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ORIGINAL ARTICLE

Comparison of a 1-day and a 2-day protocol for lymphatic mapping and sentinel lymph node biopsy in patients with nonpalpable breast cancer

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Abstract
Purpose To compare the identification rate of the sentinel node in a 1-day protocol versus a 2-day protocol in patients with a nonpalpable breast carcinoma.
Methods In the 1-day protocol an average dose of 120 MBq ^{99m}Tc-nanocolloid was injected intratumorally on the day of surgery, and in the 2-day protocol an average dose of 370 MBq ^{99m}Tc-nanocolloid was injected intratumorally the day before surgery. Both a gamma ray detection probe and patent blue were used to locate the sentinel node.
Results In 57 of 67 patients (85%) treated in the 1-day protocol and in 51 of 56 patients (91%) treated in the 2-day protocol the sentinel node was detected (p=0.311). Of the patients in the 1-day protocol and the 2-day protocol, respectively, 18 (27%) and 13 (23%) showed metastasis (p=0.975)
Conclusion There was no significant difference in the identification rate of the sentinel node between the 1-day protocol and the 2-day protocol in patients diagnosed with a nonpalpable breast carcinoma.

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Introduction

Lymphatic mapping and sentinel lymph node (LN) biopsy (SLNB) are reliable staging tools in the management of patients with breast carcinoma. In particular, patients with small, often nonpalpable breast carcinoma benefit from SLNB instead of axillary dissection as only 7.8–28.5% of patients with T1a-c breast carcinoma have tumour-positive LNs [1]. Therefore, without SLNB 70–90% of axillary dissections would be redundant in this particular group. In order to avoid disabling morbidity associated with axillary dissection such as lymphoedema, a successful SLNB is of great importance.

Nonpalpable breast carcinomas are often difficult to discern at surgery. Therefore a guide wire is usually placed preoperatively in order to localize the tumour. It is suggested that a guide wire placed intra- or peritumorally could disturb the lymph drainage pattern and thereby decrease the success rate of the SLNB [2].

Currently wide differences exist in SLNB protocols used. ^{99m}Tc-Nanocolloid radiotracer, vital dye or both are used as localizing pharmaceuticals, while injection routes include intratumoral, peritumoral, intradermal and/or subareolar injection. Injection of the localizing pharmaceutical can be done either pre- or intraoperatively, on the same day or the previous day [3, 4]. Lymphoscintigraphy can be performed using either the dynamic and/or the static technique [5]. In our hospital, both radiotracer and blue dye are injected intratumorally in patients diagnosed with a nonpalpable breast carcinoma. Therefore, in nonpalpable

breast cancer, the injection of a radiotracer needs to be guided by ultrasound or stereotaxis.

Initially patients diagnosed with a nonpalpable breast carcinoma were treated according to a 2-day protocol. This protocol was chosen to increase the number of successful SLNB due to the possibility of performing late nuclear imaging [6]. The 1-day protocol was introduced to allow all patients to be treated in day-care and to lower the radiation burden. It was unclear if there was a difference in the visualization and successful surgical removal of the sentinel node between the 1-day and the 2-day protocol and if guide wire placement influenced the success of SLNB.

The aim of this study was to compare the 1-day and 2-day protocols with regard to the identification rate and removal of the sentinel node in patients diagnosed with nonpalpable breast cancer.

Materials and methods

In this retrospective, nonrandomized, cohort study, 123 patients with a nonpalpable breast carcinoma treated between July 2002 and July 2008 were included. Women with newly diagnosed primary, nonpalpable invasive breast cancer undergoing tumour resection and SLNB were eligible for the study. Exclusion criteria were previous breast cancer in the same breast, pregnancy and palpable breast cancer.

Before the introduction of a 1-day protocol, 56 patients underwent SLNB according to a 2-day protocol. Patients in the 2-day protocol received a median dose of 370 MBq radiotracer in 0.5 cm^3 of water (range 80–550 MBq). The 1-day protocol was introduced to allow patients to be treated in day-care and to lower the radiation burden. From then on, 67 patients were included in the 1-day protocol. The first 23 patients in the 1-day protocol received a dose of 80 MBq radiotracer. Due to low visualization rates the subsequent 44 patients received a median dose of 120 MBq radiotracer (80–220 MBq) in 0.5 cm^3 of water. The nanocolloid radiotracer consisted of at least 95% human albumin colloid particles of ≤80 nm.

In both groups the radiotracer was injected intratumorally guided by either ultrasound or stereotaxis depending on the visibility of the tumour. Patients were asked to massage their breast after injection of the tracer. Patients in the 1-day protocol underwent lymphoscintigraphic imaging after 10 min, and 1 and 2 hours, and patients in the 2-day protocol underwent lymphoscintigraphic imaging directly after injection and the next morning before surgery to assess the migration of the radiotracer. After finding the sentinel node on the static images the skin was marked. Intraoperatively patients received a peritumoral injection of patent blue at the site of the maximum count found with the gammaprobe (Europrobe Strasbourg, France). First, the SLNB was performed and subsequently the primary tumour was excised, followed by histopathological analysis using regular H&E and immunohistochemical staining. In case of failure of the SLNB a regular axillary dissection was carried out.

The number of LNs seen on static imaging was compared to the number found during surgery. The hot and/or blue sentinel nodes were removed and when the exact location of the sentinel node was unclear intraoperatively the second echelon nodes were removed as well. The nodes both inside and outside the axilla were removed. The SLNB was considered successful if the tissue removed during surgery was hot and/or blue and proved to be LN tissue on histopathological assessment. The lymphoscintigraphic visualization rate and the surgical success rate were compared between the 1-day protocol and the 2-day protocol. The success rate of the SLNB in patients with a guide wire placed intratumorally before injection of the radiotracer in the 1-day protocol or the 2-day protocol was compared with that in patients without a guide wire in place during administration of the radiotracer.

Statistics

Identification and removal of one or more sentinel nodes was considered a successful SLNB. The successful removal of the sentinel node, the proportion of patients with LNs on scintigraphy and the difference in success rate of SLNB in patients with a guide wire in place during injection of the radiotracer between the two protocols were compared using the chi-squared test; $p<0.05$ was considered significant.

The numbers of sentinel nodes seen on the preoperative images and number of LN removed during surgery were compared using the independent sample *t*-test; $p<0.05$ was considered significant.

Results

The baseline characteristics in both groups were comparable, except for tumour morphology (Table 1).

The visualization rate in the 1-day protocol was 61/67 (91%) and the visualization rate in the 2-day protocol was 55/56 (98%; $p=0.087$). The mean number of nodes seen preoperatively was 1.48 (range 0–5) in the 1-day protocol and 1.88 in the 2-day protocol ($p=0.007$). The visualization rates in the two protocols for nodes outside the axilla were similar (Table 2).

The surgical success rate of the SLNB was 57/67 (85%) in the 1-day protocol and 51/56 (91%) in the 2-day protocol ($p=0.311$). The mean numbers of nodes removed were 1.64 (range 0–6) in the 1-day protocol and

Table 1 Baseline characteristics

Baseline characteristics	1-day protocol	2-day protocol	*p* value
Number of patients	67	56	
Number of tumours	68	59	
Median age (years)	59	59.5	0.955
Median size of primary (mm)	13	12	0.188
Histology			0.006
Ductal	53 (77%)	56 (95%)	
Lobular	5 (7.1%)	1 (1.7%)	
Ductolobular	8 (11.4%)	1 (1.7%)	
Mucinous	1 (1.4%)	1 (1.7%)	
Papillary	1 (1.4%)	0	
Quadrant tumours			0.119
Retroareolar	5 (7.4%)	10 (18%)	
Lateral upper quadrant	35 (52.2%)	26 (44%)	
Medial upper quadrant	7 (10.2%)	10 (18%)	
Lateral lower quadrant	10 (14.7%)	6 (11%)	
Medial lower quadrant	12 (18.0%)	5 (9%)	

1.61 (range 0–4) in the 2-day protocol (p=0.209). After finding LNs on preoperative static imaging, the mean numbers of LNs not found during surgery was 0.28 (range 0–3) in the 1-day protocol and 0.41 (range 0–4) in the 2-day protocol (p=0.664). The numbers of nodes found assisted by patent blue only was 4 in the 1-day protocol and 5 in the 2-day protocol (not significant, p=0.73). The numbers of nodes found assisted by the radiotracer and/or patent blue in the 1-day protocol and in the 2-day protocol did not differ significantly (see Table 2). Of the non-visualized sentinel nodes, 1/6 (17%) in the 1-day protocol and 1/1 (100%) in the 2-day protocol were found using patent blue.

Of the patients in the 1-day protocol, 49 (73%) showed no metastasis in the sentinel node, 3 had isolated tumour cells (4.5%), 3 (4.5%) had micrometastases (i.e. <2 mm) and 12 (18%) showed macrometastases (i.e. >2 mm). Of the patients in the 2-day protocol, 42 (76.4%) showed no metastases, 1 (1.8%) had isolated tumour cells, 3 (6%) had micrometastases and 9 (16.4%) showed macrometastases. The number of metastases in the patients in the two protocols did not differ significantly (p=0.975).

In the 1-day protocol the first 23 patients had a median dose of 80 MBq of radiotracer. After excluding these patients, the success rate of the SLNB was 88%. In 29 of 67 patients (43%) in the 1-day protocol and in 15 of the 56 patients (26%) in the 2-day protocol, a guide wire was in place when the radiotracer was injected. As shown in Table 3, the presence of a guide wire during injection of the radiotracer did not influence the success rate of the SLNB.

Table 2 Characteristics of the sentinel lymph node procedure

Sentinel node	1-day protocol	2-day protocol (%)	p
Nodes visualized by static lymphoscintigraphy			0.530
Axillary	59 (88%)	53 (95%)	
Intramammary	2 (3%)	2 (5%)	
Internal mammary chain	9 (13%)	4 (7%)	
Mean number	1.48	1.88	0.007
Visualization rate	61 (91%)	55 (98%)	0.087
Nodes retrieved at surgery			0.524
Hot not blue	23	18	
Blue not hot	4	5	
Blue and hot	31	29	
Mean number	1.64	1.61	0.209

Table 3 Influence of the presence of a guide wire on the success rate of SLNB

Protocol	Guide wire	No guide wire	Total	*p* value
1-day protocol	23/29 (80%)	34/38 (89%)	57/67 (85%)	0.247
2-day protocol	14/15 (93%)	37/41 (90%)	51/56 (91%)	0.720
Total	37/44 (84)	71/79 (90%)	108/123 (88%)	
p value	0.228	0.910		

Discussion

In this retrospective comparison of two historical cohorts of patients who underwent lymphoscintigraphy in a 1-day or a 2-day protocol we did not observe statistically significant differences in the identification and removal of the sentinel nodes. No significant difference in location of the sentinel node was found between the two protocols. Moreover, the presence of a guide wire when injecting the radiotracer did not influence the success rate of the SLNB.

There were some weaknesses in this study. A relatively small number of patients were retrospectively included. Therefore there are some possible confounders that could have influenced the results. In both protocols patients had a guide wire in place during injection of the radiotracer. It has been suggested that the presence of a guide wire can disturb the regular draining pattern and radiotracer can leak past the guide wire [2]. The numbers of guide wires in place during injection of radiotracer were comparable between the two groups. We could not demonstrate a negative influence of a guide wire placed intratumorally before injection of the radiotracer.

Next, the dosage of radiotracer injected in the 1-day protocol differed. It is suggested that a mean dose of at least 90 MBq radiotracer is needed for adequate lymphoscintigraphy [7, 8]. Possibly the higher dose of radiotracer, after excluding the first 23 patients in the 1-day protocol, resulted in the observed higher success rate of SLNB as is suggested in the literature [9]. Nevertheless, this study was nonrandomized and firm conclusions on this subject are not justified. In order to facilitate an adequate injection volume in both groups the total injected volume was 0.5 cm^3. Therefore, the dilution of the radiotracer was different in the two protocols. Although there is no consensus on the volume and dilution in the current literature, the difference in dilution could have influenced the drainage patterns and speed [10].

The patients treated in the 1-day protocol underwent lymphoscintigraphy up to 2 h after injection. In the literature, imaging up to 4 h after injection is described. Possibly, late imaging could increase the number of visualized nodes, and thereby improve the success rate of the SLNB. Finally, the success rates found in this study were lower than the rates of 90–99% reported in the literature [8, 11–13].

To our knowledge, this is the first study to compare success rates between a 1-day and a 2-day protocol in nonpalpable breast cancer. Furthermore, this study provides a concise answer to a practical question. Studies performed so far included both patients with palpable and nonpalpable breast cancer. Although the protocols in these studies differed (i.e. particle size and injection region) they also showed no differences between a 1-day and a 2-day protocol [6–9]. As has been shown previously, the combination of a radiotracer preoperatively and dye injection peroperatively was superior to the use of radiotracer or dye only [3, 14]. In our study, in the 1-day protocol in four patients (6%) and in the 2-day protocol in five patients (9%), the sentinel node was found with patent blue only. This indicates the importance of the combination technique. In cases of non-visualization preoperatively, surgeons can still rely on the patent blue [15].

The site of injection of the radiotracer is a matter of discussion. In our protocol the radiotracer was injected intratumorally, using either ultrasound or stereotactic guidance. As reported by others, intra-/peritumoral injection of the radiotracer and the patent blue is as reliable as subareolar injection [16]. After intratumoral injection, more of the internal mammary chain LNs can be found thereby affecting the adjuvant therapeutic plan and possibly long-term survival [17, 18]. In addition, injecting intratumorally allows lumpectomy with the radioguided occult lesion localization (ROLL) technique in the same procedure [19–21].

The use of a 1-day protocol or a 2-day protocol is often a choice based on local preferences driven by logistic considerations. In a 2-day protocol multiple patients can be scheduled for lymphoscintigraphic imaging and sentinel node procedures in the operating room. The advantage of the 1-day protocol is that patients only require one hospital visit and the radiation dose is minimized. Lowering the dose of radiotracer from 370 MBq in the 2-day protocol to 120 MBq in the 1-day protocol represents a threefold reduction in the radiation burden for both patients and physicians.

In conclusion, there was no significant difference in the success rate of SLNB in patients diagnosed with a nonpalpable breast carcinoma between those treated in a 1-day protocol and those treated in a 2-day protocol. In our hospital currently all patients diagnosed with a nonpalpable

breast carcinoma are treated on a day-care basis using the 1-day protocol.

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