The role of radioactive iodine-125 seed localization in breast-conserving therapy following neoadjuvant chemotherapy

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Background: Neoadjuvant chemotherapy (NAC) is increasingly used in the framework of breast-conserving therapy (BCT). Localization of the initial tumor is essential to guide surgical resection after NAC. This study describes the results obtained with I-125 seed localization in BCT including NAC.

Patients and methods: Between January 2009 and December 2010, 85 patients treated with NAC and BCT after I-125 seed localization were included. Radiological and pathological response and resection margins were retrospectively evaluated.

Results: BCT was carried out in 85 patients without secondary local excisions. Nineteen patients with unifocal tumors and seven patients with multifocal tumors showed a complete pathological response ($P = 0.18$). Tumor-free resection
interest of the present study was to evaluate the use of I-125 as an insuf
locoregional recurrence when treated with BCT. In the case of multifocal tumors, there may be an increased risk of radical resection of the primary tumor [13, 14]. Especially in tumors is important in order to carry out an oncological solution to bridge the interval between NAC and subsequent surgery. A relatively new technique is the implantation of iodine-labeled titanium seeds (I-125 seed). Some studies have already reported successful use of I-125 seed implantation in primary non-palpable breast tumors [6–9]. Until now, only one small study reported on resection of unifocal breast cancer following NAC and cCR [10]. The results of I-125 seed implantation in order to mark multifocal tumors eligible for BCT after NAC have not been previously published. The use of one or more I-125 seeds provides optimal per-operative three-dimensional orientation, especially in technical more challenging procedures like for residual multifocal tumors. In comparative studies on different localization techniques of non-palpable breast tumors, I-125 seed localization was preferred by surgeons because of its easy use and navigation possibility, perioperative logistics and patient comfort [6–9].

Some studies reported a non-significant increase in locoregional recurrence rate following NAC and BCT in patients who were initially scheduled for mastectomy [2, 11, 12]. Therefore, precise localization of the original tumor site, especially in case of remission after NAC or in multifocal tumors is important in order to carry out an oncological radical resection of the primary tumor [13, 14]. Especially in multifocal tumors, there may be an increased risk of locoregional recurrence when treated with BCT. In the case of an insufficient localization technique, a considerable number of patients may be withheld from the benefits of BCT. The main interest of the present study was to evaluate the use of I-125 as a marker in breast cancer patients treated with NAC and initially suitable for BCT. We evaluated the ability of I-125 seeds to guide adequate oncological resections as an alternative for conventional localization techniques, in both unifocal and multifocal breast cancers.

patients and methods

the study cohort

Between January 2009 and December 2010, a total of 97 patients underwent I-125 seed localization in combination with NAC. Of these, eight patients were scheduled for mastectomy based on initial tumor parameters. The remaining 89 patients were initially candidates for BCT.After completion of NAC four patients requested mastectomy themselves leaving 85 patients available for analysis in our study. Demographic data and information regarding the diagnosis, tumor size and response, surgery and pathology results were collected. The local medical ethics committee approved the routine use of I-125 seed implantation in breast cancer patients in our hospital. The experience and use of I-125 seeds were already approved in a neighboring hospital before without any reported side-effects [10]. At that time, one of the authors (EL) worked closely together with that group and introduced thereafter the I-125 seeds in our hospital in 2009. All patients received written information regarding the localization procedure and the administered radiation dose due to seed implantation.

diagnosis

All patients were diagnosed with invasive breast cancer, histologically confirmed by ultrasound (US)-guided core biopsy. Tumors were classified as either unifocal or multifocal on magnetic resonance imaging (MRI). Multifocal tumors were defined as two or more, pathologically confirmed, lesions within a ductal lobular unit (DLU), which is a triangular 60 to 70 degree-shaped breast segment from the nipple–areolar complex to the peripheral margin of the glandular tissue [15]. Tumors extending beyond a single DLU were defined as multicentric and therefore not suitable for BCT. Pathological tumor characteristics, including histological subtype, hormonal receptor status and Her2-neu amplification, were determined from the core biopsy. In case of suspicious axillary lymph nodes on US, a fine needle aspiration biopsy was carried out. If negative, as well as in clinical node negative patients, a sentinel lymph node biopsy (SLNB) was carried out before NAC. An oncologic surgeon, a medical oncologist, pathologist, radiologist and radiation oncologist carried out a multidisciplinary assessment of all patients before starting NAC.

i-125 placement

Before the start of NAC, a titanium seed containing 7 MBq of Iodine-125 (BARD Inc, BrachySource, Covington, USA) was injected into the tumor bed as described by Gray et al. [7, 8] using US guidance. The 4.5 by 0.8 mm seed was loaded into an 18 Gauge needle. The tip was sealed with sterile bone wax to prevent loss of the seed before introduction into the...
Substantial difference was seen during MRI evaluation. In tumor diameter, stable disease (SD) included tumors in which no progressive disease (PD) in case of a radiological tumor increase of >20% on MRI.

A cCR is defined as no visible residual tumor on MRI. For multifocal breast cancer, the size was measured including the gap between the tumor localizations. A cCR is defined as no visible residual tumor on MRI. Stable disease (SD) included tumors in which no progressive disease (PD) in case of a radiological tumor increase of >20% on MRI.

During surgery, we can detect the I-125 gamma-source as a 27 keV signal separately from the 140 keV radiation of Tc-99 m used for the SLNB.

Radiation dose to family members can be estimated from the calculations of the air kerma rate at 1 m from an unshielded 7 MBq I-125 source. Published data on the physics of modern brachytherapy reveal that an effective dose of 0.5 mSv can be derived for a full decay of the source at a point at a distance of 1 m. It is very unlikely that a family member would stay that close over prolonged periods of time, it is clear that the effective dose limit for public exposure of 1 mSv per year [18] will not be exceeded even when multiple sources are implanted. Tissue very near the source will be irradiated to a dose in the order of 3.8 Gy at a distance of 1 cm, under the assumption of an implant duration of 4 months and 4.7 Gy after 8 months. This would be the dose to a tissue volume of ~4 cm³, of which most parts will be removed during the surgical procedure.

Chemotherapy
NAC was administered accordingly to the Dutch national guidelines [19], and consisted of six courses of docetaxel (Taxotere, Myene Pharma, USA), adriamycin and cyclophosphamide (Baxter, USA) (TAG). In patients with Her2-neu amplified tumors (Her2-neu positive), four courses of adriamycin and cyclophosphamide (AC) were followed by 12 weekly courses of paclitaxel (Taxol, Dumex, Denmark) and trastuzumab (TH). In Her2-neu-positive patients and reduced left ventricular ejection fraction an alternative chemotherapeutic regime consisting of a combination of carboplatin (Myene Pharma, USA), paclitaxel and trastuzumab was administered.

Tumor response evaluation
Initial tumor size and response to chemotherapy were evaluated by MRI according to the RECIST (Response Evaluation Criteria in Solid Tumors) criteria [20]. All initial tumor sizes were based on MRI findings. In the case of multifocal breast cancer, the size was measured including the gap between the tumor localizations. A cCR is defined as no visible residual tumor on MRI.

Clinical partial response (cPR) was defined as regression of at least 30% in tumor diameter on consecutive MRIs. Tumors were classified as progressive disease (PD) in case of a radiological tumor increase of >20% in tumor diameter. Stable disease (SD) included tumors in which no substantial difference was seen during MRI evaluation.

Surgery
Lumpectomy (using oncoplastic techniques on indication), together with an axillary lymph node dissection (ALND) in the case of initially confirmed axillary lymph node metastases, followed 4–6 weeks after completion of NAC. A hand held gamma probe (Europrobe, EuroMedical Instrument, le Chesnay, France) is used during surgery and positioned over the anterior surface of the breast for navigation in order to obtain an optimal resection of the specimen. After resection, both the gamma probe and specimen X-rays are used to identify the I-125 seed ex vivo. No postoperative healing problems were seen due to previous I-125 seed(s) insertion.

Pathology
Pathological examination was carried out according to the standard procedures including removal of the I-125 seed(s). The latter were returned to the Nuclear Medicine Department for further processing of radioactive materials according to the Dutch regulations on nuclear energy [16].

A complete pathological response (pCR) is defined by the microscopically absence of residual tumor cells in the resection specimen. Modified Bloom and Richardson (BR) grade [21] and mitotic activity index (MAI) could not be assessed in the case of pCR since grading based on the core biopsy was not routinely carried out. Radical resection was defined according to Dutch guidelines on breast cancer treatment. Radical resection is defined as a tumor-free resection margin. Focally involved tumor margins were defined as tumor involvement in ≤4 mm of the dyed resection margin. Extensively involved margins included those in which tumor involvement extended beyond 4 mm [19].

Adjuvant radiation therapy/hormonal therapy
All patients underwent subsequent radiation therapy in the framework of BCT according to the Dutch national guidelines [19]. All receptor-positive patients received adjuvant hormonal therapy.

Statistical analysis
Statistical analyses were carried out using the SPSS software version 18.0 (SPSS Inc., Chicago, USA). A descriptive analysis was carried out using chi-square tests for categorical variables and the T-test for mean differences between continuous variables in unifocal tumors versus multifocal tumors. All statistical tests and P values were two tailed and P values of <0.05 were considered significant.

Results
From January 2009 to December 2010, 89 patients underwent breast surgery following NAC and I-125 seed implantation. BCT was carried out in 85 patients (96%). Four patients (4%) requested a mastectomy themselves and were excluded from this study.

Fifty-three patients (62%) had a unifocal and 32 (38%) a multifocal tumor. Baseline characteristics for both the groups are shown in Table 1. The overall tumor size of multifocal tumors, including the gap between the tumor localizations, was larger as compared with unifocal tumors (3.7 cm versus 3.0 cm P = 0.01). BR grade preceding NAC was more frequently unknown in the multifocal breast cancer group (19% versus 46% P = 0.04). Estrogen receptor (ER) status was positive in 57% of the unifocal versus 78% of the multifocal breast cancers (P = 0.04). Triple negative breast cancers were found in 21 patients, 15 patients (28%) with a unifocal tumor versus 6 (19%) with a multifocal tumor.

I-125 localization
In all 85 patients, US-guided implantation of one or more I-125 seeds was carried out successfully. In 63 patients (74%), one seed was placed, in 22 patients (22%) two seeds and in one patient (1.2%) three seeds. I-125 seed(s) were in situ for a median of 4 months (range 0–8 months) with a mean of 3.65 (SD 1.7 months) from insertion till date of surgery.
adjuvant radiotherapy/hormonal therapy
All patients received postoperative radiation therapy. Hormonal treatment was given to all hormone receptor-positive patients (67%) of whom three premenopausal patients underwent an additional ovariectomy. The 23 patients (27%) who had Her2-neu receptor amplification continued trastuzumab for 1 year.

clinical response
cCR was obtained in 26 patients (31%), 17 of the patients with a unifocal (32%) and nine of the patients with a multifocal tumor (28%, Table 2). cPR occurred in 51 patients (60%), including 30 patients with a unifocal (57%) and 21 patients with a multifocal tumor (66%). In the remaining eight patients (six unifocal and two multifocal tumors), no significant response was found on MRI and documented as SD. PD not responding to any chemotherapy and thus necessitating mastectomy in patients who were originally planned for BCT did not occur in this cohort.

pathological response
After completion of NAC, all patients underwent the initially planned BCT. No residual tumor (pCR) was found in 19 patients (36%) with a unifocal and in seven patients (22%) with a multifocal tumor (P = 0.18). The resection was microscopically complete in 78 patients (92%): 50 patients with a unifocal (94%) and 28 patients (88%) with a multifocal tumor (P = 0.27). Focally involved margins were found in four patients: two (6%) with a unifocal and two (4%) with a multifocal tumor (P = 0.29). No residual cancer was found in the specimen of these patients. A second local excision was not required in any of the patients. No disturbing radiation effects were seen in the specimen evaluated by the pathologists due to the inserted I-125 seeds. Also, no wound healing problems were observed.

Table 1. Baseline characteristics for 85 breast cancer patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unifocal versus multifocal</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Total (N = 85)</td>
<td>Unifocal (N = 53)</td>
</tr>
<tr>
<td>Age in years (range)*</td>
<td>51 (41–62)</td>
<td>51 (40–62)</td>
</tr>
<tr>
<td>Age in years (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>38 (45)</td>
<td>22 (41)</td>
</tr>
<tr>
<td>50–59</td>
<td>28 (33)</td>
<td>20 (38)</td>
</tr>
<tr>
<td>60–69</td>
<td>19 (22)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>≥70</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Tumor size (%)d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>4 (5)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>2–5 cm</td>
<td>69 (81)</td>
<td>46 (87)</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>12 (14)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Bloom–Richardson grade (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>18 (21)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>II</td>
<td>24 (28)</td>
<td>14 (26)</td>
</tr>
<tr>
<td>III</td>
<td>13 (15)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>30 (36)</td>
<td>24 (46)</td>
</tr>
<tr>
<td>MAI (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>29 (34)</td>
<td>13 (24)</td>
</tr>
<tr>
<td>≥10</td>
<td>6 (7)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>50 (59)</td>
<td>36 (68)</td>
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<tr>
<td>Histological type (%)</td>
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<td></td>
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<tr>
<td>Ductal</td>
<td>80 (94)</td>
<td>49 (92)</td>
</tr>
<tr>
<td>Lobular</td>
<td>5 (6)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Receptor status (%)</td>
<td></td>
<td></td>
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<tr>
<td>Triple negative (ER-/PR-/Her2-neu-)</td>
<td>21 (24)</td>
<td>15 (28)</td>
</tr>
<tr>
<td>ER positive (%)</td>
<td>55 (65)</td>
<td>30 (57)</td>
</tr>
<tr>
<td>Progesterone receptor positive (%)</td>
<td>51 (60)</td>
<td>28 (53)</td>
</tr>
<tr>
<td>Her-2-neu receptor positive (%)</td>
<td>23 (27)</td>
<td>15 (28)</td>
</tr>
</tbody>
</table>

ER, estrogen receptor; MAI, mitotic activity index; PR, progesterone receptor.
*Mean (range).
bStudent’s t-test.
Chi-square.
dInitial size of the tumor (unifocal)/largest tumor in the case of multifocal tumor involvement (MRI measurement).
*Due to the use of neoadjuvant chemotherapy BR-grade (36%), MAI (59%) and Her2-neu (27%) could not always be estimated.
Clinical response (%)a of 11 months. Associated with a poor prognostic outcome [22]. Preoperative importance in BCT to avoid local recurrences which are complete tumor-free resection margins are of utmost discussion. In the case of pCR resection margins are scored as tumor free. Chi-square. aClinical size measured with MRI. bChi-square. cIn the case of pCR resection margins are scored as tumor free.

No local recurrences were observed after a mean follow-up of 11 months.

discussion

Complete tumor-free resection margins are of utmost importance in BCT to avoid local recurrences which are associated with a poor prognostic outcome [22]. Preoperative localization is considered essential for BCT following NAC. In our study, I-125 seed tumor localization resulted in complete tumor excision rates of 92%. Proper placement of the seeds and the advantage of an accurate three-dimensional orientation during surgery are plausible explanations for this high rate of complete resections. This is in line with reports comparing conventional guide-wire versus I-125 seed localization in early breast cancer showing involved margin rates ranging from 11% to 27% [6–9]. Moreover, the I-125 seed localization technique has been reported to be preferred by surgeons because of its easy use with reduced operative times and better preoperative navigation [9]. Due to the long half-life of 60 days, detection by a gamma probe remains feasible after >4 months during which NAC is administered. The conventional guide-wire technique would also require an additional intervention, preceding surgery, creating additional logistic challenges as well as increased patient discomfort.

According to the Dutch consensus on quality control of surgical breast cancer treatment, irradical resection at the first attempt for early invasive breast cancers should be <20% in BCT [19]. In an attempt to facilitate a complete resection, several localization techniques, including guide-wire, radio-guided occult lesion localization (ROLL) and preoperative US have been used with involved margin rates sometimes exceeding >20% [23]. In BCT following NAC, even higher rates of tumor involvement of the resection margins may be expected due to larger initial tumor sizes especially in the case of a limited response to NAC and in the case of multifocal disease.

In the search for more accurate localization techniques, better discrimination between tumor involved versus normal breast tissue during surgery is an interesting target for research. Near-infrared fluorescence techniques are promising for future breast cancer surgery [24]. Until that time, localization of tumor margins with markers that can accurately define the region which should be resected seems to be the best achievable. Localization methods using injection of radioactive Nanocolloid containing fluids might diffuse in the breast tissue, thereby limiting precise resection especially in multifocal disease. Skin tattooing as an alternative preoperative localization technique before NAC has been found inferior to placement of metallic markers [25]. The latter are not traceable necessitating secondary localization with a guide wire. A multicenter retrospective analysis of 201 BCT treated by several surgeons during a 4-year period favored US-guided surgery of non-palpable breast tumors with reported involved margins of only 4 versus 21% after guide-wire localization and 25% after ROLL [23]. Further evaluation of these techniques is currently ongoing in prospective randomized, controlled trials [26]. Although the ultrasound technique may be superior to conventional localization with a guide wire a presumable learning curve with preoperative US by the surgeons may be a limitation. In our hands, the use of one or several I-125 seeds proved to be accurate in precise marking of the involved breast segment as well as multifocal disease. The technique is relatively easy to carry out and has a small learning curve. With proper use of the gamma probe, seeds can be located during surgery within a margin of ≤1 cm. A drawback in the use of radioactive seeds is the extensive administrative burden that needs to be handled with to obtain permission to proceed. A strict local protocol for quality assurance must be followed in order to guarantee that all implanted seeds are actually removed and recovered by the local Nuclear Medicine Department [16]. The main interest of the present study was to evaluate the use of I-125 seeds as a guidance marker in breast cancer patients treated with NAC, not to test the influence of NAC on the resectability rate. Therefore, firm conclusions on the role of I-125 seed localization in combination with NAC to reduce the tumor load and to transfer originally mastectomy-scheduled patients into BCT candidates are only speculative.

The results of a study by Weissenbacher et al. support radical mastectomy for multifocal tumors as these are thought to be associated with an increased risk of involved margins and higher local recurrence rates after BCT [13]. They reported multifocality/multicentricity as an independent risk factor for the local relapse rates in 576 patients after BCT, however, without distinguishing between them. This is in contrast with other studies in which multifocal tumors were not found to be associated with higher local recurrence rates following BCT [27, 28]. Therefore, patients should be carefully assessed for suitability of BCT beforehand with multifocality just as one of several factors. Confirmation of additional foci together with the tumor versus breast volume ratio is important in the
diagnostic work-up to guide the decision whether BCT might be feasible. Subsequent accurate localization of all confirmed lesions seems to be a hallmark of successful BCT. Following this Yerushalmi et al. reported local recurrence rates that were comparable for patients with multifocal tumors versus patients with unifocal tumors [27].

In our study after a mean follow-up of 11 months, no local recurrences were seen. In four patients, focal-positive margins were treated by adjustment of the radiation therapy scheme (Focally involved margin). In four patients, focal-positive margins were treated by adjustment of the radiation therapy scheme [29]. Focally involved margins can be adequately treated by boost irradiation with comparable local recurrence rates that were reported by Yerushalmi et al. [24].

conclusion

Unifocal and multifocal breast cancer, with an indication for NAC, can be successfully operated with BCT when initially localized with one or more I-125 seeds enabling complete resection rates up to 90%.

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disclosure

The authors have declared no conflicts of interest.

references