Navigating towards the unseen margins of non-palpable breast cancer
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Chapter 2

Radioactive seed localization in breast cancer treatment

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Abstract

Background
Breast cancer screening, improved imaging and neoadjuvant systemic therapy (NST) have led to increased numbers of non-palpable tumors suitable for breast-conserving surgery (BCS). Accurate tumor localization is essential to achieve a complete resection in these patients. This study evaluated the role of radioactive seed localization (RSL) in improving breast- and axilla-conserving surgery in patients with breast cancer with or without NST.

Methods
Patients who underwent RSL between 2007 and 2014 were included. Learning curves were analyzed by the rates of minimally involved (in situ/invasive tumor cells on a length of 0–4mm on ink) and positive resection margins (over 4mm on ink) after BCS, and the median resection volume over time.

Results
A total of 367 patients with in situ carcinomas and 199 with non-palpable invasive breast cancer underwent RSL before primary surgery. A further 697 patients had RSL before NST, of whom 206 also underwent RSL of a histologically verified axillary lymph node metastasis. BCS was performed in 93.2% and 87.9% of patients undergoing primary surgery for in situ and invasive tumors respectively, and 57.5% of those in the NST group. The rate of BCS with positive resection margins was low and stable over time in the three groups (9.1%, 9.7% and 11.2% respectively). The median resection volume decreased significantly with time in the invasive cancer and NST groups.

Conclusion
In the present study of more than 1200 patients and 7 years of experience, RSL was shown to facilitate breast- and axilla-conserving surgery in a diverse patient population. There was a significant reduction in resection volume while maintaining low positive resection margin rates after BCS.
Introduction

Approximately 16,000 women are diagnosed with invasive or in situ breast carcinoma each year in the Netherlands [1], and the incidence is increasing. Following the introduction and improvement of breast screening programs, more early-stage and non-palpable tumors, including both invasive cancer and ductal carcinoma in situ (DCIS), are being detected [2]. In addition, the use of neoadjuvant systemic therapy (NST) is increasing, with the aim of downsizing tumors before surgery [3]–[5]. NST based on tailored therapy regimens also leads to partial or pathological complete responses, resulting in many more non-palpable lesions that are suitable for breast-conserving surgery (BCS) instead of mastectomy [6]–[9]. The excision of non-palpable tumors is challenging and requires accurate tumor localization to achieve small excision volumes, while maintaining negative resection margins, avoiding re-excisions and maintaining low local recurrence rates [10].

To improve the surgical outcome of non-palpable lesions, several tumor localization methods have been developed. For more than 20 years, the standard method has been wire-guided localization (WGL). This involves a wire being inserted into the center of the tumor under ultrasound or stereotactic guidance shortly before surgery. During surgery, the wire is used as a guide to estimate the center and borders of the tumor. Several studies have shown that WGL is associated with high rates of positive resection margins, varying between 13 and 58 per cent [11]. Other major disadvantages of WGL are possible dislocation of the wire, patient discomfort and poor cosmetic outcome [2], [12]–[14]. Intraoperative ultrasonography is another technique that provides per-operative visualization of the tumor, and has been shown to lead to fewer positive resection margins than WGL [15], [16]. However, not all non-palpable lesions, such as DCIS and tumors with a complete clinical response after NST, are visible on ultrasound imaging [17]. Another approach is the use of radioactive guidance, including both radio-guided occult lesion localization (ROLL) and radioactive seed localization (RSL). ROLL is based on the injection of a liquid radioactive tracer ($^{99m}$Tc) into the center of the tumor a few hours before surgery. A γ probe is used during surgery to localize the tracer and associated primary tumor. With RSL, a radioactive iodine ($^{125}$I)-labelled seed is placed in the center of the tumor under ultrasound or stereotactic guidance. Similar to ROLL, a γ-detector probe provides per-operative guidance to the tumor location. Several randomized clinical trials and cohort studies [11], [18]–[20] have shown that the use of ROLL or RSL results in fewer positive resection margins and re-excisions, and a better cosmetic outcome compared with WGL. Therefore, both RSL and ROLL are preferred to WGL.

RSL has several advantages over ROLL. The point-source activity of the seed used in RSL allows more precise tumor localization in comparison with the diffuse activity of the liquid tracer.


99mTc-labelled tracer. Furthermore, multiple seeds could be used to the bracket edges of extensive DCIS or multifocal invasive tumors; this has been demonstrated previously by the use of multiple wires in, for example, large clusters of calcifications [21]–[24]. Another advantage of 125I-labelled seeds is the long half-life of 59.6 days, allowing seed implantation up to 12 months before surgery, which is useful in patients treated with NST [10], [25]–[30]. Finally, seed implantation is also possible in proven metastatic axillary lymph nodes. Tumor-positive axillary lymph nodes can be marked with a seed before NST and then removed selectively, a procedure known as MARI (Marking of Axillary lymph node by Radioactive Iodine seed) [30], [31]. In November 2007, RSL was introduced at the Netherlands Cancer Institute for use only in patients with large invasive breast tumors undergoing NST. Since 2008, it has also been used to localize proven metastatic lymph nodes in the NST setting, as well as in patients with (mainly screen-detected) small and non-palpable lesions undergoing primary surgery. During 2011, use of multiple 125I-labelled seeds was introduced as a lesion-bracketing system for extensive and multifocal tumors. The purpose of the present study was to evaluate the role of RSL in patient-tailored breast- and axilla-conserving treatment. All patients who underwent RSL in this institute in the first 7 years were evaluated with regard to patient and tumor characteristics, type of surgery and resection margins. Learning curves for the use of RSL were assessed by analyzing changes in positive and minimally involved resection margin rates, and breast resection volume over time.

**Methods**

A retrospective review was undertaken of all consecutive RSL procedures in women with breast cancer at the Netherlands Cancer Institute between November 2007 and April 2014. Patients were divided into groups based on their treatment. The first two groups consisted of women who underwent primary surgery for non-palpable tumors – those with in situ carcinomas and those with small invasive tumors – in whom the seed was placed at least 2 weeks before surgery. The third group comprised patients who underwent NST, followed by surgery. Patients in this group had invasive breast tumors and NST was indicated owing to tumor size and/or lymph node status. Before the start of NST, a seed was placed in the breast tumor and, if present, also in positive lymph nodes in the axilla. The clinical response to NST was assessed by using contrast-enhanced MRI (CE-MRI) (Philips Medical Systems, Best, The Netherlands). The following clinical data were retrieved from the electronic medical record: age, location and number of seeds, clinical (cT), response (yT) and pathological (pT) tumor category, type of surgery, postoperative resection margin status and resection specimen volume.
Radioactive seed implantation

RSL radiation protocols and documentation regarding acquisition, handling and storage in the radionuclide laboratory, the radiology department, during surgery and in the pathology department have been described previously [32], [33]. For RSL, $^{125}$I-labelled seeds of 4.5 × 0.8 mm (STM1251; Bard Brachytherapy, Carol Stream, Illinois, USA) were used. The seeds are a source of photon radiation with an average energy of 27 keV. At the time of implantation, the seeds used for localization of primary tumors had a minimum activity of 7.4 – 10.7 MBq, whereas those used in the axillary lymph nodes had a lower activity (between 1.6 and 7.0 MBq). The activity of seeds in the axilla was lower because of the superficial position. Furthermore, the activity was limited to prevent a therapeutic effect, which could hamper clinical tumor response evaluation. Seeds were stored at the radionuclide laboratory of the department of nuclear medicine and transported to the department of radiology in a single lead vial for implantation. At radiology the seeds were placed in an 18-G needle with a pre-waxed needle tip. Patients in whom the tumor was visible on ultrasonography underwent ultrasound-guided seed implantation. If the breast tumor was occult on ultrasound imaging, stereotactic RSL was performed under X-ray mammography guidance. For localization in an axillary lymph node (referred to as a MARI node), a seed was placed under ultrasound guidance in a previously proven metastatic lymph node. The location of the seed in the breast and/or axilla was always confirmed by an additional mammogram and/or a radiograph of the axilla. In general, one seed was placed in the center of the tumor. Multiple seeds were used to bracket edges of the tumor in a subgroup of patients with extensive or multifocal tumors. Bracketing allowed BCS to be offered to these patients, instead of standard mastectomy. In most patients, extensive tumors were larger than 4 cm in diameter and multifocal tumors were defined as having two or more separate but adjacent tumor foci. For multicentric tumors, separate seeds were positioned in the centers of the tumors as far as possible (maximum 3). In general, tumors smaller than 3 cm were suitable for BCS. The final decision on BCS was made in a multidisciplinary meeting, and was dependent on the patient’s preference, the volume ratio of breast and tumor, the presence of extensive DCIS, the clinical response to NST (if administered) and the genetic profile.

Radioactive seed localization during surgery

Surgery was guided by audible and visual feedback of a hand-held γ-detector probe (Neoprobe®; Johnson & Johnson Medical, Hamburg, Germany). The three-dimensional extent of tumor to be resected was determined using a combination of preoperative imaging modalities (mammography, ultrasonography and CE-MRI), and knowledge and expertise of the surgeon. For patients who underwent surgery after NST, tumor extent was determined...
on CE-MRI acquired shortly before surgery. For BCS, the surgeon aimed to resect a spherical volume of tissue including the tumor, the seed and a resection margin of 10mm beyond the identified tumor border. Resections were typically performed from the skin to the underlying fascia. In patients with a clinical complete response, the aim was to resect a margin of only 10mm around the $^{125}$I-labelled seed during BCS, independent of the original tumor extent. When multiple seeds were used for bracketing, a segmental block of tissue around the seeds was resected, ensuring removal of all seeds with an adequate margin. After surgery, the excision cavity was examined with the $\gamma$ probe to ensure that all seeds had been removed. The excised specimen containing the seed was stored in a lead container for transport to the pathology department. Additionally, a planar X-ray of the specimen was acquired to confirm the presence of the seed(s) in the specimen and/or lymph node. Removal of seeds in the axilla was performed before breast tumor removal. The $\gamma$ probe was used to scan the surface of the axilla. In patients undergoing BCS, a separate incision was made to remove the MARI node. In patients undergoing mastectomy, the incision was made close to the point of the greatest activity of the seed in the axilla, but still in the area of the planned incision for mastectomy.

Pathological examination

After inking, the breast tumor specimen was cut in 5-μm sections, and the seed was removed simultaneously guided by the $\gamma$ probe. Lymph nodes were bisected and embedded completely in paraffin. All blocks were cut at three levels with a minimum of 150-μm intervals. The seed was extracted from the lymph node specimen with use of a $\gamma$ probe. The seed(s) was placed in a lead container and transported to the long-term storage facility in the nuclear medicine department [30], [34]. Standard pathological assessment was done on the specimen. According to national guidelines, resection margins were considered negative when no invasive cells or carcinoma in situ cells were present on the inked edge of the excised specimen [35]. Margins were considered minimally involved when invasive cells or carcinoma in situ cells were found over a maximum length of 4mm on the inked edge of the specimen. If tumor cells were found on a length larger than 4mm or in multiple (small) areas, the resection margin was considered positive. The volume of the resection specimen was estimated using the formula for the volume of a cube. Dimensions of the resection specimen were measured in the pathology department before fixation and reported in the patient’s medical record.
Statistical analysis

The change in positive and minimally involved resection margin rates following the introduction of RSL (November 2007) was analyzed using a binary linear regression model. The change in median resection volume over time was analyzed with linear regression after log transformation of values. P < 0.05 was considered statistically significant. SPSS® version 20.0 (IBM, Armonk, New York, USA) was used for statistical computation.

Results

In total, 1263 patients with 1619 implanted seeds were included in the study (Figure 1). A total of 367 patients undergoing primary surgery for in situ carcinomas received 436 seeds, whereas 199 patients having initial surgery for invasive cancers received 236 seeds. In the NST group, 697 patients received 947 seeds. The MARI procedure was performed in 212 patients. Patient- and surgery-related data are shown in Table 1, and tumor characteristics in Table 2.

Primary surgery group with in situ tumors

A total of 375 tumors were localized in 367 patients. Single-seed RSL was used in 318 breast tumors, whereas multiple-seed RSL was applied in 54. Three patients underwent localization

![Figure 1](image-url)  
*Figure 1. Total number of seeds in the breast in patients undergoing radioactive seed localization before primary surgery for in situ breast carcinoma or invasive breast cancer, in patients having neoadjuvant systemic therapy (NST), and number used for marking of axillary lymph nodes, between November 2007 and April 2014.*
of a MARI node and had primary surgery because they declined the proposed NST. As expected, more patients underwent RSL under stereotactic guidance (33.6%) than in the NST group. RSL was performed mostly for localization of DCIS (79.7%) or benign lesions such as fibroadenomas (16.8%). Of the 367 patients, 342 (93.2%) actually underwent BCS (Table 1). BCS was guided by one seed in 292 operations, and the margins were complete, minimally involved and positive in 84.6%, 6.8% and 8.6% respectively. The other 50 BCS operations were guided by multiple seeds, with rates of complete, minimally involved and positive resection margins of 76%, 12% and 12% respectively. In the whole group, the rates of complete, minimally involved and positive resection margins following BCS were 83.3%, 7.6% and 9.1% respectively.

**Primary surgery group with invasive tumors**

A total of 206 invasive tumors were localized in 199 patients. Single-seed RSL was used in 174 breast tumors, and multiple-seed RSL in 29. Another three patients had localization of a MARI node and underwent primary surgery. Seed placement was performed mostly under ultrasound guidance (91.1%). The majority of the patients underwent RSL for localization of non-palpable invasive ductal carcinoma (81.3%) or invasive lobular carcinoma (13.8%). Of the 199 patients, 175 (87.9%) underwent BCS (Table 1). Resection margins were complete, minimally involved and positive in 81.6%, 9.2% and 9.2% of the 152 BCS procedures guided by one seed. In 23 patients (13.1%) BCS was guided by multiple seeds, with complete, minimally involved and positive resection margins in 17 (74%), three (13%) and three (13%) patients respectively. In the whole group, the rates of complete, minimally involved and positive resection margins after BCS were 80.6%, 9.7% and 9.7% respectively.

**Primary neoadjuvant systemic therapy group**

A total of 902 tumors were localized before NST in 697 patients. Single-seed RSL was used in 654 tumors and multiple-seed localization in 42. Seed implantation in a MARI node was performed in 206 patients. Almost all seeds (97.6%) were placed using ultrasound guidance. Biopsy before NST revealed mainly invasive ductal carcinoma (80.3%) and invasive lobular carcinoma (12.2%). Implanted seeds were still detectable at the time of surgery with a residual activity between 0.2 and 2.1 MBq. Some 401 (57.5%) of the 697 patients underwent BCS, and 268 (38.5%) had a mastectomy (Table 1). Twenty-six patients (3.7%) did not have any surgery at all, either at the patient's request or because of emerging metastatic spread. Of the 401 patients who had BCS, 376 operations (93.8%) were guided by one seed. Margins were complete, minimally involved and positive in 80.9%, 8.2% and 10.9% of procedures respectively. The other 25 BCS procedures were guided by multiple seeds, with minimally
involved and positive resection margins in one (4%) and four (16%) patients respectively. In the whole NST group, the rates of complete, minimally involved and positive resection margins after BCS were 80.8%, 8.0% and 11.2% respectively.

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Patients had metastasis or underwent surgery at another hospital. NST, neoadjuvant systemic therapy; RSL, radioactive seed localization; MARI, marking of axillary lymph node by radioactive iodine seed; BCS, breast-conserving surgery.

### MARI procedure for metastatic axillary nodes

A total of 206 patients underwent a MARI procedure. In the first years after implementation of this procedure, both removal of the MARI node and axillary lymph node dissection (ALND) was performed. The first 105 patients were included in a prospective trial to assess whether the pathological response in the MARI node was indicative of the pathological response in the additional lymph nodes. The results showed that in 7.1% of the patients positive nodes were found elsewhere in the axillary specimen while the MARI node was negative [31]. Thereafter, the clinical protocol was changed and the MARI procedure was used for staging after NST; patients with a clinically restricted tumor load in the axilla and a negative MARI

### Table 1. Patient- and surgery-related characteristics

<table>
<thead>
<tr>
<th></th>
<th>$^{125}$I- surgery-in situ</th>
<th>$^{125}$I- surgery-invasive</th>
<th>$^{125}$I- NST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of seeds</td>
<td>436</td>
<td>236</td>
<td>947</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>367</td>
<td>199</td>
<td>697</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>55 (27-89)</td>
<td>60 (27-85)</td>
<td>49 (19-84)</td>
</tr>
<tr>
<td>Single-seed RSL in breast</td>
<td>318</td>
<td>174</td>
<td>654</td>
</tr>
<tr>
<td>Multiple-seed RSL in breast</td>
<td>54</td>
<td>29</td>
<td>42</td>
</tr>
<tr>
<td>RSL in axilla (MARI)</td>
<td>3</td>
<td>3</td>
<td>206</td>
</tr>
</tbody>
</table>

### Type of surgery

<table>
<thead>
<tr>
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<th>$^{125}$I- surgery-invasive</th>
<th>$^{125}$I- NST</th>
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</thead>
<tbody>
<tr>
<td>Breast Conserving Surgery</td>
<td>342 (93.2%)</td>
<td>175 (87.9%)</td>
<td>401 (57.5%)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>22 (6.0%)</td>
<td>22 (11.1%)</td>
<td>268 (38.5%)</td>
</tr>
<tr>
<td>Axillary Lymph Node Dissection only</td>
<td>3 (0.8)</td>
<td>0 (0.0%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>No surgery*</td>
<td>0 (0.0%)</td>
<td>2 (1.0%)</td>
<td>26 (3.7%)</td>
</tr>
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</table>

### BCS guided by 1 seed

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<tr>
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<th>$^{125}$I- surgery-in situ</th>
<th>$^{125}$I- surgery-invasive</th>
<th>$^{125}$I- NST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete margins</td>
<td>292 (85.4%)</td>
<td>152 (86.9%)</td>
<td>376 (93.8%)</td>
</tr>
<tr>
<td>Minimally involved margins</td>
<td>20 (6.7%)</td>
<td>14 (9.2%)</td>
<td>31 (8.2%)</td>
</tr>
<tr>
<td>Positive margins</td>
<td>25 (8.7%)</td>
<td>14 (9.2%)</td>
<td>41 (10.9%)</td>
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</table>

### BCS guided by > 1 seed

<table>
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<tr>
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<th>$^{125}$I- surgery-in situ</th>
<th>$^{125}$I- surgery-invasive</th>
<th>$^{125}$I- NST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete margins</td>
<td>50 (14.6%)</td>
<td>23 (13.1%)</td>
<td>25 (6.2%)</td>
</tr>
<tr>
<td>Minimally involved margins</td>
<td>38 (76.0%)</td>
<td>17 (73.9%)</td>
<td>20 (80.0%)</td>
</tr>
<tr>
<td>Positive margins</td>
<td>6 (12.0%)</td>
<td>3 (13.0%)</td>
<td>4 (16.0%)</td>
</tr>
</tbody>
</table>
node during surgery were offered axilla-conserving surgery by removal of the MARI node and axillary radiation treatment. The remaining 101 patients with a MARI node were treated according to this new protocol. ALND was performed in 46 (45.5%) of these 101 patients. In the remaining 55 patients (54.5%) the axilla was treated by radiation therapy only, as there was a pathological complete response in the MARI node.

**Learning curves**

The learning curve for RSL was assessed by examination of the positive and minimally involved resection margin rates, and the median resection volume of the BCS specimens, over time (Figure 2).

*Primary surgery group with in situ tumors*

Among 342 patients who underwent BCS, the mean rates of positive and minimally involved resection margins were 9.1% and 7.6% respectively. No significant changes in positive (P=0.513) and minimally involved (P=0.548) resection margin rate over time were noted. The median resection volume was reduced from 72.0 cm$^3$ in 2008 to 38.3 cm$^3$ in 2014, but this reduction was not statistically significant (P=0.336).

*Primary surgery group with invasive tumors*

For the 175 patients who underwent BCS, the mean rate of positive resection margins throughout the years was 9.7%. There was no evidence of a significant change in positive resection margin rate following the introduction of RSL (P=0.669). However, there was a significant reduction in minimally involved resection margin rates over time (P<0.001), with a mean of 9.7%. The median resection volume also showed a significant time trend, and was reduced from 198.0 cm$^3$ in 2008 to 46.3 cm$^3$ in 2014 (P<0.001).

*Primary neoadjuvant systemic therapy group*

The mean rates of positive and minimally involved resection margins after BCS throughout the years were 11.2% and 8.0% respectively. Again, there was no evidence of changes in positive (P=0.242) and minimally involved (P=0.080) resection margin rates over time. The median resection volume was reduced significantly from 119.5 cm$^3$ in 2008 to 45.0 cm$^3$ in 2014 (P<0.001).

**Workflow**

Before RSL was implemented in November 2007, an institution-specific protocol was written that contained guidelines for the use of radioactive iodine seeds in the radionuclide
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laboratory, the radiology department, during surgery in the operating room and in the pathology department. An accompanying online form was devised, which is stored in each patient’s record, to track the location of the seed both before and after implantation. Despite the guidelines and the accompanying form, eight incidents occurred between 2008 and 2010 in the operating room, and radiology and pathology departments. A total of three seeds were lost and had to be reported to the health inspectorate. As a consequence, RSL procedures were stopped between January 2010 and June 2010 (Figure 1). An additional risk and safety analysis was performed, after which the accompanying form and department-specific protocols were adapted. Thereafter, another two incidents with seeds being lost in the operating room occurred in 2010 and 2011, and these were reported to the health inspectorate. Most probably, the lost seeds fell out of the resection specimen while being transported to the cup used for transportation to the pathology department. These incidents led to two adjustments in the operating room protocol: the people involved were instructed to scan the resection specimen in the cup to confirm the presence of \( ^{125}I \)-labelled seed, and to scan the excision cavity in the breast to ensure removal of seed from the patient. Both are performed with a \( \gamma \) probe that is capable of switching between the energy window

<table>
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<tr>
<th>Table 2. Tumor characteristics</th>
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<tr>
<td></td>
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<tr>
<td>Benign</td>
</tr>
<tr>
<td>is</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>not assessable</td>
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</tbody>
</table>

\( ^{125}I \)-surgery-in situ

|                          |          |          |          |
| Benign                  |          |          |          |
| is                      | 0 (0%) | -        | 6 (3.0%) |
| 1                       | 9 (4.5%) | -        | 9 (4.5%) |
| 2                       | 159 (79.9%) | -        | 151 (75.9%) |
| 3                       | 28 (14.1%) | -        | 25 (12.6%) |
| 4                       | 2 (1.0%) | -        | 5 (2.5%) |
| not assessable          | 1 (0.5%) | -        | 1 (0.5%) |

\( ^{125}I \)-surgery-invasive

|                          |          |          |          |
| Benign                  |          |          |          |
| is ***                  | 1 ** (0.1%) | 157 (22.5%) | 151 (21.7%) |
| 1                       | 15 (2.2%) | 59 (8.5%) | 70 (10.0%) |
| 2                       | 89 (12.8%) | 109 (15.6%) | 272 (39.0%) |
| 3                       | 378 (54.2%) | 251 (36.0%) | 156 (22.4%) |
| 4                       | 206 (29.6%) | 114 (16.4%) | 27 (3.9%) |
| not assessable          | 8 (1.1%) | 4 (0.6%) | 3 (0.4%) |

\( ^{125}I \)-NST

|                          |          |          |          |
| Benign                  |          |          |          |
| is ***                  | 0 (0.0%) | 3 (0.4%) | 18 (2.6%) |

Values in parentheses are percentages. *Seeds were placed mainly in fibroadenomas or other benign lesions (ductal hyperplasia, etc.). †This patient received neoadjuvant systemic therapy (NST) for an invasive carcinoma, but also underwent radioactive seed localization for a sclerotic papilloma in the contralateral breast. ‡In situ carcinoma in combination with an invasive carcinoma.
of the 125I-labelled seed (27 keV) and the liquid technetium (140 keV) [36]. The resection specimen is also scanned with the γ probe at both settings in the pathology department. This is especially important if both breast tumor and sentinel node are removed during the same surgical procedure. Since these adjustments, no other seeds have been lost.

![Graphs showing resection margins and volume](image)

**Figure 2.** a–c Rate of minimally involved and positive resection margins, and d–f median resection volume, for patients undergoing radioactive seed localization before primary breast-conserving surgery (BCS) for in situ breast carcinoma (a, d) or invasive breast cancer (b, e), and in patients having neoadjuvant systemic therapy (NST) before BCS (c, f), between November 2007 and April 2014. Values in parentheses are number of BCS procedures each year. Error bars show the binomial confidence interval.
Discussion

This study has shown that RSL can be used to facilitate breast- and axilla-conserving surgery. There was a significant reduction in resection specimen volume for patients with non-palpable invasive tumors who underwent primary surgery and in patients who had NST, while the positive resection margin rates were low and stable over the years in all three groups. The present study included a large and diverse patient population, reflecting the real-life clinical scenario of most breast units.

The rate of initial complete resection in single-seed RSL-guided BCS for clinically occult breast cancer was 84.6% and 81.6% for patients having primary surgery for in situ and invasive tumors respectively. The definition of positive resection margins was based on the Dutch guidelines [35]: the finding of tumor cells on a length of more than 4mm or on multiple (small) areas in the resection specimen. The definition of positive resection margins is not uniform in previous studies of RSL, varying between residual tumor cells at the resection plane or at a distance of 2mm from the resection plane. In these studies, the positive resection margin rates varied between 3 and 27 per cent for radioactive seed-guided BCS using a single seed [29], [37]. The mean rates of incomplete surgery (minimally involved and positive resection margins) of 15.4% and 18.4% after primary BCS for in situ and invasive tumors respectively in the present cohort compare favorably and can be considered as a clinically acceptable level, especially in comparison with the mean positive margin rates achieved with ROLL (9–30%) and WGL (13–58%) [11]. Both ROLL and WGL are associated with more complex logistics than RSL. With ROLL, injection of technetium, and additional scintigraphy to verify correct diffusion of the technetium tracer into the tumor and lymph nodes, have to be performed on the day before surgery. In WGL, the wire needs to be inserted 1 day before or on the day of surgery, and the procedure is associated with patient discomfort [38], [39]. RSL does not require any additional pre-operative procedures. Migration of the seed in the breast is negligible and independent of time in situ [32]. Furthermore, the γ probe used is capable of distinguishing the activity of both liquid technetium (140 keV) and iodine-labelled seeds (27 keV), which makes removal of the breast tumor and the sentinel node possible during the same procedure.

The use of RSL was extended by multiple-seed implantation to facilitate BCS in patients with more extensive DCIS and multifocal invasive tumors. Bracketing such tumors with multiple wires was first described in 1987, in an attempt to offer patients BCS instead of mastectomy [40]. Several studies have reported the use of multiple-wire localization in patients with diffuse DCIS or multifocal invasive tumors [23], [41]. In the present cohort, a total of 83 patients in the primary surgery groups had multiple seeds implanted in the breast. BCS was
actually performed in 73 of these patients, of whom 75% had complete resection margins. Thus 55 of 73 patients with multiple seeds underwent successful BCS who would otherwise have been candidates for mastectomy. Furthermore, the total rate of incomplete surgery among patients with multiple seeds (24% (12 of 50) and 26% (6 of 23) for in situ and invasive tumors respectively) compares favorably with rates obtained when multiple wires are used (56–58%) [23], [41]. These results further encourage the use of multiple seeds in patients with extensive DCIS or multifocal invasive tumors, to enable BCS with acceptable positive resection margin rates.

At the authors’ institute, all patients undergo RSL before NST. This policy has the advantage that BCS can be performed in patients with a clinical complete or partial response, without any additional localization procedures. Another option would be to place clips before NST and subsequently use RSL only in patients with a clinical complete or partial response in whom BCS is indicated [42]. This is especially applicable in countries where it is not permitted legally to leave a $^{125}$I-labelled seed in situ for several months. In the Netherlands, $^{125}$I-labelled seeds can be left in the patient for the whole duration of NST, in some instances up to 12 months. In the present study, 57.5% of patients in the NST group underwent BCS; the mean rate of complete resection margins was high and stable during the years, at 80.9% for patients in whom one seed was used and 80% for those who received multiple seeds. Three other studies have reported on the use of RSL in the NST setting. In the study by Gobardhan and colleagues [43], rates of minimally involved and positive resection margins were 4 and 2 per cent respectively for patients with unifocal tumors who had single-seed RSL, and both 6 per cent for patients with multifocal tumors in whom multiple seeds were used. Resection margins were defined according to Dutch guidelines, as in the present study. However, the positioning of multiple seeds was not clearly described in relation to tumor edges. The second study [10] reported a mean rate of 6.0% incomplete surgery, but the definition of incomplete surgery was not clearly described, so a fair comparison cannot be made with the present findings. In the third study [34], ROLL (83 patients) and RSL (71) were compared in patients treated with BCS after NST. The rate of incomplete surgery was similar in both groups (13%). Although there was no difference in incomplete surgery rate in that study, RSL remains the preferred localization technique at the Netherlands Cancer Institute, as clinical response monitoring with good tumor localization is possible during and at the end of NST.

CE-MRI is the most helpful tool for assessing response in these patients, but is not completely reliable. In particular, BCS after NST for diffuse or extensive tumors, which often show non-mass enhancement on MRI, will always be associated with a risk of incomplete resection margins owing to diffuse tumor growth [44]. In the present study, 157 patients in the NST group showed a clinical complete response before surgery as determined by clinical examination.
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and no enhancement at MRI, but only 151 of these had a pathological complete response in the resection specimen. RSL is especially useful in patients in whom there is discordance between the clinical and pathological response, as it provides accurate surgical guidance towards the original tumor bed, even after months of NST, and is essential for complete removal of all tumor cells.

In terms of learning curves, the rate of positive resection margins was low and stable in all three groups over the study interval. The significant reduction in the rate of minimally involved resection margins in patients undergoing primary surgery for invasive cancer can probably be explained by the high rate in the first year in which RSL was introduced. Comparable results were achieved in another study28 that reviewed the first 1000 single- and multiple-seed RSL procedures for localization of non-palpable breast lesions. In the present cohort, time trends for resection volume were similar for patients in the groups undergoing surgery for invasive tumors and those having NST, with the median resection volumes being reduced by more than 50 per cent. Large reductions in median resection volume were noted especially in the first years after introduction of RSL. This was probably due to the point-source guidance provided by the seed and experience gained with RSL-guided surgery. Furthermore, the introduction of NST regimens has led to more frequent downsizing of the tumor load before surgery. Better imaging techniques, mainly CE-MRI, have made clinical response evaluation at the end of NST more reliable, leading to more realistic tumor volume estimations before surgery. It is likely that these smaller resection volumes have led to better cosmesis and patient satisfaction [45], [46].

By using the MARI procedure it is technically possible to mark proven metastatic axillary lymph nodes with 125I-labelled seeds before the start of NST. The MARI node can subsequently be used for staging after NST. Patients with a clinically restricted tumor load in the axilla and a negative MARI node after NST can be offered axilla-conserving surgery by removal of the MARI node followed by axillary radiation treatment.

Two other institutes [47], [48] have also reported on the introduction of RSL into clinical practice. They noted that RSL was a safe and effective procedure, easy to learn, and allowed simplified operative scheduling in patients with non-palpable invasive or in situ breast tumors. In comparison with these studies, here the use of RSL was extended further to include patients with larger palpable tumors or with metastatic axillary lymph nodes, and by using multiple-seed RSL in patients with diffuse and extensive tumors. The present results are in line with previous findings, even in a more diverse patient population. However, there are still requirements that remain necessary for successful implementation of RSL into clinical practice [32]. First, it is important that handling of every seed is documented properly
in a specific patient record. An online form is useful for tracking the location of the seed before and after implantation. Second, safe use of RSL can be achieved only if protocols are evaluated regularly and all involved personnel are aware of the associated risks.

Seven years of experience with more than 1200 patients has shown the applicability of RSL in four clinical situations: for localization of non-palpable in situ carcinomas, larger invasive carcinomas and axillary lymph nodes, and the use of multiple-seed RSL in patients with extensive/diffuse tumors such that they can be offered BCS instead of a standard mastectomy. Use of RSL has enabled precise BCS in terms of steady, low positive resection margin rates and significantly lower resection volumes over the years. Successful implementation of RSL into clinical practice requires a dedicated multidisciplinary team and regular evaluation to maintain its safe use.

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