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A Randomized Prospective Comparison of Patient-Assessed Satisfaction and Clinical Outcomes with Radioactive Seed Localization Versus Wire Localization

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Abstract

Background—Radioactive seed localization (RSL) has emerged as an alternative to wire localization (WL) in patients with non-palpable breast cancer. Few studies have prospectively evaluated patient satisfaction and outcomes with RSL. We report the results of a randomized trial comparing RSL to WL in our community hospital.

Materials and Methods—We prospectively enrolled 135 patients with non-palpable breast cancer between 2011 and 2014. Patients were randomized to RSL or WL. Patients rated the pain and the convenience of the localization on a 5-point Likert scale. Characteristics and outcomes were compared between groups.

Results—Of 135 patients enrolled, 10 were excluded (benign pathology, palpable cancer, mastectomy and previous ipsilateral cancer) resulting in 125 patients. Seventy patients (56%) were randomized to RSL and 55 (44%) to WL. Fewer patients in the RSL group reported moderate to severe pain during the localization procedure compared to the WL group (12% versus 26%, respectively, $p=0.058$). The overall convenience of the procedure was rated as very good to excellent in 85% of RSL patients compared to 44% of WL patients ($p<0.0001$). There was no difference between the volume of the main specimen ($p=0.67$), volume of the first surgery ($p=0.67$), or rate of positive margins ($p=0.53$) between groups.

Conclusions—RSL resulted in less severe pain and higher convenience compared to WL, with comparable excision volume and positive margin rates. High patient satisfaction with RSL provides another incentive for surgeons to strongly consider RSL as an alternative to WL.

Keywords

radioactive seed localization; wire localization; patient satisfaction

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

INTRODUCTION

Wire localization (WL) of non-palpable breast cancers has several disadvantages for both the surgeon and the patient. The skin entry site of the wire is often remote from the ideal skin incision, making it difficult for the surgeon to confirm the exact site of the lesion in the breast. In addition, the wire may also be improperly positioned in relation to the tumor or may be displaced prior to the procedure, resulting in unsuccessful retrieval of the lesion.^{1, 2} There are potential operating room delays, as patients undergoing WL cannot be scheduled as the first case of the day. Finally, patient issues include a prolonged operative day resulting in patient inconvenience, moderate pain associated with the procedure, and potential for a syncopal episode.

These disadvantages have led to the development of radioactive seed localization (RSL) as an alternative to WL. RSL involves placement of an iodine-125 (¹²⁵I) impregnated titanium seed into the breast lesion under radiographic guidance up to five days preoperatively. The surgeon then utilizes a handheld gamma probe to localize the lesion intraoperatively and remove it. In 2001 Gray et al. published the first randomized prospective trial comparing RSL to WL, demonstrating fewer positive margins and a smaller volume of excision with RSL.³ Since then, one additional randomized prospective study and several validation studies have shown comparable positive margin rates and volumes of excision between RSL and WL.⁴⁻⁷

Few studies have evaluated patient satisfaction in a prospective fashion, and no studies have evaluated RSL outcomes in a community hospital. In this study, we report the results of a randomized prospective trial comparing our initial experience with RSL to WL in our community hospital.

METHODS

Patient eligibility

Following approval from our institutional review board, 135 patients were prospectively enrolled into this randomized trial between January 2011 and February 2014. Inclusion criteria included women over 18 years of age with a non-palpable invasive carcinoma or in situ ductal carcinoma of the breast who were eligible for breast conservation. Patients could have multifocal disease or more extensive disease that required bracketing, as long as they were still considered appropriate candidates for breast conservation. All patients signed informed consent prior to randomization.

Localization technique

The localization was performed with either mammographic or ultrasound guidance, at the discretion of the radiologist. A ¹²⁵I impregnated titanium seed containing between 0.125 and 0.25 mCi was utilized during RSL. The seeds were loaded into an 18 gauge spinal needle after the tip was occluded with sterile bone wax. Following local anesthetic administration, the skin was punctured with the spinal needle. The tip of the needle was advanced to the lesion, and the seed deployed by advancing the stylet (Figure 1). Seeds were placed up to

five days prior to surgery. WL was performed on the day of the surgical procedure using a Homer needle to localize the lesion. A post-procedural mammogram was performed after RSL and WL to confirm appropriate position of the seed/wire. Placement of a second seed due to poor initial seed placement occurred in three patients at various time points throughout the study; in these patients the initial seed was located 1 cm from the target.

Surgical technique

The NeoProbe system (Mammotome, Cincinnati, Ohio), which detects both ^{99}Tc sulfur colloid and ^{125}I was used to perform the segmental resection and sentinel lymph node (SLN) biopsy in the RSL group, and SLN biopsy alone in the WL group. With the gamma probe set to ^{125}I , the point of maximal activity was marked on the breast. An incision was made directly over this point and the segmental resection was carried out using the gamma probe as a guide. Intraoperative X-ray was performed for all patients undergoing RSL and WL to confirm retrieval of the seed/wire and the titanium marker. For RSL cases, the specimen containing the seed was transported to pathology on the X-ray grid where the seed was extracted from the specimen by pathology personnel and placed in a lead container in a locked cabinet.

All specimens were oriented with suture by the surgeon in the operating room. Intraoperative excision of additional margins was performed at the discretion of the surgeon based on specimen X-ray and palpation. Margins were painted in pathology for margin assessment and were evaluated using perpendicular inked margins. Margins were considered positive when tumor was present at the inked margin. Three-dimensional volume of the main specimen and additional margins were measured by the pathologist.

Statistical analysis

The study was randomized so that the two groups of patients were balanced in terms of clinical parameters. Patients were randomized to either RSL or WL in a 1 to 1 randomization. Randomization was done on a patient-by-patient basis, not on a tumor-by-tumor basis. Clinical outcomes such as volume of the main specimen, volume at the first surgery, and margin status were compared for the two surgical groups using the Wilcoxon Rank-Sum test and Fisher's exact test. Patient-reported satisfaction scores were obtained via survey methods. Patients completed a brief questionnaire scored on a 5-point Likert scale regarding their experience in terms of pain of the procedure (1 = no pain, 2 = very mild, 3 = mild, 4 = moderate, and 5 = severe pain) and overall convenience of the localization procedure (1 = poor, 2 = fair, 3 = good, 4 = very good, and 5 = excellent). For analysis, we combined the values of 4 and 5 to represent moderate to severe pain; similarly, we combined the values of 4 and 5 to represent very good to excellent convenience. Patients in the RSL group completed the questionnaire immediately after the localization, while patients in the WL group completed the questionnaire at their first postoperative visit. Due to temporal differences in how each of the two surgical techniques is conducted, it was difficult to pinpoint a common time point to administer the surveys in order to have a valid comparison for satisfaction. We provide data on satisfaction (measure of pain and measure of convenience) for the two surgical groups and any direct comparison is interpreted with caution.

There were six patients with two lumpectomies, and thus represented twice in the arm in which they were randomized. Of these six patients, four had bilateral synchronous breast cancer and two had multiple ipsilateral breast cancer. These cancers were treated as independent data points, as is routinely done. However, we conducted sensitivity analyses to examine whether results differed with and without these patients. There were no discernible differences.

No formal sample size calculation was done for this study. Rather, we accrued patients for three years which was in line with available resources. At the time the study closed, we had enrolled a total of 135 patients, of which 125 were included in the analyses. Patients were analyzed by intention to treat. One patient was randomized to the seed, but received the wire due to nuclear regulatory issues. Her questionnaire was excluded from the analysis, but the remainder of her data was included.

RESULTS

Figure 2 demonstrates the study flow of the 135 patients enrolled. Following exclusions, 70 patients (56%) were randomized to RSL and 55 patients (44%) were randomized to WL. Two patients in the RSL group and four patients in the WL group had > 1 cancer for a total of 72 and 59 cancers, respectively. The majority of patients had a single seed or wire placed (84.3% versus 80.0%, respectively). Reasons for placement of > 1 seed or wire included bracketing (seed = 6, wire = 7), bilateral breast cancer (seed = 1, wire = 3), multiple ipsilateral breast cancer (seed = 1, wire = 1) and poor initial seed/wire placement (seed = 3, wire = 0). Localization occurred at a median of two days prior to surgery (range, 0–5 days) in the RSL group. All wires were placed on the day of surgery.

Baseline clinical and pathologic characteristics were similar between the groups (Table 1). Following the procedure, 94.3% of patients in the RSL group and 83.6% of patients in the WL group completed the survey. There were no differences found in the distribution of baseline pain scores between the two groups ($p = 0.404$). Fewer patients in the RSL group ($n = 8$, 12%) experienced moderate to severe pain during the localization procedure compared to the WL group ($n = 12$, 26%) ($p = 0.058$); notably, the median pain scores were similar. Eighty-five percent of patients in the RSL group rated the convenience of the procedure as very good to excellent compared to 44% of patients in the WL group ($p < 0.0001$) (Figure 3).

Surgical outcomes are depicted in Table 2. There was no difference in the volume of the main specimen ($p = 0.67$) or the volume of the first surgery ($p = 0.67$) between the RSL group and the WL group. The rate of any positive margin was similar between the RSL (19.4%) and WL (15.3%) groups ($p = 0.53$). Positive anterior/posterior margins were seen in 11.1% of RSL cases versus 3.4% of WL cases ($p = 0.20$).

Complications with the seed occurred in 11/72 (15.3%) of the procedures performed and included: poor initial seed placement ($n = 3$); seed displacement during successful excision of the lesion ($n = 6$); and failure to remove the seed in the first specimen ($n = 2$). Complications occurred with similar frequency throughout the study period (2011 = 17.4%,

2012 = 16.7%, 2013 = 12.9%, $p = 0.63$). No documented complications were reported with the wire during placement; however, wire displacement during successful excision of the lesion occurred in seven of 59 (11.9%) of the procedures. All targeted lesions were successfully retrieved. No seeds were lost, and no wires were transected during the study. In RSL patients undergoing SLN biopsy ($n = 41$), the SLN identification rate was 100%.

DISCUSSION

Over the last decade, RSL has emerged as an alternative to WL for preoperative localization of non-palpable breast lesions. Since it was first described by Gray et al. in 2001, there have been over 20 peer-reviewed publications describing its methodology, safety, and comparability to WL.^{4–18} The majority of studies have demonstrated RSL to be non-inferior, if not superior, to WL, with a low reported complication rate.^{3–6, 9–10, 13} Most published experience with seed localization arises from large academic institutions, and few randomized studies have focused on patient satisfaction of RSL.^{4,9} In this study, we performed a prospective comparison of patient satisfaction and outcomes with RSL versus WL in a community hospital. To the best of our knowledge, this is the first prospective evaluation of RSL in a community hospital setting.

One of the disadvantages of WL is the reported pain associated with preoperative wire placement. A recent Canadian randomized trial reported that patients experienced less pain with RSL than WL ($p = 0.04$).⁴ Similar to Lovrics et al., fewer patients in our study reported moderate to severe pain after the RSL procedure compared to the WL procedure ($p = 0.058$). Notably, however, some degree of pain was reported by the majority of patients with either procedure (RSL, 76%; WL, 85%), which is expected given that both RSL and WL require insertion of a needle into the breast to place the localization device. However, the observation that WL resulted in more severe pain may be reflective of the patient's awareness of the needle in the breast following the localization procedure. The patient's inability to see the seed externally following RSL may contribute to the perception of RSL as a less painful procedure.

WL is usually performed on the day of surgery, often prolonging the operative day for the patient. RSL, however, can be performed up to five days prior to surgery, which uncouples the radiologic and operative procedures. In our study, 99% of the patients had their seed localization prior to the day of surgery, which likely resulted in higher patient assessed convenience of RSL, with 85% rating the convenience of the RSL procedure as very good to excellent compared to 44% of the WL patients ($p < 0.0001$). Similarly, in a prospective validation study by Gray et al., patients rated the convenience of the RSL procedure significantly higher when the seed was placed at least one day prior to surgery compared to those having their seed placed on the day of surgery ($p < 0.01$).⁹ Although not directly measured in our study, other studies have also demonstrated that RSL is more convenient for the surgeon, by allowing for earlier operating room start times and avoidance of operating room delays associated with a difficult localization or syncope during wire localization.^{5,13} This improvement in operating room efficiency is particularly notable in high-volume centers. In a recent study by Memorial Sloan Kettering Cancer Center, all 10 surgeons reported that RSL simplified scheduling of operative cases and improved patient flow in the

operating room.⁵ The surgeons at our institution similarly felt that RSL was more convenient than WL and that RSL should be the preferred approach for localization of nonpalpable breast lesions.

Similar to studies by Lovrics et al. and Murphy et al., we noted no difference in excision volume or rate of positive margins between RSL and WL.^{4,5} However, we did note more positive anterior/posterior margins with RSL compared to WL (11.1% versus 3.4%, respectively; $p = 0.20$), although not significant in this data set. Although RSL allows for a more precise skin incision due to the placement of the seed within millimeters of the target, determination of lesion depth may be less precise and is based on surgeon estimation relying largely on mammographic images. Anterior/posterior estimation of margins cannot be performed until “flaps” are made around the specimen; this less-precise estimation of anterior/posterior margins may have attributed to the observed, albeit non-significant, higher positive anterior/posterior margin rate with RSL.

Our study has notable limitations. First, the patients in the RSL group completed their survey post-localization while the WL patients completed their survey at their first postoperative visit. This could result in recall bias, with patients in the WL group reporting more pain or less pain depending on their memory of the event. Of note, however, a review article by Erskine et al. reports evidence showing that recall of acute pain may be more accurate than recall of chronic pain due to the episodic nature of the event.¹⁹ Pain recall in WL patients may also have been impacted by their perception of post-surgical pain intensity, resulting in falsely elevated pain scores. Taking the aforementioned limitations into consideration, it was difficult to determine a time point to administer the survey, given the difference in the timing of the two localization procedures. An attempt to dispense the survey to the WL patients after their procedure (but immediately prior to surgery) has equal potential to bias the survey results given patient anxiety over their impending surgery and the pain associated with other procedures, such as placement of the intravenous. In addition, more patients completed their surveys after RSL compared to WL (94.3% versus 83.6%, respectively), which had more to do with the timing of the localization rather than a difference in patient compliance in each group. Additional survey results could potentially alter the findings noted in our study due to the small total sample size ($n = 125$). Furthermore, given the small sample size, the study may have been underpowered to detect a difference in specimen volume and margin positivity, even if one existed.

In conclusion, RSL of non-palpable breast cancers resulted in less severe pain in RSL patients compared to WL patients. Patients consistently ranked the convenience of the localization procedure higher with RSL than WL, possibly related to seed placement > 1 day prior to surgery. In this convenience sample, RSL results in comparable excision volumes and positive margin rates with no reported patient morbidity. High patient satisfaction with RSL provides yet another incentive for surgeons to strongly consider RSL as an alternative to WL.

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Synopsis

Radioactive seed localization (RSL) was compared to wire localization (WL) in a randomized prospective trial in a community hospital setting. RSL resulted in less severe pain and higher convenience compared to WL.

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Figure 1.

(a) Technique for a placement of the I^{125} seed into the breast using mammographic guidance and (b) mediolateral mammogram view performed during seed localization demonstrating the seed in position

Figure 2.
Study flow

Figure 3A: Pain Before Procedure

Figure 3B: Pain During Procedure

Figure 3C: Overall Convenience

Figure 3. Distribution of survey results for a pain before, b pain during, and c overall convenience of radioactive seed localization versus wire localization

Table 1

Clinical and Pathologic Characteristics of RSL Versus WL Patients

Characteristic	RSL		WL		p value
	N	%	N	%	
Patients	70	56.0	55	44.0	
Cancers (n)	72	55.0	59	45.0	
Median age (yrs)	67		64		0.55
Histology					0.33
DCIS	24	33.3	16	27.1	
Invasive	48	66.7	43	72.9	
Median tumor size (cm)					
DCIS	0.8 (0.3–2.5)		0.69 (0.2–3.4)		0.62
Invasive	0.85 (0.1–2.7)		0.9 (0.1–3.6)		0.96
Tumor grade ^a					0.71
I	19	41.3	18	43.9	
II	21	45.7	19	46.3	
III	6	13.0	4	9.8	
Multifocality ^a	2	4.2	7	16.3	0.11
Extensive intraductal component ^a	4	8.3	2	4.7	0.78
Lymphovascular invasion ^a	8 (47) ^b	17.4	5 (41) ^b	12.2	0.50
Estrogen receptor status					0.32
Positive	66	91.7	50 (58) ^b	86.2	
Negative	6	8.3	8 (58) ^b	13.8	
Axillary surgery ^c					0.80
SLNB	41	87.2	35	83.3	
ALND	1	2.1	2	4.8	
No axillary surgery	5	10.6	5	11.9	
Lymph node status ^c					0.40

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Characteristic	RSL N	%	WL N	%	p value
Positive	10	23.8	6	16.2	
Negative	32	76.2	31	83.8	

RSL, radioactive seed localization; WL, wire localization; DCIS, ductal carcinoma in situ; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection

^aIncludes invasive cancers only (RSL, n = 48; WL, n = 43)

^bDenominator reflects number of patients with available data.

^cDenominator reflects number of axillary procedures (RSL, n = 42; WL, n = 37)

Table 2

Surgical Outcomes of RSL Versus WL Patients

Characteristic	RSL (n = 72)	WL (n = 59)	p value
Volume main specimen (cm ³)			0.67
Mean	77.0	67.4	
Median	54.2	45.5	
Range	7.2–516.4	12.1–252.9	
Volume first surgery (cm ³)			0.67
Mean	88.8	77.2	
Median	63.8	57.3	
Range	9.5–519.3	12.1–262.2	
Margin Status (n, %)			
Any positive margin ^a	14 (19.4%)	9 (15.3%)	0.53
Positive anterior/posterior	8 (11.1%)	2 (3.4%)	0.20
Positive radial	6 (8.3%)	7 (11.9%)	

RSL, radioactive seed localization; WL, wire localization

^aIncludes anterior, posterior and radial margins