Improvements in locoregional treatment of breast cancer
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GUIDING BREAST-CONSERVING SURGERY IN PATIENTS AFTER NEOADJUVANT SYSTEMIC THERAPY FOR BREAST CANCER. A COMPARISON OF RADIOACTIVE SEED LOCALIZATION WITH THE ROLL TECHNIQUE


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Guiding breast-conserving surgery after systemic treatment

ABSTRACT

Background
Radioguided occult lesion localization (ROLL) with technetium-99m colloid (ROLL-99mTc) is commonly used to perform breast-conserving surgery in patients with nonpalpable breast tumors. Radioactive seed localization is a relatively new technique that localizes the tumor with a radioactive iodine-125 (125I) seed. The feasibility and outcome of these techniques after neoadjuvant systemic treatment has not been widely investigated.

Methods
All patients treated with neoadjuvant systemic treatment between 2007 and 2010 in the Netherlands Cancer Institute who underwent breast-conserving surgery with the ROLL-99mTc technique (n = 83) or with 125I seed localization (n = 71) were analyzed. The weight of the resected specimen, the margins, and the percentage of patients requiring a second surgical intervention as a result of positive margins were assessed.

Results
Patient and tumor characteristics and systemic treatment regimens were comparable between both groups. The median weight of the resected specimen (53 vs. 48 g), the median smallest margin (3.5 vs. 3.0 mm), and the risk for additional surgery for incomplete resections (7 vs. 8 %) did not differ significantly between patients treated with the ROLL-99mTc technique and 125I seed localization.

Conclusions
The ROLL-99mTc technique and 125I seed localization demonstrate comparable results when used to perform breast-conserving surgery after neoadjuvant systemic treatment. Because 125I seed localization does not require additional radiological localization shortly before surgery, it simplifies surgery scheduling. Therefore, we prefer 125I seed localization to perform breast-conserving surgery after neoadjuvant systemic treatment.
INTRODUCTION

Neoadjuvant systemic treatment, also known as primary, induction, or preoperative systemic treatment, is considered the standard of care for the management of locally advanced breast cancer and is also increasingly used for women with earlier stage disease. An important aim of neoadjuvant systemic treatment is to decrease the size of the primary tumor, thereby allowing breast-conserving therapy. Indeed, neoadjuvant chemotherapy results in a decrease of tumor volume to such an extent that breast-conserving surgery can be performed in 25 to 32 % of the patients who were originally scheduled for mastectomy. Complete pathological response rates after neoadjuvant systemic treatment vary across histological subtypes and can be as high as 65 %, while complete clinical response rates are even higher. Because it is difficult to localize the original tumor bed after a complete clinical and radiological response, marking the tumor before the start of neoadjuvant systemic treatment is required to enable breast-conserving surgery afterwards. The pathological confirmation of the response of the original cancer bearing area is mandatory because even after a complete radiological response about half of the patients do have residual microscopic cancer. Wire localization is currently the standard method for surgical excision of nonpalpable breast lesions. However, this localization technique is associated with high rates of positive margins, leading to reoperations, an increased risk of local recurrences and a poor cosmetic outcome. In the Netherlands Cancer Institute (NKI–AVL), two alternative methods are used to localize nonpalpable breast cancer after primary systemic treatment. With the ROLL-99mTc technique a twist marker is inserted into the tumor before the start of neoadjuvant systemic treatment. Before surgery, a small amount of nanocolloid labelled with technetium (99mTc) marks the original tumor bed. The second localization technique uses a radioactive iodine (125I) seed to mark the tumor before the start of the systemic treatment. When comparing these techniques, most studies demonstrated a lower rate of positive margins after breast-conserving surgery with 125I seed localization or with the ROLL-99mTc technique as compared to wire-localization.

In the present observational study, we compared the ROLL-99mTc technique and 125I seed localization in patients who were treated with breast-conserving surgery after neoadjuvant systemic treatment. Outcome parameters were the weight of the resected specimen, the rate of tumor free margins and the percentage of patients requiring a second surgical intervention due to positive margins.

PATIENTS AND METHODS

Patients
All patients treated with neoadjuvant systemic treatment for invasive breast cancer between January 2007 and December 2010 at the NKI–AVL were eligible for this study. During the inclusion period, patients with invasive breast cancer >3 cm and/or involved lymph nodes were eligible for treatment within a neoadjuvant systemic treatment protocol. The tumor size was assessed clinically and with contrast-enhanced magnetic resonance imaging (MRI). Before neoadjuvant treatment, biopsies of the breast tumor were performed to determine the histological subtype and receptor status. Tumors were classified according to the standard criteria of the World Health Organization. Nodal status before neoadjuvant systemic treatment was determined by ultrasound-guided fine-needle aspiration or, when negative, sentinel node biopsy before the start of systemic treatment. This study was approved by the institutional ethical...
committee and informed consent was obtained from all patients. Adjuvant radiotherapy and systemic treatment were given according to Dutch national guidelines.

**Tumor localization**
Before the start of the systemic treatment, the tumor was localized under ultrasound guidance. In case of the ROLL-99mTc technique, a radiopaque O-shaped twist marker (BARD GmbH, Türkenfeld, Germany) was inserted in the centre of the tumor. In case of 125I seed localization, an iodine-125-radiolabelled (125I) seed (STM1251, Bard Brachytherapy, Inc., Carol Stream, IL, USA) with a half-life time of 60 days used. The 125I seeds arrived at the Department of Radiology in a single lead vial and were inserted into the tumor via an 18 gauge needle. In general one 125I seed was used to mark the tumor, except for two patients with a multifocal tumor in whom three 125I seeds were inserted to mark the different lesions. The 125I seed is a source of photon radiation with an average energy of 27 keV. The titanium-encapsulated seeds are 4.5 x 0.8 mm and are available with a minimum apparent activity of 0.2 mCi. Although the dose of the 125I seeds used for localization of breast tumors is low, it requires authorization by the Dutch government. Furthermore, some safety issues need to be addressed. Storage and surveillance of the 125I seeds is organized in our Nuclear Medicine Department. Radiation safety protocols and detailed documentation regarding the acquisition, handling and storage including guidelines for patients and hospital staffs are described previously.21 In both procedures a mammography was performed to confirm correct placement of the twist marker (Fig. 1a) or the 125I seeds (Fig. 1e).

**Neoadjuvant systemic treatment and response evaluation**
All patients received neoadjuvant systemic treatment (Table 1). Contrast-enhanced MRI (Philips Medical Systems B.V., Best, the Netherlands) was used for response evaluation as reported previously by our group.9,22 After completion of the systemic treatment and just before surgery, an MRI was performed to determine the response and decide whether breast-conserving surgery could be offered to the patient. Patients without enhancement in the original tumor area on MRI after systemic treatment were considered complete radiological responders.

**Planning and accomplishment of breast surgery**
In case of the ROLL-99mTc technique, on the day before \( n = 55 \) or on the day of surgery \( n = 28 \), a dose of 0.2 ml nanocolloid (Amersham Cygne, Eindhoven, the Netherlands) labelled with 99mTc (average dose of 37 MBq) was injected into the centre of the residual tumor or, in case of a complete radiological response, at the site of the twist marker. After this injection, a scintigraphy with planar anterior and prone lateral images with hanging breast was obtained with a dual-head gamma-camera (Siemens, Symbia T, Erlangen, Germany) in order to check the correct placement of the tracer at the site of the injection and to exclude leakage (Fig. 1b). In case of 125I seed localization, surgery was performed after the systemic treatment without additional localization procedures. The wide local excision was guided by a handheld gamma-probe (Neoprobe, Johnson & Johnson Medical B.V., Hamburg, Germany) at its lowest sensitivity setting. This gamma-probe is equipped with a 99mTc setting as well as an 125I setting and can therefore be used for both procedures by switching the setting (Fig. 1c, f). The excision was performed from skin to the pectoral fascia. The extent of the excision was based on the results of the MRI that was made after completion of the systemic treatment and before surgery. In patients with a complete radiological response, only a limited excision was performed around the 99mTc or the 125I seed, and no intention was made to
remove the complete initial tumor bed. In these patients the aim of surgery was to confirm this response by pathological examination of a specimen from the former tumor bed. In case of a partial radiological response, the aim of the local excision was to remove all residual enhancing tumor seen on MRI. Adequate removal of the marked tumor bed was confirmed by the absence of background radioactivity in the remaining breast tissue. A specimen mammography was performed after excision of the breast tumor in both procedures to confirm the presence of either the twist marker or the $^{125}$I seed in the specimen (Fig. 1d, g). In case of $^{125}$I seed localization, the specimen was stored in a lead container equipped with a radioactivity warning sticker before being transported to the pathology department.

In patients with a positive sentinel node (>0.2 mm) or axillary lymph node metastases proven by fine needle aspiration before neoadjuvant systemic treatment, an axillary lymph node dissection was performed during the same operation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ROLL-99mTc (n=83)</th>
<th>$^{125}$I seed (n=71)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [Median (range)]</td>
<td>50 (28-69)</td>
<td>49 (31-68)</td>
<td>0.219</td>
</tr>
<tr>
<td>Clinical tumor stage prior to systemic treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>8 (10%)</td>
<td>6 (7%)</td>
<td>0.133</td>
</tr>
<tr>
<td>T2</td>
<td>53 (73%)</td>
<td>61 (72%)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>10 (14%)</td>
<td>18 (21%)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Clinical nodal stage prior to systemic treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (SNB-)</td>
<td>18 (22%)</td>
<td>20 (28%)</td>
<td>0.352</td>
</tr>
<tr>
<td>N+ (SNB+/FNA+)</td>
<td>65 (78%)</td>
<td>51 (72%)</td>
<td></td>
</tr>
<tr>
<td>Tumor histopathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma</td>
<td>74 (89%)</td>
<td>65 (92%)</td>
<td>0.652</td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td>6 (7%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Other invasive type</td>
<td>3 (4%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Receptor-based subtype*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER- / PR- / HER2-</td>
<td>16 (19%)</td>
<td>19 (27%)</td>
<td>0.540</td>
</tr>
<tr>
<td>ER+ / HER2-</td>
<td>38 (46%)</td>
<td>30 (42%)</td>
<td></td>
</tr>
<tr>
<td>HER2+</td>
<td>29 (35%)</td>
<td>22 (31%)</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant systemic treatment regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ddAC*</td>
<td>48 (58%)</td>
<td>48 (68%)</td>
<td></td>
</tr>
<tr>
<td>CD^</td>
<td>4 (5%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>PTC†</td>
<td>25 (30%)</td>
<td>19 (27%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (7%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Patient- and tumor-related characteristics

No: no clinical evidence of lymph node metastasis, including a negative ultrasound and sentinel node biopsy negative or only isolated tumor cells; N+: Axillary lymph node metastasis diagnosed by fine needle aspiration or metastasis ≥0.2 mm in sentinel node biopsy; Nx: lymph node status unknown; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor.

*Receptor-based subtype as established on the pre-systemic treatment biopsy.

# Doxorubicine 60 mg/m² and Cyclophosphamide 600 mg/m² q 2 weeks x 6.

^ Docetaxel 75 mg/m² and Capecitabine 1,000 mg/m² BID orally during 14 days, q 3 weeks x 6.

† Paclitaxel 70 mg/m², Trastuzumab 2 mg/m² and Carboplatin AUC-3 mg/ml/min on days 1, 8, 15, 22, 29, 35 q 8 weeks x 3
Guiding breast-conserving surgery after systemic treatment

Pathological examination and outcome parameters
The total weight of each specimen was recorded. In case of $^{125}$I seed localization the pathologist extracted the $^{125}$I seed from the specimen with benefit of a gamma-radiation detector. Consequently, the $^{125}$I seed was placed in a lead container and transported to the long-term storage facility at the Nuclear Medicine Department.

For the analysis of the tumor response to the systemic treatment, we defined a complete pathological response of the breast as the absence of invasive carcinoma in the specimen at microscopic examination, regardless of the presence of carcinoma in situ.$^{23}$ The response was classified as pathological partial response when residual invasive tumor was still present. In case of a pathological partial response, the margins of the specimen were examined. The margin was defined as the smallest distance from the invasive part of the tumor to the nearest edge of the excised specimen. The margins were defined as clear when no invasive cells or carcinoma in situ cells were present in the margin on microscopic evaluation.

Statistical analysis
The outcome of patient- and tumor characteristics and postoperative parameters between both groups was compared using a $\chi^2$ test for dichotomous variables and Wilcoxon rank sum test for continuous variables. A $p$ value of $<0.05$ was considered statistically significant.

RESULTS
Patient characteristics
A total of 178 breast cancer patients underwent breast-conserving surgery after neoadjuvant systemic treatment during the inclusion period. In 24 patients, the tumor was still palpable or excision was performed using a different localization method. From the remaining 154 patients, breast-conserving surgery was performed with the use of ROLL-$^{99m}$Tc technique in 83 patients and with the use of $^{125}$I seed localization in 71 patients. There was no significant difference between both groups in patient and tumor characteristics (Table 1).

Tumor localization
In all cases the twist marker or $^{125}$I seeds were placed in the correct position, as confirmed by mammography. No radiologist experienced difficulties with placing the twist marker or the $^{125}$I seed, and no complications occurred.

Radiological and pathological response
Complete radiological response occurred in 42 of 83 (51 %) patients treated with the ROLL-$^{99m}$Tc technique, a complete pathological response was observed in 25 patients (30 %). Among patients treated with $^{125}$I seed localization, complete radiological response occurred in 36 of 71 (51 %) patients and a complete pathological response was seen in 27 patients (38 %) (Table 2).
Table 2. Treatment outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ROLL-$^{99m}$Tc (n=83)</th>
<th>$^{125}$I seed (n=71)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary dissection</td>
<td>65 (78%)</td>
<td>49 (69%)</td>
<td>0.190</td>
</tr>
<tr>
<td>Radiological response MRI after systemic treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>41 (49%)</td>
<td>35 (49%)</td>
<td>0.990</td>
</tr>
<tr>
<td>Complete response</td>
<td>42 (51%)</td>
<td>36 (51%)</td>
<td></td>
</tr>
<tr>
<td>Pathological response after systemic treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual tumor</td>
<td>58 (70%)</td>
<td>44 (62%)</td>
<td>0.301</td>
</tr>
<tr>
<td>Complete response</td>
<td>25 (30%)</td>
<td>27 (38%)</td>
<td></td>
</tr>
<tr>
<td>Weight of resected specimen</td>
<td>Median in g (range)</td>
<td>53 (11-204)</td>
<td>48 (9-346)</td>
</tr>
<tr>
<td>Margin</td>
<td>Median in mm (range)</td>
<td>3.5 (0-15)</td>
<td>3.0 (0-12)</td>
</tr>
<tr>
<td>Resection of invasive part</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical</td>
<td>72 (87%)</td>
<td>62 (87%)</td>
<td>0.915</td>
</tr>
<tr>
<td>Irradical</td>
<td>11 (13%)</td>
<td>9 (13%)</td>
<td></td>
</tr>
<tr>
<td>Number of surgical interventions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resected in prim surgery</td>
<td>77 (93%)</td>
<td>65 (92%)</td>
<td>0.778</td>
</tr>
<tr>
<td>Resected in 2nd surgery</td>
<td>6 (7%)</td>
<td>6 (8%)</td>
<td></td>
</tr>
<tr>
<td>Intervention needed for incomplete excision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6 (7%)</td>
<td>6 (8%)</td>
<td></td>
</tr>
<tr>
<td>Re-resection</td>
<td>1 (1%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>5 (6%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

Surgical outcome

At the time of surgery, the $^{125}$I seeds were in situ for a median time of 17 weeks (range, 8–31 weeks). Because of the long half-life time of 60 days, the seed is still traceable during surgery. None of the surgeons experienced difficulties in performing a local excision around the $^{125}$I seed, nor when the lesion was localized with $^{99m}$Tc. At the Pathology Department, the presence of the inserted twist marker or $^{125}$I seed in the specimen was confirmed in all patients.

The surgical outcomes are listed in Table 2. The median weight of the specimen was comparable for both study groups: 53 g (range, 11–204 g) in the group of patients treated with the ROLL-$^{99m}$Tc technique and 48 g (range, 9–346 g) in the group of patients treated with $^{125}$I seed localization.

Eleven of the 83 patients (13%) treated with the ROLL-$^{99m}$Tc technique had positive margins at pathology examination. Five of these patients were treated with adjuvant radiotherapy with a boost on the original tumor bed, because of a positive margin involving the pectoral fascia ($n=1$) or only focally positive margins ($n=4$). The remaining six patients with positive margins underwent a second surgical intervention. One patient was treated with an additional local excision and the other five patients underwent a mastectomy.

Nine of the 71 patients (13%) treated with $^{125}$I seed localization had pathologically positive margins. Three of these patients were treated with adjuvant radiotherapy with a boost on the original tumor bed, because of a positive margin involving the pectoral fascia ($n=2$) or only focally positive margins ($n=1$). The remaining six patients with positive margins underwent a second surgical intervention. Three patients were treated with an additional local excision and the other three patients underwent a mastectomy.
The median margin of resected residual tumor was 3.5 mm (range, 0–15 mm) in the group of patients treated with ROLL-99mTc technique and 3.0 mm (range, 0–12 mm) in the group of patients treated with $^{125}$I seed localization.

**Follow-up**

No major postoperative complication occurred in both groups. After a median follow-up of 51 months (range, 5–67 months), 15 of the 83 patients treated with the ROLL-99mTc technique experienced recurrence of their disease: one DCIS local recurrence in the ipsilateral breast, two regional recurrences in the periclavicular region with concurrent distant metastasis, and twelve patients presented with distant metastases without evidence of loco-regional recurrence. Six women died as a result of their distant disease recurrence after a mean follow-up of 22 months (range, 4–45 months).

The median follow-up of the 71 women treated with $^{125}$I seed localization was 32 months (range, 11–53 months). Seven patients developed distant metastases and one patient presented with a locoregional recurrence and concurrent distant metastases. Those eight patients died within 24 months of follow-up. No isolated local recurrences occurred in this group.

**DISCUSSION**

One of the most important goals of neoadjuvant systemic treatment as opposed to adjuvant systemic treatment is to increase the chance for breast-conserving surgery in women who were originally scheduled for a mastectomy. To safely omit a mastectomy, reliable measurement of the tumor response is required. Although the imaging modalities for response monitoring are improving, histological examination of a biopsy of the former tumor bed remains the golden standard. To enable a local excision of the former tumor bed after a clinical complete response, it is crucial to precisely mark the tumor before admission of neoadjuvant systemic treatment.

As described in the introduction, there are several methods to localize nonpalpable breast cancer. Localization with an $^{125}$I seed or with the ROLL-99mTc technique have several advantages in common as opposed to the more commonly used wire-localized excision, which is currently the standard method of excision of nonpalpable breast lesions. Both $^{125}$I seed localization and the ROLL-99mTc technique are easy radiological and surgical procedures to perform, and the tumor can be identified in three dimensions offering great flexibility in making a cosmetic incision. Incorrect placement of the marker, the radiotracer or the $^{125}$I seed is rare and an average lower weight of the specimen has been reported. When compared to wire-localization, both the ROLL-99mTc technique and the $^{125}$I seed localization were the preferred method by surgeons and ranked by patients as less painful. And most importantly, excellent results in terms of tumor-free margins were observed with both $^{125}$I seed localization and the ROLL-99mTc technique. Although in a randomized trial from Lovrics et al., similar results were reported with regard to involved margins, when $^{125}$I seed localization was compared to wire localization, most other studies demonstrated a lower rate of positive margins after $^{125}$I seed localization or the ROLL-99mTc technique compared to wire localization. Because of these advantages we currently use these two methods in our institute. Van Riet et al. demonstrated that $^{125}$I seed localization in breast cancer patients who underwent breast-conserving surgery after neoadjuvant chemotherapy, was a successful technique leading to a high percentage of negative margins. When comparing this new method to the ROLL-99mTc technique, we did not see
a significant difference in the percentage of patients who required a second surgical intervention to obtain negative margins (8 vs. 7%). Furthermore the median weight of the lump (48 vs. 53 g) and the median smallest margin (3.0 vs. 3.5 mm) were comparable.

The ROLL-\(^{99m}\)Tc technique has the advantage that it is in general easy to introduce in a centre as a localization technique because it uses techniques and materials that are already used in most clinics, e.g., for the sentinel node procedure. A disadvantage of the ROLL-\(^{99m}\)Tc technique is the short half-life time of 6 hours of the \(^{99m}\)Tc. The injection of the \(^{99m}\)Tc is conducted under ultrasound guidance and this radiological intervention has to be performed shortly before surgery. This may therefore lead to scheduling conflicts for the surgeon, the radiologist, and hospital staff. Moreover, this technique requires two separate invasive procedures for the patient: marking the tumor with a metal marker before the start of systemic treatment and an injection with \(^{99m}\)Tc to visualize the tumor bed before surgery. This disadvantage can be overcome with the use of \(^{125}\)I seed localization. Because of the long half-life of the \(^{125}\)I seed of 60 days, the \(^{125}\)I seed can be placed before the start of the neoadjuvant systemic treatment, e.g., directly after a breast biopsy procedure or standard imaging, it will still be traceable after completion of the systemic treatment, and does not interfere with the sentinel node procedure.

In none of the patients the surgeons experienced difficulties to trace the \(^{125}\)I seed, even when it had been in situ for more than half a year. In addition, the \(^{125}\)I seed is a point source of radiation unable to diffuse, as opposed to the fluid used in the ROLL-\(^{99m}\)Tc technique, and migration of the seed is rarely seen.\(^{15,21,25}\) Theoretically, this enables a more precise excision, without unnecessary removal of healthy tissue.

We concluded that \(^{125}\)I seed localization is an attractive method for localizing breast tumors before neoadjuvant systemic treatment to enable breast-conserving surgery and has essentially replaced the traditionally placed twist marker in our tertiary-care medical center. In hospitals without \(^{125}\)I seed availability, the ROLL-\(^{99m}\)Tc technique is a good alternative provided that a radiopaque marker is placed before the start of the systemic treatment.
REFERENCES


