Integrating new imaging modalities in breast cancer management
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Heading towards radioactive seed localisation in non-palpable breast cancer surgery? A meta-analysis

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Abstract

Wire-guided localisation is the most commonly used technique for intraoperative localisation of non-palpable breast cancer. Radioactive seed localisation (RSL) is becoming more popular and seems to be a reliable alternative for intraoperative lesion localisation. The purpose of the present meta-analysis was to evaluate the use of RSL. Primary study outcomes were irradicality and re-excision rates. In total 3168 patients were included. The clinical adaptation shows growing confidence in RSL and further growth is expected.
Introduction

Three decades of breast cancer screening changed the patient population of breast cancer patients dramatically. Two requirements for screening, with the purpose to reduce the mortality, are: the time of diagnosis should advance and early treatment should have advantages over treatment at the time of clinical presentation. [1] With these assumptions in mind, women from all over the world receive mammograms when reaching a certain age. Nowadays, incidence-based mortality studies with longer follow-up periods among European women invited for screening show a general reduction of breast cancer mortality. [2] However, discussion remains on whether or not this reduction is caused by screening, or that other factors, such as changes in the systemic treatment or improvements in diagnostic imaging, may also be held responsible. [3]

Breast cancer screening has changed the type and stage of detected breast cancer lesions. More than 25% of the radiological suspicious breast lesions are considered clinically occult or non-palpable. [4] The surgical removal of non-palpable breast tumours requires a specific approach. The main challenge of resecting non-palpable lesions is to ensure clear margins while minimizing the resection of healthy-tissue and cosmetic damage. [5] For this purpose, three different techniques are used for intraoperative tumour localisation; wire, ultrasound (US), and radioguided localisation (i.e. guided by a radiopharmacon or radioactive marker). At present, wire-guided localisation (WGL) is still the most commonly used technique for non-palpable breast cancer (75%). [4, 6] Nonetheless, wire placement is a cumbersome technique for both the surgeon and the patient. The limitations of WGL include 1) technical complications such as wire dislodging [7,8], migration [9–11], kinking or fracture; 2) logistic challenges as the wire is to be placed a maximum of one day in advance of surgery; 3) higher patient discomfort as opposed to alternative techniques, [12,13] and 4) poor cosmetic outcome [14, 15]. Dislodging and poor localisation are causes for relatively high irradicality rates for WGL ranging from 10% to 50%. [4,8,16–23] Radioguided occult lesion localisation (ROLL) was developed in 1996, and is nowadays used in several institutes as a reliable alternative for WGL. [5,20,24–29] The principle of this technique consists of an image (frequently ultrasound and stereotaxis) guided intratumoural injection of a radioactive tracer (most commonly used is $^{99m}$Technetium ($^{99m}$Tc) macroaggregate albumin), which is retained within the tumour and can be detected by the
surgeon using a gamma probe. More recently, in 1999, a radioguided procedure called radioactive seed localisation (RSL) was introduced. \cite{30,31} RSL is based on the implantation of an $^{125}$iodine ($^{125}$I)-seed in the centre of the tumour under mammographical or ultrasound guidance, also allowing intraoperative localisation using a gamma probe. Transcutaneous measurements determine the location of the maximum $^{125}$I gamma counts, which is marked on the skin, and accordingly the incision is made at this site. The gamma probe is further used to guide the excision of the $^{125}$I-seed and lesion. Correct $^{125}$I-seed removal is confirmed by a measurement of no $^{125}$I-signal in the wound and an $^{125}$I-signal measurement in the specimen. Several advantages of RSL over ROLL have been described; one of which is the source geometry of the $^{125}$I-seeds. The seed is a fixed metal point source, of which the position with respect to the tumour can be validated using mammography, instead of a gradually diffusing radiotracer that is used in a ROLL procedure. A second advantage of the $^{125}$I-seed is its relatively long half-life of 60 days, which allows its use in patients that are treated with primary systemic treatment prior to surgery.

Accordingly, $^{125}$I-seeds are now used as standard clinical care in a number of hospitals worldwide. Many of which have reported their experiences in single centre studies. Through this meta-analysis we aim to evaluate the clinical use and performance of RSL in localisation of breast lesions during breast conserving surgery. In this setting, the performance of RSL was measured by factors such as the irradicality of resection margins and the need for secondary surgery.

**Methods**

**Search strategy**

To retrieve all relevant literature, a broad search was performed in the electronic databases of PubMed, Medline, Scopus, and Cochrane using a query syntax consisting of “breast cancer” and “radioactive seed localisation” including synonyms like: “RSL”, “radio guided seed localisation”, “breast”, and “$^{125}$iodine-seeds”. The references of the found papers were examined to identify additional articles. Additionally, the same query was used in Google Scholar to identify additional articles.

The PubMed search query performed the 26th of March 2014 resulted in a total of 35 citations. This same query performed in Scopus resulted in 51 citations and 2 citations in Cochrane. All query results were compared and unique records were denoted.
Eligibility criteria

Studies were included in the meta-analysis if they met all of the following inclusion criteria: (1) Articles published or submitted up to March 2014, (2) availability of the full text article in English, and, (3) evaluating the performance of RSL, whether or not compared to other techniques.

The primary endpoints for this meta-analysis were irradicality and secondary surgery. Secondary endpoints included information on the excision times, resected volume, complications, the surgeon’s preference, the used surgical techniques, the indications for implantation, and the type of $^{125}$I-seed. Articles were included when at least one of the outcomes was evaluated. All authors were contacted for information on missing parameters and information on potential overlap between studies from the same institute or author. This resulted mainly in additional information about the activity of the $^{125}$I-seeds and information about overlap between studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Study type</th>
<th>Institute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray et al. (2001)</td>
<td>43</td>
<td>A retrospective review of a prospective database</td>
<td>Lee Moffitt Cancer Centre, Tampa, Florida</td>
</tr>
<tr>
<td>Gray et al. (2001)</td>
<td>51</td>
<td>Prospective</td>
<td>Lee Moffitt Cancer Centre, Tampa, Florida</td>
</tr>
<tr>
<td>Cox et al. (2003)</td>
<td>64</td>
<td>Prospective</td>
<td>Lee Moffitt Cancer Centre, Tampa, Florida</td>
</tr>
<tr>
<td>Gray et al. (2004)</td>
<td>100*</td>
<td>Prospective</td>
<td>Mayo clinic, Scottsdale, Arizona</td>
</tr>
<tr>
<td>Hughes et al. (2008)</td>
<td>383*</td>
<td>Prospective</td>
<td>Mayo clinic, Scottsdale, Arizona</td>
</tr>
<tr>
<td>Riet et al. (2009)</td>
<td>47</td>
<td>Data were collected prospectively, Retrospective matched-pair analysis</td>
<td>Catherina hospital Eindhoven</td>
</tr>
<tr>
<td>Rao et al. (2010)</td>
<td>33</td>
<td>Retrospective matched-pair analysis</td>
<td>University of Texas, Southwestern Medical centre Dallas,Texas</td>
</tr>
<tr>
<td>Riet et al. (2010)</td>
<td>325</td>
<td>Prospective</td>
<td>Catherina hospital Eindhoven</td>
</tr>
<tr>
<td>Lovrics et al. (2011)</td>
<td>152</td>
<td>Prospective, randomized, multicentre study</td>
<td>McMaster University and St. Joseph's Healthcare Hamilton Canada</td>
</tr>
<tr>
<td>McGhan et al. (2011)</td>
<td>767</td>
<td>Retrospective</td>
<td>Mayo clinic, Scottsdale, Arizona</td>
</tr>
<tr>
<td>Alderliesten et al.</td>
<td>48</td>
<td>Prospective</td>
<td>NKI AVL Amsterdam The Netherlands</td>
</tr>
<tr>
<td>Dauer et al. (2013)</td>
<td>1223</td>
<td>Retrospective</td>
<td>Memorial Sloan-Kettering Cancer Centre New York</td>
</tr>
<tr>
<td>Donker et al. (2013)</td>
<td>71</td>
<td>Retrospective</td>
<td>NKI AVL Amsterdam The Netherlands</td>
</tr>
<tr>
<td>Gobardhan et al. (2013)</td>
<td>85</td>
<td>Retrospective</td>
<td>Amphia Hospital, Breda, Tilburg The Netherlands</td>
</tr>
<tr>
<td>Murphy et al. (2013)</td>
<td>431*</td>
<td>Data from prospectively maintained, registered database</td>
<td>Memorial Sloan-Kettering Cancer Centre New York</td>
</tr>
<tr>
<td>Sung et al. (2013)</td>
<td>232*</td>
<td>Retrospective review</td>
<td>Memorial Sloan-Kettering Cancer Centre New York</td>
</tr>
</tbody>
</table>

*Included in another study  **124 included in another study
Included articles

The search strategy included 30 unique records. All of the 30 articles were included for full text evaluation. Finally, 4208 patients in 16 articles were eligible for inclusion based on the outcome parameters. (Figure 1: flow chart). [30–45] After contact with the authors we concluded that only 12 articles included original patients, 1 article contained original patients and patients from previously reported studies, and 3 articles contained a patient population that overlapped with previously reported work. Excluding all double patients resulted in 3168 individual patients. Though, the data from Murphy et al. (431 RS procedures) and Sung et al. (232 RSL procedures), was also included by Dauer et al. (1223 RSL procedures) [40,43,44] However, Dauer et al. did not report all parameters, and therefore, this article was excluded for the analysis of the irradicality rate and the re-operation rate, accordingly the work of Murphy et al. and Sung et al. was included to include as many as possible RSL procedures for the primary outcomes. The paper by Hughes et al. (383 procedures) with both original RSL procedures (259) and RSL procedures (124) later used in McGhan et al. as well was entirely included for statistical analysis since the different groups were described all together in the paper. [34,45] Altogether 2732 patients in 14 articles were included for the rate of irradicality. [30–32,34–39,41–45]

Statistical evaluation

Accordingly, all parameters were tabulated for the meta-analysis. For statistical analysis all outcomes were described in averages corrected for sample size. For the graphical display we used forest plots to visualize the results of the irradicality, one of the primary outcomes. In the visualisation the squares around the average values stands for the accuracy of the estimation (sample size) and the horizontal line represents the 99% CI. Funnel plots were generated to visually assess potential publication bias (not added to the paper). Results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. [46]

Results

Characteristics of the included studies

This meta-analysis included articles published between 2001 and 2014. The first two articles describing the use of RSL were published in 2001 by Gray et al. performed at the Lee Moffitt Cancer Centre in Tampa (Florida, USA). [30,31] The first article describing the use of RSL in Europe was published by van Riet et al. in 2009. [35,36]
The majority of the articles consisted of prospectively collected data and all of the studies were single centre studies except for one multi-centre and one multi-site study. [34,38] Six studies compared RSL direct with WGL and 1 compared it to ROLL. [30,33,34,37,38,41,43] We will however not elucidate in depth the performances of WGL and ROLL within this article, for further reading on this subject we refer to a review from Lovrics et al. [26]

The number of patients included in the different studies ranged from 33 to 1223 patients. The therapeutic regimes in which RSL was used varied from application of the technique in a neoadjuvant chemotherapy (NAC) setting to a pure surgical approach. Three articles focused just on patients with NAC, 3 articles combined NAC and non-NAC patients, and 8 articles described usage without NAC.

**Primary & secondary outcomes**

All study characteristics and results are listed in Tables 1+2. Non-palpable breast cancer included ductal carcinoma in situ (DCIS), Invasive Ductal Carcinoma (IDC), Lobular carcinoma in situ (LCIS), Invasive Lobular Carcinoma (ILC), and other infiltrating types. The average age of patients was 60.4 years (range: 27-93 years old).

**Irradicality & second surgery:** Though in all included studies the primary endpoint 'irradicality of resection margins' was defined, there was no consensus on this definition, which ranged from tumour cells in the resection plane itself to tumour cells at a distance of 2mm to the resection plane. Taking the definitions of the articles into account, in 2732 patients 10.3% (range: 3-30.3) of the procedures was irradical and 14.2% (range: 4-42) of 2415 patients in 12 studies underwent secondary surgery. The indications for secondary surgery differed between institutes and is higher than the percentage of irradical procedures because some centres perform additional surgery at margins <2mm. The irradicality is visualized by a Forest plot in Figure 2. The 3 studies only including patients after NAC had irradicality rates <15%, the non-NAC and NAC group are respectively only 8 and 3 studies and therefore not suitable to compare, further is the patient population different and would a statistical comparison be unrealistic. (Figure 3)

**Surgery time:** Only 4 articles describe the RSL or total surgical procedure time varying from 5.4 to 50 minutes. This parameter is not further evaluated because of the low reporting rate and the high variety in these outcomes.
Excision volume: The volumes or weight of tissue excised is denoted in 5 studies (for this study, weight is converted in volume). The volume is estimated based on the weight to have all the measures in the same parameter. The average volume of 5 studies (1077 patients) was 86cc (range: 0.2-311) excised tissue. Further evaluation about the effect of the specimen volume on the irradiability rate demonstrated no apparent correlation and is difficult in interpret because of varying patient populations and the fact that this parameter misses for most studies.

Complications: Of the 14 included articles, 8 studies described the complication rate. There were no complications in 2 articles and 5 articles described low complication rates ranging from 0.4% to 2% and 1 study reported a complication rate of 12.1%. This variation in complication rate is most likely caused by differences in the definition of complications between institutes. In general, the main complications were related to either the surgery (e.g. wound infections, hematoma and cellulites) or directly to the use of the $^{125}\text{I}$-seed (e.g. seed misplacement in 3 cases, vasovagal response to deployment of seed in 4 cases, failure to deploy in 3 cases, wrong incision in 1 case, seed migration in 1 case, or seed loss in 1 case).

Costs: Both Cox et al., Rao et al., and McGhan et al. included a paragraph about the costs associated with RSL. McGhan et al. described the positioning for RSL favourably with costs of 60 US dollars instead of 170 for WGL. However, this was a large cohort study and therefore potentially more cost-efficient. When looking just at the material costs, RSL is roughly 15-40 US dollars compared to 20 US dollars for WGL. Rao et al. describe the costing of 17 US dollars for seed and 21 US RSL dollars for WGL[32,37,47]

Table 2: Results and outcome parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Studies</th>
<th>No of patients</th>
<th>Average (SD, Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irradicality</td>
<td>16</td>
<td>2732</td>
<td>10.3% (3-30.3)</td>
</tr>
<tr>
<td>Re-excision</td>
<td>14</td>
<td>2415</td>
<td>14.2% (4-42)</td>
</tr>
<tr>
<td>RSL time</td>
<td>4</td>
<td>866</td>
<td>(5.4-50min)</td>
</tr>
<tr>
<td>Volume (cc)</td>
<td>5</td>
<td>1077</td>
<td>86cc (0.2-311)</td>
</tr>
<tr>
<td>Complications</td>
<td>8</td>
<td>2461</td>
<td>No complications to 12.1%</td>
</tr>
<tr>
<td>$^{125}\text{I}$-activity</td>
<td>15</td>
<td>3292</td>
<td>3-13MBq</td>
</tr>
<tr>
<td>Age</td>
<td>12</td>
<td>2638</td>
<td>60.4 years (27-93)</td>
</tr>
<tr>
<td>NAC or non-NAC</td>
<td>14</td>
<td>2732</td>
<td>3xNAC, 8xnon-NAC, 3x combined.</td>
</tr>
<tr>
<td>Study type</td>
<td>16</td>
<td>4055</td>
<td>7x retrospective, 9x prospective</td>
</tr>
</tbody>
</table>
Marker characteristics

The different institutes used a variety of $^{125}\text{I}$-seed activities, ranging from 3 to 13 MBq. In the recent studies from 2013 a trend is evolving towards the use of seeds with lower activities. This might be the result of a chancing paradigm, from the early days when hot $^{125}\text{I}$ brachytherapy seeds were used, to a more standardized procedure in which low-activity $^{125}\text{I}$-seeds dedicated for RSL are used. After contacting the institute where 13 MBq $^{125}\text{I}$-seeds were used, they confirmed that 8 MBq seeds were used in their current clinical protocol.

The brands of the used $^{125}\text{I}$-seeds within this meta-analysis were limited to:

- **Best 125 Iodine-seed**, Best Medical International, Inc. Springfield, VA, USA, distributed by MPM Medical, Freehold, NJ, USA (used by Sung et al.)[44]
- **BrachySource I-125 seed**, BARD Inc, Covington, USA (used by Gobardhan et al., Alderliesten et al., and Donker et al.)[39,41,42]
- **Iodine-125 seed**, Cardinal Health, Woodland Hills, CA, USA (used by Gray et al., Hughes et al.)[31,34]
- **Iodine-125**, Draximage, Montreal, Canada (used by Lovrics et al.)[38]
- **IsoSeed® 125**, Bebig Isotopen-und Medizin Technik, Berlin, Germany (used by Riet et al.)[35]
- The $^{125}\text{I}$-seeds of the different brands vary little with respect to design, dose-rate constant, anisotropy function, radial dose function, and anisotropy factor. Additionally, all types are approximately of the same size (+- 4 mm long axis, 0.8mm short axis).
Surgical techniques

All articles described roughly the same surgical procedures, consisting of: (1) transdermal localisation of the highest activity with a handheld $^{125}$I-gamma probe before incision, (2) the gamma probe guides the resection of the tumour, and (3) as verification method for the $^{125}$I-seed removal, the absence of $^{125}$I-detection with the gamma probe in the breast. Moreover, localisation of the $^{125}$I-seed in the specimen is confirmed by measuring radioactivity in the excised tissue. Some institutes perform additional specimen radiographs to precisely localize the $^{125}$I-seed in the specimen. Accordingly, the specimen is transported for pathological examination. The ex vivo specimen radiographs can be used to direct cavity re-excition but are mostly used as confirmation of $^{125}$I-seed removal.

Multiple studies describe the RSL procedures in combination with sentinel lymph node biopsies (SLNB). The SLNB uses the radioisotope $^{99m}$Tc. This radioisotope has an energy peak of 140 keV but due to the Compton effect there are photons with energy that overlapping the energy spectrum of $^{125}$I and therefore could potentially affect the procedure (figure 4). Because of this overlap in energy spectrum there is a risk that the gamma probe in the $^{125}$I setting receives counts from the $^{99m}$Tc signal, resulting in a wide

Figure 2: Forest plot of the irradicality rate per study. [30–45] The studies that included patients from other articles are listed as well, although not taken into account for the statistics of this specific parameter. [33,40]
local excision based on the $^{99m}$Tc activity instead of an excision based on the activity of the radioactive iodine seed. This can be avoided by cautious evaluated protocols for the combination procedure. All studies describe that choosing the energy windows specifically for the energy peak of the isotopes of interest makes sure that the signal is specific enough for detection of just the isotope of interest without measuring the other isotope.

Five articles describe the preference of the surgeon. In 5 studies the RSL procedure was ranked as easy to learn and had the surgeon’s preference. [26,30,34,40,45] This is mainly because surgeons feel familiar with the RSL technique since it uses commonly used techniques (e.g. gamma probe) and therefore it is easy to learn.

**Discussion**

The purpose of the present meta-analysis was to evaluate all studies reporting breast cancer patients having intraoperative tumour localisation by RSL. An increase in the incidence of non-palpable breast cancer and a likely further increase in the future because of more advanced detection techniques demands for accurate intraoperative localisation techniques. The commonly used WGL has, as previously described, certain disadvantages that may be overcome by using RSL. Wire placement follows another route than the surgical removal and causes therefore difficulties in placement considering skin incision and locating the tip of the wire. RSL overcomes this problem by easier placement and detection. RSL also overcomes some of the disadvantages of ROLL by being a point source and being detectable on a mammogram.

The first publications on RSL appeared more than 14 years ago and the in last 3 years the publication rate is rising, as is the total number of patients in studies. (Figure 5) These figures take only data into account of centres using RSL and publishing about it.

To our knowledge there are more centres using this technique.

Our study included 16 articles of which 12 articles had 100% unique patients. The studies were prospective and retrospective studies with patient populations ranging from 33 to 1223. 2732 patients were included for weighted average analysis of different parameters. The different approaches and experiences of the institutes were described and important parameters as the irradicality rates and re-excision rates were tabulated. Other outcome values as the procedure time, volume, weight, and tumour size were not recorded in all studies. An interesting secondary outcome was the $^{125}$I-seed activity, which varied between different institutes. Optimizing the $^{125}$I-seed activity may safe
significant radiation exposure for patients. Furthermore, the irradicality rate was different for institutes, possibly due to the definition of irradical, and therefore difficult to compare.

**Figure 4:** This graph demonstrates the relation between $^{99m}$Tc and $^{125}$I in black and red. The black curve is the $^{125}$I-signal, as seen in the graph the $^{99m}$Tc is prevalent in the window of $^{125}$I and thereby influences the count rates of $^{125}$I.

The overall irradicality rate varied between 3 to 30.3% with a weighed average of 10.3%. This reported irradicality rate falls within the normal range comparing it with other techniques, with irradicality rates varying from 10-50%. One study comparing ROLL with RSL by Donker et al. included 154 patients after neoadjuvant systemic therapy, and demonstrated no significant difference between these techniques 7 vs. 8%. [22,23,41] Six studies compared RSL with WGL. [30,33,34,37,38,43] Respectively the percentages of irradicality for the different studies comparing WGL vs. RSL were; Gray et al. 57 vs. 26, Gray et al 24 vs.10, Hughes et al. 46 vs. 27, Rao et al. 27 vs. 30, Lovrics et al. 12 vs. 11, and Murphy et al. 6 vs. 8. Though, these results are not entirely conclusive, 3 studies show a significantly better performance of the RSL technique, while in 3 other studies the technique showed a better performance, though these differences were not significant different. The overall percentage of irradicality that we found in this study for 2732 patients seems to be within the low range of irradicality rates of WGL. Of the aforementioned comparison studies, only Murphy et al. had a better irradicality rate of 5.5% compared to our average of 10.3%, their RSL irradicality
rate was also better than average with 7.7%. The most recent status report from the annual meeting of the American society of breast surgeons reported that in the first studies lower rates of positive margins, re-excision, and reduced operative time for radioguided surgery were observed when applying RSL. Later studies with more patients demonstrated a smaller impact on the rate of positive margins although no study showed a higher rate of positive margins while using radioguided surgery. [48] Limitations of the results are the missing data for some of the parameters. This may lead to publication bias of certain outcome parameters.

There is no study mentioning the radiation exposure, in terms of effective patient dose, to patients induced by this technique, especially when the $^{125}\text{I}$-seed is implanted prior to neoadjuvant therapy.

Considering costs and surgeons preference, RSL is the technique of choice at our institute. Since handling and disposal of the radioactive seeds comes with an extensive legislative process, it is an investment to start the use $^{125}\text{I}$-seeds in a save manner within the clinical setting. However, once the logistics for safe use of this technique are organized, the advantages of the other aspects of the procedure outweigh this effort.

As mentioned before, surgical planning of patients is more flexible and most important, the patient discomfort decreases when using this technique. With the current available techniques we believe that $^{125}\text{I}$ RSL will establish a more prominent position in the management of surgery for non-palpable breast cancer. Other applications will also gain more interest: e.g. $^{125}\text{I}$-seeds can be implanted in the axillary lymph node containing metastasis to assess the pathological nodal response after neoadjuvant systemic treatment. Thereby axilla-conserving surgery in patients with good response can possibly be accomplished. [49,50] And recently the first publications for its use in local radiation therapy for long lesion / liver metastasis / Lymph nodes in head and neck area are published. [51-53]

The use of radioisotopes enables the possibility to improve radioguided surgery; in recent years navigation techniques to guide the surgeon to the lesion have been introduced. Freehand-SPECT for $^{125}\text{I}$-seeds or portable gamma cameras are examples and are more increasingly used in clinical practice. [54,55]
Figure 5: Publication rate per year. There are 2 articles in 2013 that are also part of another paper published in 2013.

**Conclusion**

The findings of the present study indicate that RSL is a reliable surgical technique for patients with non-palpable breast lesions. The clinical adaptation in the past decade shows a growing confidence of this technique and further growth is expected.

**Acknowledgements**

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References


