






Surgical outcomes after radioactive ^{125}I seed versus hookwire localization of non-palpable breast cancer: a multicentre randomized clinical trial

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Abstract

Background: Previous studies have suggested improved efficiency and patient outcomes with ^{125}I seed compared with hookwire localization (HWL) in breast-conserving surgery, but high-level evidence of superior surgical outcomes is lacking. The aim of this multicentre pragmatic RCT was to compare re-excision and positive margin rates after localization using ^{125}I seed or hookwire in women with non-palpable breast cancer.

Methods: Between September 2013 and March 2018, women with non-palpable breast cancer eligible for breast-conserving surgery were assigned randomly to preoperative localization using ^{125}I seeds or hookwires. Randomization was stratified by lesion type (pure ductal carcinoma in situ (DCIS) or other) and study site. Primary endpoints were rates of re-excision and margin positivity. Secondary endpoints were resection volumes and weights.

Results: A total of 690 women were randomized at eight sites; 659 women remained after withdrawal (^{125}I seed, 327; HWL, 332). Mean age was 60.3 years in the ^{125}I seed group and 60.7 years in the HWL group, with no difference between the groups in preoperative lesion size (mean 13.2 mm). Lesions were pure DCIS in 25.9 per cent. The most common radiological lesion types were masses (46.9 per cent) and calcifications (28.2 per cent). The localization modality was ultrasonography in 65.5 per cent and mammography in 33.7 per cent. The re-excision rate after ^{125}I seed localization was significantly lower than for HWL (13.9 versus 18.9 per cent respectively; $P = 0.019$). There were no significant differences in positive margin rates, or in specimen weights and volumes.

Conclusion: Re-excision rates after breast-conserving surgery were significantly lower after ^{125}I seed localization compared with HWL. Registration number: ACTRN12613000655741 (<http://www.ANZCTR.org.au/>).

Introduction

The number of non-palpable breast cancers requiring preoperative image-guided localization continues to increase as a result of more screen-detected cancers and neoadjuvant chemotherapy^{1,2}.

Hookwire localization (HWL) has been used widely since the 1970s, but is associated with high positive margin (20–40 per cent) and re-excision (30–50 per cent) rates^{3–5}. Other disadvantages of HWL include technical difficulties (such as wire

transection and migration), inefficient use of radiology bookings, and impact on theatre time^{6–8}.

Radioguided occult lesion localization using ^{125}I seeds is the most widely used non-wire localization technique, involving a radiologist placing a 4.5×0.8-mm titanium seed containing ^{125}I into the lesion under image guidance. The 27-keV photons emitted are detected at surgery using the γ probe already used widely for sentinel node biopsy. Use of radioactive ^{125}I seeds decouples the localization procedure from surgery, thereby improving scheduling and efficiency⁸. The seed provides precise real-time three-

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dimensional intraoperative surgical guidance, potentially resulting in improved surgical outcomes. Retrospective cohort studies and individual RCTs have been discordant, and a recent meta-analysis⁹ of five previous RCTs failed to show a significant reduction in positive margins (involved or very close) or re-excision rates.

The primary objectives of this study were to compare positive radial margin and re-excision rates following initial breast-conserving surgery (BCS) in patients with biopsy-proven non-palpable invasive or *in situ* breast cancer randomized to either ¹²⁵I seed or HWL localization.

Methods

Women who were candidates for BCS were recruited into this prospective multicentre RCT (Australian New Zealand Clinical Trials Registry number 12613000655741) between September 2013 and March 2018. Ethical approval was obtained from all hospital sites, and the study was undertaken according to the National Statement on Ethical Conduct in Human Research 2007¹⁰. The study was performed at eight tertiary care institutions: Royal Perth (RPH), Sir Charles Gairdner (SCGH), Fiona Stanley, and St John of God Subiaco Hospitals in Perth; Monash Hospital, Melbourne; Robina, Gold Coast University Hospitals, Gold Coast; Westmead Hospital, Sydney; and Waikato Hospital, New Zealand. Fifty breast surgeons and 64 radiologists were involved. Before study commencement, the lead sites (RPH and SCGH) conducted two pilot studies to test seed-handling protocols and train multidisciplinary team members^{11,12}. Thereafter at least one surgeon and one pathologist from each external site participated in a training course for ¹²⁵I seed handling. Radiological insertion of iodine seeds is similar to placing a breast marker and does not require special training. Each site handled radioactive seeds according to state safety regulations, and individualized institutional seed-handling protocols were developed.

Inclusion and exclusion criteria

Study inclusion criteria included: age 18 years and over, histologically confirmed non-palpable *in situ* cancer including pleomorphic lobular carcinoma *in situ* or invasive non-palpable breast cancer requiring localization, including neoadjuvant chemotherapy responders and women undergoing planned BCS. Multifocal and bilateral disease were allowed. Exclusion criteria were male sex, pregnancy or lactation, multicentric disease, contraindications to BCS, and classical lobular carcinoma *in situ* only.

Randomization

After obtaining written consent, each participant was randomized to lesion localization using either ¹²⁵I seed or HWL. Centrally concealed computer-generated block randomization was performed via a secure online database. Randomization was stratified according to study site and core biopsy histopathology (ductal carcinoma *in situ* (DCIS) only and other malignant pathology) of the index lesion. Participants with multifocal or bilateral lesions received the same localization method for all lesions. To satisfy local radiation protection guidelines, the number of seeds per participant was restricted to two, with combined activity of both seeds below 4 MBq. Typical radiation doses have been published elsewhere¹³.

Lesion localization

Localization was performed with either mammographic (grid, stereo, or tomosynthesis) or ultrasound guidance. Seed

placement was performed using 18-G needles containing an ¹²⁵I seed, up to 8 days before surgery. HWL was done on the morning of surgery, by insertion of a 9-cm modified Kopans hookwire.

Two wires or seeds were used to bracket larger (above 20 mm) lesions at the discretion of the radiologist. The position of seeds and wires was assessed on two-view mammograms after insertion, and, if considered unsatisfactory following discussion with the surgeon, another hookwire was inserted; a further seed was not inserted to avoid surgical confusion. Participants scheduled to have sentinel node biopsy underwent sentinel node mapping (predominantly guided by ^{99m}Tc radiotracer) according to site-specific protocols.

Surgical procedure and retrieval of seeds

A standard dual-energy γ probe was used to detect and remove the breast lesion and seed(s), and, where appropriate, the sentinel node. Blue dye alone was used for sentinel node localization at one trial site. The surgeon aimed to resect a cylindrical volume of tissue including the marker clip and seed with a radiological resection margin of 10 mm beyond the identified tumour border, or, in patients with complete clinical and radiological response after neoadjuvant chemotherapy, a 10-mm radius surrounding the marker clip. Routinely, resections were performed from skin to pectoralis fascia. When multiple seeds were used for bracketing¹⁴, a block of tissue was resected to encompass seeds and an adequate margin.

Retrieval of seeds was confirmed by presence of an ¹²⁵I signal in the specimen and absence of this signal in the surgical bed, together with visualization of the seed on intraoperative specimen radiography (IOSR). Strict seed-tracking protocols were maintained. Specimens were oriented using sutures and markers such as large titanium LIGA[®] clips (Ethicon, Somerville, NJ, USA), to aid radiographic margin identification (large clips were used to avoid confusion with seeds on the specimen radiograph).

Intraoperative re-excision was performed when the margin was deemed close, based on the IOSR report or surgical suspicion. Frozen-section/immediate pathological margin assessment was not done. Seeds were retrieved by the pathologist from the fresh or fixed specimen¹⁵, and specimens were inked, sectioned, and processed with standard histopathological protocols. Specimens were weighed and measured before fixation. The volume of the main resection specimen was estimated using the formula for volume of a cube.

Self-reported ease of use

Radiologists and surgeons were asked to rate their ease of use of ¹²⁵I seed localization and HWL using a 7-point Likert scale.

Adjuvant treatment

Postoperative management of the participants was decided by the local multidisciplinary tumour board, using individual site definitions for involved and close tumour margins, tumour biology, patient factors such as age, expected adjuvant treatment, and whether or not further margin excision was possible.

Data and statistical analysis

Before the RCT, an audit at two tertiary referral centres in Western Australia found a re-excision rate of 30 per cent, comparable to that in the worldwide literature⁵. Based on this, a power calculation with the aim of detecting a reduction in re-excision rates from 30 to 20 per cent with a significance level of 5 per cent (two-tailed) and 90 per cent power was done. A sample size of 293 participants per arm was required and, to allow for an attrition

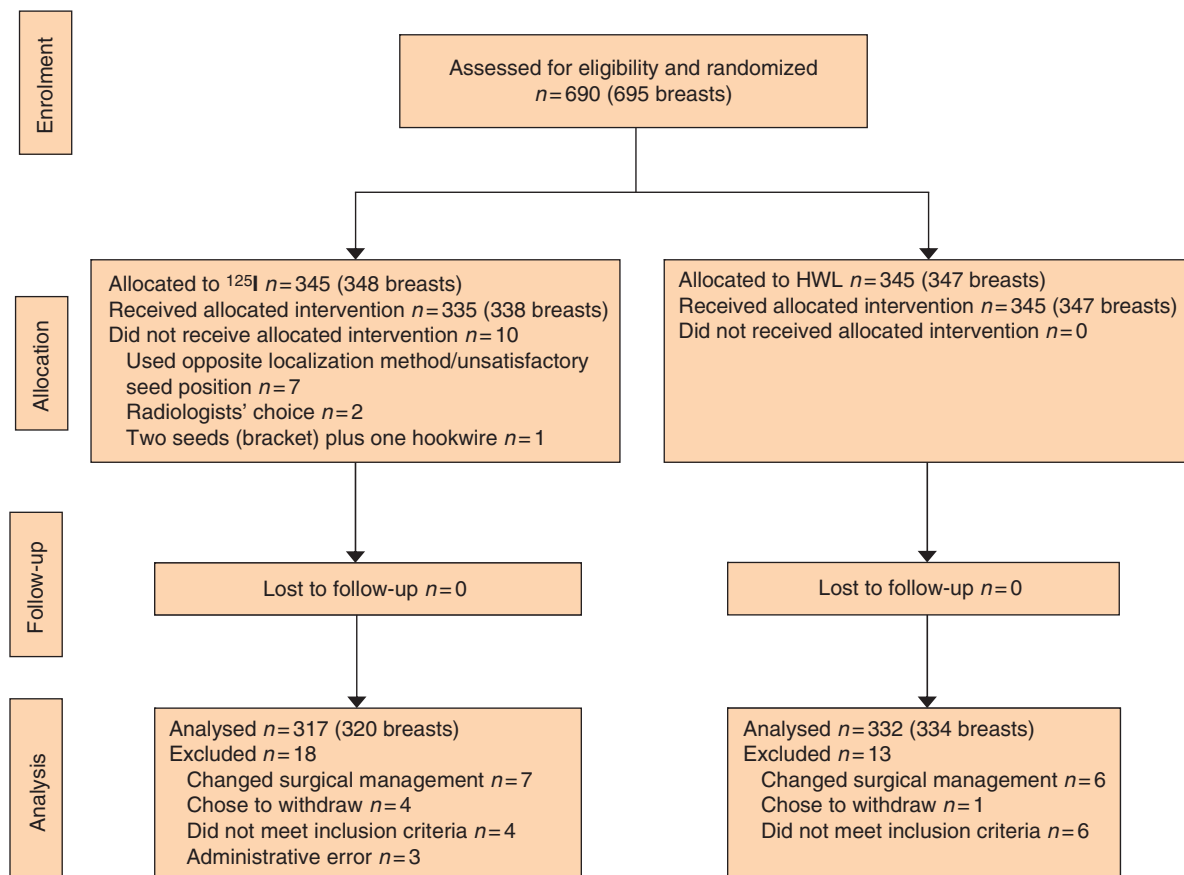


Fig. 1 CONSORT diagram for the trial

HWL, hookwire localization.

rate of 10 per cent in each study arm, a total sample size of 650 women was specified *a priori*.

A breast level analysis was performed for positive margin and re-excision rates. Tumour size was measured as the maximum dimension of the largest invasive focus. The weight and dimensions of the initial breast specimen were used to calculate specimen volume. Weights and dimensions of additional margins excised during surgery were not added to the initial specimen. The closest radial margin including additional cavity shaves taken at the first operation was used for analysis.

Demographic and clinical characteristics were summarized using mean(s.d.) values for continuous variables, and frequencies and percentages for categorical variables. Logistic regression using generalized estimating equations (PROC GENMOD in SAS[®] version 9.4; SAS Institute, Cary, NC, USA) was used to test for differences between arms in primary (re-excision rates and positive margins) and secondary (specimen weight and volume) outcomes, allowing for correlations within stratified blocks. Statistical comparisons were made using the Z test. Additional adjustment for known confounders (number of cavity shaves taken; lesion size on imaging; participant age; *in situ* only versus invasive with/without *in situ* disease at core biopsy) was undertaken and effect estimates were compared in the main analysis, with assessment of linearity for continuous variables based on restricted cubic splines. The primary analysis was by intention-to-treat and a supplementary per-protocol analysis was also undertaken.

Distributions of difficulty scores for localization and excision were summarized within study arms as median (i.q.r.) values, and compared with the Wilcoxon rank sum test (PROC

NPAR1WAY in SAS[®]). Comparisons of difficulty scores were stratified by modality of localization (mammography versus ultrasonography) as a *post hoc* subgroup analysis. All tests of statistical significance were two-sided. The level chosen for statistical significance was $P < 0.050$.

Results

A total of 690 participants gave written informed consent and 31 were withdrawn after randomization (18 from the ^{125}I seed arm and 13 from the HWL arm), for reasons shown in the CONSORT diagram (Fig. 1). After withdrawals, 327 participants (330 breasts) remained in the ^{125}I seed arm and 332 participants (334 breasts) in the HWL arm. In the ^{125}I seed group, seven participants underwent HWL due to suboptimal seed position, two had HWL at radiologist discretion, and one woman with multifocal disease on imaging underwent bracketing with two seeds and a HWL. All participants in the HWL arm received their allocated localization device.

Participant demographics and imaging features are shown in Table 1. Mean patient age was 60.7 years in the HWL group and 60.3 years in the ^{125}I seed group. The mean size of the lesions in both groups was identical (13.2 mm). Some 25.9 per cent of the index lesions were pure DCIS on core biopsy, with the remainder being invasive disease with or without an *in situ* component. Insertion of seed or wire was performed using ultrasound guidance in most cases (65.5 per cent), with mammographic guidance techniques (stereotactic, grid, tomosynthesis) used in 33.7 per cent. Most participants had only one wire or seed inserted for lesion localization, but 40 had more than one seed (18 patients) or wire (22) inserted to

Table 1 Patient and imaging characteristics

	Wire (n = 332; 334 breasts, 340 lesions)	Seed (n = 327; 330 breasts, 333 lesions)	Total (n = 659; 664 breasts, 673 lesions)
Age (years)*	60.7(10.4)	60.3(10.2)	60.5(10.3)
Radiological lesion size (mm)*†	13.2(8.9)	13.2(8.9)	13.2(8.9)
Sentinel node biopsy performed			
Yes	245 (73.4)	244 (73.9)	489 (73.6)
No	89 (26.6)	86 (26.1)	175 (26.4)
Neoadjuvant therapy			
Yes	8 (2.4)	11 (3.4)	19 (2.9)
No	324 (97.6)	316 (96.6)	640 (97.1)
Mammogram findings			
Clip only	4 (1.2)	5 (1.5)	9 (1.3)
Calcification	90 (26.5)	100 (30.0)	190 (28.2)
Distortion	18 (5.3)	18 (5.4)	36 (5.3)
Localized increased density	31 (9.1)	38 (11.4)	69 (10.3)
Mass	151 (44.4)	138 (41.4)	289 (42.9)
Mass and calcification	14 (4.1)	13 (3.9)	27 (4.0)
Visible, not specified	5 (1.5)	7 (2.1)	12 (1.8)
Not visible	27 (7.9)	14 (4.2)	41 (6.1)
Ultrasound findings			
Visible	248 (72.9)	245 (73.6)	493 (73.3)
Not visible	52 (15.3)	46 (13.8)	98 (14.6)
Not done	40 (11.8)	42 (12.6)	82 (12.2)
Preoperative MRI			
Yes	25 (7.4)	33 (9.9)	58 (8.6)
No	315 (92.6)	300 (90.1)	615 (91.4)
Guidance method for localization			
Mammography	113 (33.2)	114 (34.2)	227 (33.7)
Ultrasonography	226 (66.5)	215 (64.6)	441 (65.5)
Not specified	1 (0.3)	4 (1.2)	5 (0.7)
Lesions where bracketing used			
Yes	26 (7.6)	22 (6.6)	48 (7.1)
No	314 (92.4)	311 (93.4)	625 (92.9)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.).

†Radiological size not recorded for eight breasts (hookwire, 2; seed, 6); size derived from largest measurement on mammography or ultrasonography, and tumour size summed for eight breasts with multifocal tumours.

bracket either a single large lesion (greater than 20 mm) or an apparent multifocal lesion on preoperative imaging.

Final pathology

The final pathology characteristics of the localized lesions are reported in Table 2 with 24.7 per cent being DCIS only and the remainder having invasive disease, with or without DCIS, with no difference between the ^{125}I seed and HWL groups. The most common mammographic lesion types were a mass (with or without microcalcification) (46.9 per cent) or microcalcifications (28.2 per cent) (Table 1). Of the 591 lesions assessed with ultrasonography, 493 (83.4 per cent) were visible. In nine cases a biopsy marker clip was the only visible target for preoperative localization; four had had a complete response to neoadjuvant treatment, with no residual malignancy on final histopathology, and in one the lesion had been removed completely by vacuum-assisted diagnostic core biopsy. Preoperative MRI was performed infrequently (8.6 per cent of cases), with no difference in incidence between the two study arms.

Surgical outcomes

The rates of involved margins and reoperation, and specimen weights and volumes are summarized in Table 3. On intention-to-treat and per-protocol analyses, no statistically significant differences were observed in rates of positive margins in ^{125}I seed (5.5 per cent) and HWL (7.8 per cent) groups ($P=0.183$). A significant reduction in the re-excision rate was observed for ^{125}I seed

localization compared with HWL (13.9 versus 18.9 per cent respectively; $P=0.019$). The weights and volumes of the main tissue specimens (where recorded) were similar for the two groups.

The magnitude of estimates for surgical outcomes, and statistical significance of the differences between groups, were not changed substantially by adjusting for co-variables, or when per-protocol analysis was undertaken (data not shown). The incidence of additional intraoperative cavity margin excision was similar for the two groups. Over half of participants in ^{125}I seed and HWL groups had one or more additional intraoperative cavity margins taken (57.3 and 57.8 per cent respectively), predominantly due to apparent close margins on IOSR (more than 98 per cent). A similar number of participants in each group underwent sentinel node biopsy (73.4 per cent for ^{125}I seed versus 73.9 per cent for HWL). Failure to identify a sentinel node using $^{99\text{m}}\text{Tc}$ radiotracer was reported in two cases (1 in each study arm).

Adverse events

Suboptimal positioning of seed or wire requiring corrective wire insertion occurred in 9 and 13 cases respectively. In one malpositioned hookwire, the wire tip was embedded in the pectoral muscle and transected during surgery. The wire tip could not be removed and subsequently migrated into the pleural cavity. No further surgery was performed. There were no reported cases of seed migration after insertion. All lesions and seeds were

Table 2 Tumour characteristics

	Wire (n = 334 breasts)	Seed (n = 330 breasts)	Total (n = 664 breasts)
Tumour category			
pTis	80 (24.0)	83 (25.2)	163 (24.5)
pT1a/b	98 (29.3)	86 (26.1)	184 (27.7)
pT1c	124 (37.1)	111 (33.6)	235 (35.4)
pT2	31 (9.3)	45 (13.6)	76 (11.4)
pT3	1 (0.3)	1 (0.3)	2 (0.3)
No residual tumour	0 (0)	4 (1.2)	4 (0.6) [†]
Nodal status			
NX	81 (24.3)	77 (23.3)	158 (23.8)
N0	217 (65.0)	221 (67.0)	438 (66.0)
N1	31 (9.3)	30 (9.1)	61 (9.2)
N2	4 (1.2)	2 (0.6)	6 (0.9)
N3	1 (0.3)	0 (0)	1 (0.2)
Pathological classification*			
DCIS only	80 (24.0)	84 (25.5)	164 (24.7)
Invasive only	96 (28.7)	105 (31.8)	201 (30.3)
Invasive + DCIS	158 (47.3)	141 (42.7)	299 (45.0)

Values in parentheses are percentages. *Pathological classification from core biopsy for four breasts with no residual tumour (ductal carcinoma in situ (DCIS) only, 1; invasive only, 1; invasive + DCIS, 2). [†]Pathological complete response to neoadjuvant therapy (3 breasts); tumour completely removed at core biopsy (1 breast).

Table 3 Surgical and specimen outcomes by localizing modality

	Seed (n=330)	Wire (n=334)	Seed versus wire	P
Surgical outcomes			Odds ratio	
Reoperation (%)	13.9 (10.7, 18.0)	18.9 (14.8, 23.8)	0.70 (0.52, 0.94)	0.019 [‡]
Positive margins (%)	5.5 (3.5, 8.4)	7.8 (5.4, 11.0)	0.68 (0.39, 1.20)	0.183 [‡]
Specimen outcomes			Difference	
Estimated weight (g)*	44.7 (36.3, 53.1)	40.4 (34.1, 46.6)	4.3 (-1.5, 10.2)	0.146 [‡]
Estimated volume (ml) [†]	86.4 (74.0, 98.8)	3.9 (73.1, 94.6)	2.6 (-4.5, 9.6)	0.476 [‡]

Values in parentheses are 95 per cent confidence intervals. *Weight missing for 63 breasts (seed, 28; wire, 35). [†]Estimated volume missing for 11 breasts (seed, 7; wire, 4). [‡] Z test.

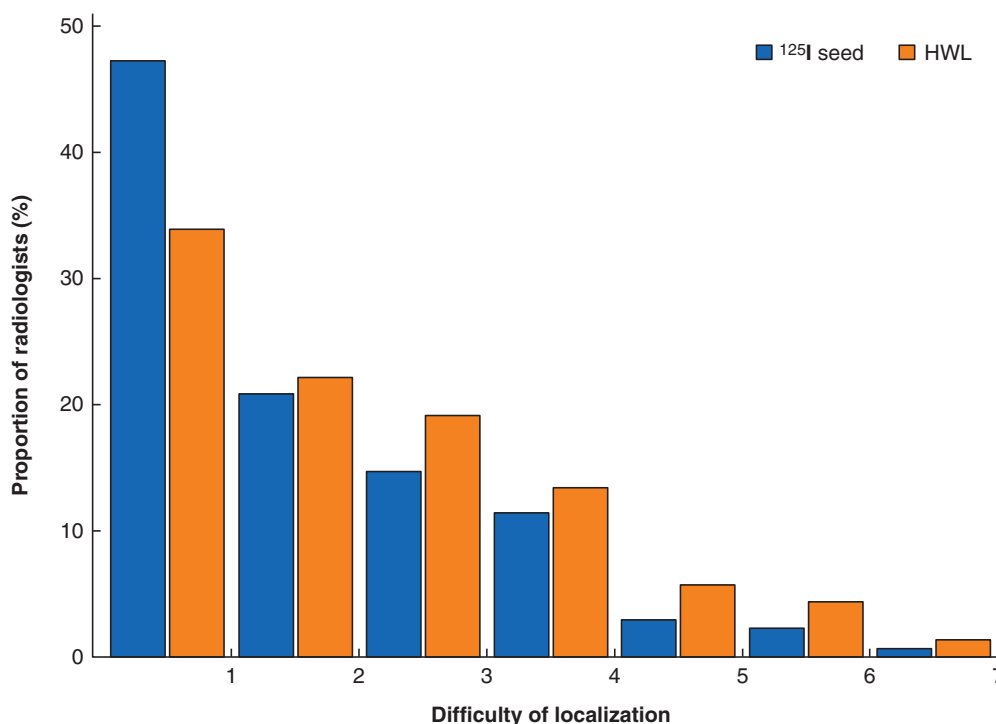


Fig. 2 Radiologists' degree of difficulty of localization using seed versus hookwire

¹²⁵I seed localization (n=307) versus hookwire localization (HWL) (n=298). Difficulty of localization: 1, not at all difficult; 7, very difficult.

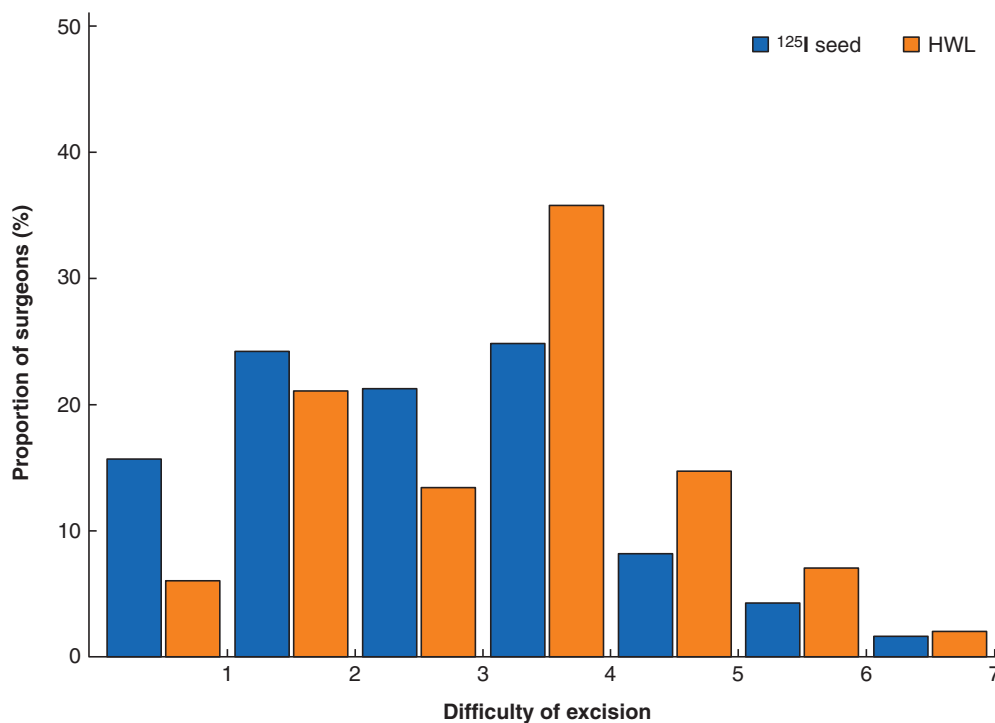


Fig. 3 Surgeons' degree of difficulty of excision using seed versus hookwire

¹²⁵I seed localization (n=307) versus hookwire localization (HWL) (n=298). Difficulty of excision: 1, not at all difficult; 7, very difficult.

removed successfully. There were several cases in which the seed was observed to separate from the tissue specimen during surgery, particularly when it had been placed at the superficial aspect of the lesion. One case of seed loss between excision and obtaining a specimen radiograph occurred early in the trial; the surgeon had experienced difficulty in using the γ probe and the radiologist mistook a LIGA[®] clip attached to an orientation suture for a seed on IOSR. By the time the pathologist reported that the seed was missing, theatres had been cleared and the seed could not be found. One episode of seed transection by the pathologist occurred during removal from the specimen. No other adverse events were reported.

Results of user self-reporting

The degrees of difficulty for ¹²⁵I seed and HWL were self-reported by a subset of radiologists and surgeons on a scale of 1 (not at all difficult) to 7 (very difficult) (Fig. 2). Radiologist-reported difficulty of localization was the same for ¹²⁵I seed localization and HWL (median 2 (i.q.r. 1–3)), indicating that the majority of radiologists reported difficulty below the scale mid-point, regardless of whether seed or wire was used. There was, however, a statistically significant difference in the distributions of ratings by localizing device ($P < 0.001$). A rating of 1 was reported more frequently by radiologists using ¹²⁵I seed, and ratings greater than 1 were reported more frequently by radiologists using HWL (Fig. 2).

Self-reported difficulty of excision by surgeons was lower for ¹²⁵I seed (median 3 (i.q.r. 2–4)) than for HWL (4 (2–4)) ($P < 0.001$). Surgeons using ¹²⁵I seed were more likely to report difficulty below the scale mid-point; whereas surgeons using HWL were more likely to report difficulty at or above the scale mid-point (Fig. 3).

Discussion

Limitations in HWL of breast lesions have led to the development of several non-wire localization methods. Radioactive seed localization using ¹²⁵I seeds was first described in 2001, with subsequent cohort studies^{8,11,16,17} showing that both radiologists and surgeons found seeds easier to use, with improved efficiency, convenience, and patient preference. Retrospective studies indicated equivalent or lower re-excision rates, but improved surgical outcomes have not been shown by subsequent RCTs^{18–20}.

The present RCT is the first to show a significant reduction in re-excision rates with ¹²⁵I seed localization compared with HWL (13.9 versus 18.9 per cent; $P = 0.019$), a finding that persisted after adjustment for co-variables (number of cavity shaves taken, lesion size on imaging, and presence of *in situ* only versus invasive disease with or without an *in situ* component). Although most trial sites used a radial margin of less than 2 mm rather than 'no tumour on ink' as the main indicator for re-excision, decisions for reoperation were dependent on locally agreed institutional protocols plus individual decisions discussed at tumour boards.

Although a statistically significant reduction in the proportion of positive margins (tumour on ink) was not demonstrated in this study, it should be noted that the observed difference was in the expected direction (5.5 per cent for ¹²⁵I seed versus 7.8 per cent for HWL), and that the study was powered primarily to detect a reduction in the reoperation rate rather than positive margins. The positive margin rates for ¹²⁵I seed versus HWL in this study were similar to those of other reports indicating a 1–3 per cent difference^{18–20}. Langhans and colleagues¹⁹ considered a radial margin width of less than 2 mm as positive, which could possibly account for their higher margin positivity rate. On the other hand, Lovrics et al.¹⁸ and Bloomquist and co-workers²⁰ both defined a positive margin as 'tumour on ink'.

The finding in the present study that there was no significant differences in mean weights and volumes of the main excision specimens in ^{125}I seed and HWL groups is consistent with results of previous RCTs. Lesion size on preoperative imaging is likely to influence the weight and volume of tissue surgically excised. The mean radiological lesion size in the study by Langhans *et al.*¹⁹ was 9 mm for both ^{125}I seed and HWL, smaller than the mean lesion size of 13 mm in the present study. All lesion types were included in the present study, whereas Langhans and colleagues¹⁹ excluded lesions not visible on ultrasound imaging and those removed with an oncoplastic procedure.

Both radiologists and surgeons found ^{125}I seed easier to use than HWL, echoing findings from an initial pilot study¹¹. Improved ease of use for ^{125}I seed localization was noted particularly by surgeons, as shown in other studies^{18,21}. For radiologists, insertion of a seed is similar to placing a marker clip after a breast biopsy, and thus no additional skills are required. Instances of suboptimal positioning of either seeds or wires requiring corrective action during the study were infrequent; however, it is important to note that patients with a malpositioned seed inserted days before surgery require a corrective HWL on the day of surgery. An important disadvantage of HWL is the potential for wire migration and transection. By contrast, as in other studies²², there were no cases of seed migration in the present study. Although procedure times were not measured, other investigators^{18,21} have noted that surgeons found no difference or that ^{125}I seed was faster. Other advantages of ^{125}I seed localization include significantly lower levels of patient anxiety and pain¹⁶, and improved efficiency related to decoupling of radiological and surgical lists with elimination of avoidable delays^{8,20,23,24}.

The results of this study add high-level evidence to other published literature showing that the use of ^{125}I seed localization rather than HWL in BCS of non-palpable breast cancer gives superior surgical outcomes⁹.

The present study has limitations. Data regarding tumour grade, hormone receptor, extensive intraductal component and lymphovascular invasion were not collected. The randomization makes it unlikely, however, that the groups were unbalanced for these factors. Moreover, a universally applied definition for clear margins was not applied during the study. Before publication of the Society of Surgical Oncology–American Society for Radiation Oncology (SSO–ASTRO) margin guidelines (for invasive disease in March 2014 and for DCIS in August 2016)^{25,26}, no consensus existed. From late 2016 onwards, when the majority of patient recruitment took place, the SSO–ASTRO margin definitions were in use at all sites bar one. The reduced re-excision rate observed in the ^{125}I seed arm is therefore applicable to contemporary surgical practice. Furthermore, as with most surgical intervention trials, it was not possible to blind the treating team to the intervention received by the patient, and this may have biased decisions regarding re-excision at tumour boards. Given the size of the trial and involvement of multiple centres, systematic use of different treatment protocols for ^{125}I seed localization *versus* HWL was unlikely.

Some practical issues need to be overcome to enable widespread implementation. There is considerable variability in the regulations regarding handling of low-activity ^{125}I seeds between countries and even between states, with some insisting that a medical physicist accompany the seed throughout its journey. In Australia, the Australasian College of Physical Scientists and Engineers in Medicine is currently lobbying radiation councils in each state for the development of uniform guidelines that reflect

the low-risk nature of ^{125}I seeds. Moreover, access to a radiation safety officer to assist with seed dispensing and disposal processes is needed. Finally, reduced re-excision rates and improvements in utilization of radiology and theatre lists are likely to lead to improved cost-effectiveness.

Recent publications have highlighted the potential advantages of using other non-wire preoperative lesion localization techniques that avoid ionizing radiation, such as magnetic seeds and radiofrequency devices²⁷. Although the lack of exposure to ionizing radiation and the need for radioactive substance tracking make these options attractive, issues that warrant consideration include the lack of mature, large-scale efficacy data, the large size of the implantable device (for example, 12 mm for the Savi Scout[®], Merit Medical, South Jordan, UT, USA) and associated metallic artefacts (such as the Magseed[®], Endomagnetics Ltd, St John's Innovation Park, Cambridge, UK), which may preclude the use of MRI to monitor neoadjuvant treatment²⁷. It is important to note that ^{125}I seed localization utilizes existing technology, as most γ probes already used for sentinel node detection can also detect ^{125}I , whereas alternative non-wire techniques mandate the purchase of proprietary-owned detector technology and consumables.

This RCT found a significant difference in re-excision rates with the use of ^{125}I seeds *versus* HWL. Importantly, this was demonstrated in a multicentre real-world setting involving a large number of radiologists and surgeons, and a broad group of patients without the exclusions imposed in other studies^{19,28}. The pragmatic nature of these data ensures that ^{125}I seed localization is ready to implement in many breast practices.

Collaborators

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