software (SPSS Inc., Chicago, IL). Frequency tables were analyzed with chi-squared test and continuous distributions with Mann-Whitney *U* test.

Independent variables with p-values < 0.15 in the univariable analyses were entered into a backward stepwise binary logistic regression analysis to evaluate their association with need for reoperation due to insufficient margins in a multivariable model. At each step of the analysis, the variable with the highest p-value was eliminated until the remaining variables had p-values < 0.05.

For breast cancer events, we excluded patients with bilateral disease (n = 51), earlier breast cancer (n = 28), other malignancy (apart from DCIS or basal cell carcinoma) within five years (n = 44), distant metastasis diagnosed within 12 months after primary operation (n = 2) and those who underwent a completion mastectomy (n = 26). In addition, we excluded patients who were followed-up for less than three years due to migration to other hospital district (n = 14).

The remaining 579 patients went through a Kaplan-Meier survival analysis for local recurrence-free survival (LRFS), and the ROLL and RSL groups were compared with the log-rank test. Other breast cancer events were assessed with Fisher's exact test simply comparing event counts.

3. Results

The patient and tumour characteristics are summarized in Table 1 as well as adjuvant therapy. ROLL was performed in 318 (42.7%) patients and RSL in 426 (57.3%). The patients in the ROLL group were slightly younger (p = 0.033). The median tumour size was 10 mm (1–40 mm) in the ROLL group and 11 mm (1–55 mm) in the RSL group (p = 0.219). There were no differences between the groups regarding pT1a-c subgroups (p = 0.815).

Histological subtypes were distributed similarly in the groups (p = 0.469), but the tumours in the ROLL group had higher proliferation index Ki-67 (p = 0.031). Patients in the RSL group had more often multifocal (p = 0.013) tumours; 60 (14.1%) tumours in the RSL group were multifocal compared to 26 (8.2%) in the ROLL group. No significant differences between the ROLL and RSL groups were found regarding specimen weight, grade of tumours or lymph node status.

79 (24.8%) patients in ROLL group and 120 patients (28.2%) in the RSL group underwent oncoplastic BCS (p = 0.311). Various oncoplastic techniques were used and the amount of resected tissue varied substantially depending on the surgical technique (range 8–1893 g) [13].

More patients in the RSL group received adjuvant endocrine treatment.

3.1. Reoperations

Surgical margins were wider in the ROLL group, though the median of the smallest lateral surgical margin was 10 mm in the both groups (p = 0.011) (Table 1). However, there was no statistically significant difference in insufficient surgical margins or reoperation rate between the groups (p = 0.112) in the univariable analysis. 42 (5.6%) patients were reoperated because of insufficient margins, 13 (4.1%) in the ROLL group and 29 (6.8%) in the RSL group (Table 2).

Risk factors for reoperations in the univariable analysis were multifocality of the tumour (p < 0.001) and extensive intraductal component (EIC) (p < 0.001). Altogether, 86 patients had multifocal tumours, 18 (20.9%) of them underwent a reoperation, compared to 24 (3.6%) out of 658 patients with unifocal tumours. Twelve (20.0%) patients out of 60 with EIC underwent a reoperation compared to 30 (4.4%) out of 684 without EIC.

In the multivariable binary logistic regression analysis multifocality of the tumour (p < 0.001) and EIC (p < 0.001) remained risk factors for reoperation (Table 3). Furthermore, larger tumour size (p = 0.011) and smaller specimen weight (p = 0.014) were statistically significant factors predicting a reoperation. There was no statistically significant difference in the reoperation rate between the ROLL and RSL (p = 0.204) in the multivariable binary logistic regression analysis either.

The second operation was a re-excision for 11 patients (26.2%) and mastectomy for 31 (73.8%). Five patients underwent a re-excision in the ROLL group and six in the RSL group, a completion mastectomy was performed in eight patients in the ROLL group and in 23 the RSL group (p = 0.226).

3.2. Breast cancer recurrence

Altogether 579 patients remained for survival analysis of LRFS, 258 in the ROLL group and 321 in the RSL group (Table 4). The median follow-up time in the ROLL group was 81 (8–94) months and 64 (3–73) months in the RSL group. Seven (2.7%) patients in the ROLL group developed an ipsilateral LR and three (0.9%) in the RSL group. The five-year LRFS estimates for ROLL and RSL groups were 98.0% and 99.4%, respectively (log-rank test, p = 0.323, Fig. 2).

All breast cancer events are summarized in Table 4. Distant metastases were detected in three (1.2%) patients in the ROLL group and likewise in three (0.9%) in the RSL group (Fisher's test, p = 1.000).

Table 1
Patient and tumour characteristics for ROLL and RSL.

		ROLL N = 318 (42.7%)		RSL N = 426 (57.3%)		p-value
		N	%	N	%	
Surgery	Conventional BCS	239	75.2%	306	71.8%	0.311
	Oncoplastic BCS	79	24.8%	120	28.2%	
Reoperation due to insufficient margins	No	305	95.9%	397	93.2%	0.112
	Yes	13	4.1%	29	6.8%	
Reoperation	Re-excision	5	38.5%	6	20.7%	0.226
	Mastectomy	8	61.5%	23	79.3%	
Histology	Invasive ductal carcinoma	230	72.3%	291	68.3%	0.469
	Invasive lobular carcinoma	39	12.3%	63	14.8%	
	Other invasive	49	15.4%	72	16.9%	
Pathological T stage	pT1	304	95.6%	400	93.9%	0.461
	pT2	14	4.4%	25	5.9%	
	pT3	0	0.0%	1	.2%	
Multifocal tumour	No	292	91.8%	366	85.9%	0.013
	Yes	26	8.2%	60	14.1%	
EIC	0	287	90.3%	397	93.2%	0.145
	1	31	9.7%	29	6.8%	
Tumour grade	1	145	45.6%	203	47.7%	0.444
	2	130	40.9%	156	36.6%	
	3	43	13.5%	67	15.7%	
ER	Negative	22	7.0%	26	6.1%	0.644
	Positive	294	93.0%	399	93.9%	
PR	Negative	77	24.4%	103	24.2%	0.967
	Positive	239	75.6%	322	75.8%	
Ki-67	0–15%	216	69.0%	308	72.5%	0.031
	16–30%	58	18.5%	88	20.7%	
	>30%	39	12.5%	29	6.8%	
HER-2	Negative	296	93.7%	391	92.0%	0.387
	Positive	20	6.3%	34	8.0%	
Lymph node status	pN0	259	81.4%	330	77.5%	0.243
	pN1mic	24	7.5%	31	7.3%	
	pN1mac	35	11.0%	65	15.3%	
Radiotherapy	No	10	3.1%	20	4.7%	0.288
	Yes	308	96.9%	406	95.3%	
Adjuvant treatment	No	101	31.8%	95	22.3%	0.020
	Endocrine treatment	141	44.3%	226	53.1%	
	Chemotherapy	8	2.5%	16	3.8%	
	Both	68	21.4%	89	20.9%	
		Median (range)		Median (range)		
Age (years)		62 (38–83)		64 (36–91)		0.033
Tumour size (mm)		10 (1–40)		11 (1–55)		0.219
Smallest lateral surgical margin (mm)		10 (0–30)		10 (0–40)		0.011
Specimen weight (g)		55 (12–996)		60 (8–1893)		0.142

Abbreviations: ROLL, radioguided occult lesion localization; RSL, radioactive seed localization; BCS, breast conserving surgery; EIC, extensive intraductal component. ER, estrogen receptor; PR, progesterone receptor; Ki-67, proliferation marker; HER-2, human epidermal growth factor receptor.

Nineteen patients died during the follow-up, 11 (4.3%) in the ROLL group and eight (2.5%) in the RSL group (Fisher's test, $p = 0.250$). Only one (0.4%) patient in ROLL group and two (0.6%) in the RSL group died from breast cancer (Fisher's test, $p = 1.000$).

3.3. Patients with pure DCIS

The results for patients with DCIS are summarized in Table 5. ROLL was performed only in 13 cases and RSL in 30. There was no statistically significant differences between the groups regarding size, multifocality or grade of DCIS, or regarding reoperation rates or adjuvant treatment.

4. Discussion

4.1. Main message

This study showed that ROLL and RSL provided similar outcomes regarding insufficient margin status, reoperation rates and LRFS in patients with impalpable invasive breast cancer treated with BCS. Instead of localization method, the risk factors for reoperations were multifocality of the tumour, larger tumour size, EIC and smaller specimen weight. This is consistent with previous studies [11,13]. There were more multifocal tumours in the RSL group. ROLL was not used in our unit if the tumour was multifocal in preoperative imaging; previously patients with multifocal lesions underwent WGL.

4.2. Reoperations

In our series, the reoperation rate due to insufficient margins was low (5.6%) compared to previous studies of ROLL or RSL. In the systematic review and meta-analysis by Lovrics et al. [4] the reoperation rate after ROLL excision was 6.2–33.3% and after RSL 7.8–9.6%. In more recent studies the reoperation rate after both ROLL and RSL has shown to be 7–13% [5,9–11,18–20]. Velazco et al. though, showed lower re-excision rate in their study of RSL (2.3–4.1%) [21]. Insufficient surgical margins and indications for reoperation are variable in the studies, making the comparison of studies difficult.

There are only few previous studies comparing ROLL and RSL. Van der Noordaa et al. compared these two localization techniques in their study [9] and did not find significant difference in reoperation rates (ROLL 10% vs. RSL 9%). Neither did Donker et al. [10], who

Table 2
Patient and tumour characteristics for reoperations due to inadequate margins.

		Reoperation due to inadequate margins				
		Yes		No		p-value
		N = 42 (5.6%)		N = 702 (94.4%)		
		N	%	N	%	
Localization method	ROLL	13	31.0%	305	43.4%	0.112
	RSL	29	69.0%	397	56.6%	
Reoperation	Re-excision	11	26.2%	0	0.0%	
	Mastectomy	31	73.8%	0	0.0%	
Histology	Invasive ductal carcinoma	28	66.7%	493	70.2%	0.863
	Invasive lobular carcinoma	6	14.3%	96	13.7%	
	Other invasive	8	19.0%	113	16.1%	
Multifocal tumour	N	24	57.1%	634	90.3%	<0.001
	Ye	18	42.9%	68	9.7%	
EIC	0	30	71.4%	654	93.2%	<0.001
	1	12	28.6%	48	6.8%	
Tumour grade	1	13	31.0%	335	47.7%	0.107
	2	21	50.0%	265	37.7%	
	3	8	19.0%	102	14.5%	
ER	Negative	5	11.9%	43	6.2%	0.141
	Positive	37	88.1%	656	93.8%	
PR	Negative	13	31.0%	167	23.9%	0.300
	Positive	29	69.0%	532	76.1%	
Ki-67	0–15%	27	65.9%	497	71.3%	0.491
	16–30	11	26.8%	135	19.4%	
	>30%	3	7.3%	65	9.3%	
HER-2	Negativ	36	85.7%	651	93.1%	0.072
	Positiv	6	14.3%	48	6.9%	
Lymph node status	pN0	28	66.7%	561	79.9%	0.095
	pN1mic	4	9.5%	51	7.3%	
	pN1mac	10	23.8%	90	12.8%	
		Median (range)		Median (range)		
Age (years)		64 (36–85)		62 (38–91)		0.243
Tumour size (mm)		13 (1–40)		10 (1–55)		0.112
Specimen weight (g)		50 (12–298)		58 (8–1893)		0.055

Abbreviations: ROLL, radioguided occult lesion localization; RSL, radioactive seed localization; EIC, extensive intraductal component.
ER, estrogen receptor; PR, progesterone receptor; Ki-67, proliferation marker; HER-2, human epidermal growth factor receptor.

Table 3
Risk factors for reoperation using binary logistic regression analysis.

		OR	95% C.I. for OR		p-value
			Lower	Upper	
Lymph node status	pN0	1			0.900
	pN1mic	1.185	0.333	4.223	0.793
	pN1mac	1.226	0.476	3.155	0.673
HER-2	Negative	1			
	Positive	1.506	0.445	5.095	0.510
ER	Negative	1			
	Positive	0.498	0.128	1.945	0.316
Tumour grade	1	1			0.294
	2	1.880	0.849	4.163	0.119
	3	1.382	0.465	4.113	0.560
Localization method	ROLL	1			
	RSL	1.614	0.771	3.381	0.204
Multifocal tumour	No	1			
	Yes	8.968	4.263	18.866	<0.001
EIC	No	1			
	Yes	6.214	2.626	14.702	<0.001
Tumour size		1.077	1.017	1.140	0.011
Specimen weight		0.988	0.979	0.998	0.014

Abbreviations: OR, odds ratio; C.I. confidence interval; HER-2, human epidermal growth factor receptor; ER, estrogen receptor.
ROLL, radioguided occult lesion localization; RSL, radioactive seed localization; EIC, extensive intraductal component.

compared ROLL and RSL after neoadjuvant treatment (ROLL 7% vs. RSL 8%). Theunissen et al. [11] compared all WGL, ROLL and RSL and they found that RSL results in a higher negative surgical margin rate and lower reoperation rate.

4.3. Specimen weight

In this study we did not find any difference in specimen weight between the ROLL and RSL ($p = 0.143$), similarly to other previously published studies [9–11]. Our study material includes all patients

Table 4
Breast cancer events observed during follow-up.

	ROLL (N = 258)	RSL (N = 321)	p-value (Fisher)
Follow-up time, median (range)	81 (8–94) months	64 (3–73) months	
Event	N (%)	N (%)	
Ipsilateral breast recurrence	7 (2.7%)	3 (0.9%)	0.119
Contralateral breast recurrence	3 (1.2%)	2 (0.6%)	0.660
Regional lymph node recurrence	3 (1.2%)	1 (0.3%)	0.329
Ipsilateral axilla[a]	1 (0.4%)	1 (0.3%)	
Contralateral axilla[b]	1 (0.4%)	0	
Supraclavicular node[c]	1 (0.4%)	0	
Distant metastasis	3 (1.2%)	3 (0.9%)	1.000
Death from breast cancer	1 (0.4%)	2 (0.6%)	1.000
Death from any cause	11 (4.3%)	8 (2.5%)	0.250

Abbreviations: ROLL, radioguided occult lesion localization; RSL, radioactive seed localization.
[a] The patients in both groups had concomitant LR.
[b] The patient had concomitant LR and distant metastasis.
[c] The patient had concomitant distant metastasis.

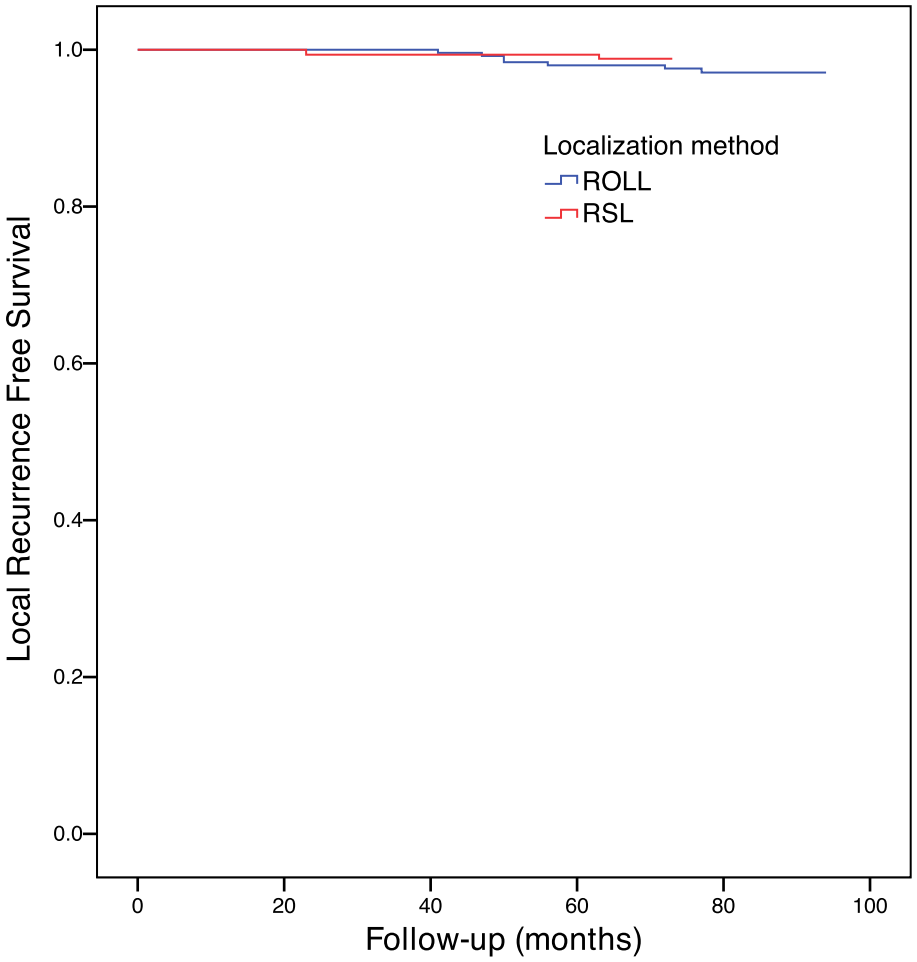

Fig. 2. Kaplan-Meier survival analysis for local recurrence-free survival after breast conserving surgery using radioguided occult lesion localization (ROLL) or radioactive seed localization (RSL).

who underwent BCS, with either conventional or oncoplastic resection, therefore there is a wide range in specimen weights. We did not evaluate specimen volumes, since determining tumour-resection volume ratio in large oncoplastic resection specimens is not relevant.

In our study, the RSL group included more often multifocal disease and this possibly increased the specimen weights of the group. However, larger specimen weights may not result in poorer aesthetic result in the era of oncoplastic surgery, which is used more and more in our unit [22].

4.4. Local recurrences

In our series, there was no difference in the estimated five-year

Table 5
ROLL and RSL for DCIS cases.

		ROLL N = 13 (30.2%)		RSL N = 30 (69.8%)		p-value
		N	%	N	%	
Surgery	Conventional BCS	8	61.5%	23	76.7%	0.310
	Oncoplastic BCS	5	38.5%	7	23.3%	
Reoperation due to insufficient margins	No	12	92.3%	25	83.3%	0.435
	Yes	1	7.7%	5	16.7%	
DCIS multifocality	No	12	92.3%	25	83.3%	0.435
	Yes	1	7.7%	5	16.7%	
DCIS grade	1	1	7.7%	2	6.7%	0.405
	2	3	23.1%	14	46.7%	
	3	9	69.2%	13	43.3%	
	NA	0	0.0%	1	3.3%	
Radiotherapy	No	2	15.4%	1	3.3%	0.154
	Yes	11	84.6%	29	96.7%	
Adjuvant treatment	Endocrine treatment	0	0.0%	1	3.3%	0.497
	Endocrine treatment and chemotherapy[a]	0	0.0%	2	6.7%	
Ipsilateral breast recurrence		0	0.0%	1	3.3%	0.505
		Median (range)	Median (range)			
Age (years)	60 (49–83)	58 (43–88)	0.276			
DCIS histological size (mm)	10 (4–30)	12 (3–40)	0.936			

Abbreviations: DCIS, ductal carcinoma in situ; ROLL, radioguided occult lesion localization.
RSL, radioactive seed localization; BCS, breast conserving surgery; NA, Not available.
[a] Chemotherapy due to contralateral invasive breast cancer.

LRSF for ROLL and RSL groups (Fig. 2). There are only few previous studies reporting LR rates after BCS using ROLL or RSL. Theunissen et al. [11] reported a LR rate of 6.6% in the ROLL group (median follow-up 51 months) and no recurrences in the RSL group (median follow-up 33 months). A recent study by Aljohani et al. [19] reported a LR of only 0.3%, but the median follow-up time was just 37 months in the RSL group.

Contralateral breast cancer recurrences, regional lymph node recurrences and breast cancer deaths were rare in our study.

4.5. Strengths and limitations of the study

In this study, we reviewed a large number of patients. This is a single-center study, the diagnostic and treatment protocols, including surgical practice, are standardized at our institution.

A limitation of this study is that data was collected retrospectively. Consequently, the RSL group patients had more often multifocal disease and received more often endocrine treatment, perhaps partly due to the multifocality, as there was no difference in tumour sizes. In addition, we excluded DCIS from the main analysis due to the small number of cases, especially in the ROLL group. DCIS is a known risk factor for positive margins and this may bias our findings. Among DCIS patients, we did not find statistically significant differences between ROLL and RSL, neither in the DCIS characteristics nor in the reoperation rate, possibly due the very small number of patients.

Furthermore, the guidelines for adequate surgical margins changed at the beginning of the study period in 2010. The new recommendation 'no ink on tumour' was introduced gradually, hence the indication for reoperation is not standard throughout the study period and was favoring RSL.

4.6. Other aspects of ROLL and RSL

Even though we did not find any difference in surgical outcome or oncological safety between ROLL and RSL, there are some clear advantages with RSL. The seeds are visible in mammography and their correct positioning is easy thus to confirm. RSL might also provide more accurate localization, since there is a risk of dispersion of Tc-99 m during the injection for ROLL. With RSL, it is possible to mark multiple lesions or a large microcalcification area with 2–3 seeds, which is a clear advantage compared to ROLL.

RSL provides flexible scheduling and logistics, since the seed can be placed weeks or even several months before surgery, for example in patients undergoing neoadjuvant treatment. It is quite common that when inserting the seed, the radiologist detects another suspicious lesion not identified in earlier imaging and biopsies or even re-planning of surgery may be needed [5]. Hence, we schedule the RSL well before operation.

On the other hand, due to the long half-life of I-125 seed, careful handling and disposal protocols are needed [9]. An advantage of ROLL is that it can be performed simultaneously with SNLB using a single injection of radiolabeled colloid [23,24].

4.7. Future aspects

Because WGL, ROLL and RSL have all some disadvantages, several new localization methods have been developed [24–26]. Non-ionizing markers using magnetic technology and radiofrequency energy are already in clinical use as well as intraoperative US. In addition, many other techniques are under investigation. Long-term evidence is needed to evaluate the feasibility of these new localization methods.

5. Conclusion

ROLL and RSL provided similar surgical outcomes in terms of margin status, reoperation rates and LRFS in patients with impalpable invasive breast cancer treated with BCS.

Conflicts of interest

None.

Ethics

This retrospective study did not require an ethics committee permission, but was approved by the institutional research board of Helsinki University Hospital.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.07.004.

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