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Original Article

Comparison between preoperative and intraoperative injection of ^{99m}Tc Dextran-500 for sentinel lymph node localization in breast cancer

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Abstract: A retrospective study was conducted from a review of the medical records of patients with early-stage, invasive breast cancer who underwent surgical treatment and sentinel node biopsy with a radiotracer from January 2008 to August 2012 at a single institution (221 patients included). The patients were grouped according to the time of ^{99m}Tc Dextran-500 injection, which was preoperatively (with lymphoscintigraphy) (81 patients) or intraoperatively (140 patients). The purpose of the report is to compare the results of sentinel node biopsy of early-stage breast cancer patients who were subjected to intraoperative ^{99m}Tc Dextran-500 injections with the patients who received preoperative injections. The following parameters were analyzed: clinical tumor staging, histological and pathological results, size and number of tumor foci, peritumoral vascular invasion, number of lymph nodes removed, size of lymph node metastasis and hormone receptor expression.There were no differences in sentinel lymph node localization whether ^{99m}Tc Dextran-500 was injected preoperatively or intraoperatively.

Keywords: Sentinel lymph node, breast cancer, ^{99m}Tc Dextran-500, intraoperative injection, preoperative injection, lymphoscintigraphy

Introduction

Breast cancer is the second most common type of cancer in the global population and the most common type of cancer among women [1]. It is estimated that 1 in 9 women will develop breast cancer during their lifespan [2]. The prognostic factors for breast cancer include the histological type and grade, tumor size and axillary status. Among these parameters, the axillary status is the most powerful when predicting survival in the absence of distant metastases [3].

Modern screening methods have enabled the early diagnosis of breast cancer in the absence of axillary lymph node (LN) metastases. As a result, axillary dissection became excessive, and patients were unnecessarily exposed to associated morbidities [4, 5]. Sentinel lymph node biopsy (SNB) was introduced to reduce unnecessary axillary dissection. This surgical approach conserves the regional lymphatic chain for axillary staging because it restricts lymphatic dissection only to patients whose biopsies show metastasis in at least one LN [5, 6].

There are numerous methods for sentinel lymph node (SN) removal in breast cancer. The main materials injected for SN localization and posterior SNB are patent blue dye solution and radiopharmaceuticals (RPs). In a recent meta-analysis conducted by Pesek et al. [7], that analyzed 183 articles with a total of 9,306 patients, the use of patent blue dye alone was associated with a higher false negative rate, while the lowest false negative rates were observed when patent blue dye was used in combination with RPs. There are numerous SNB techniques that

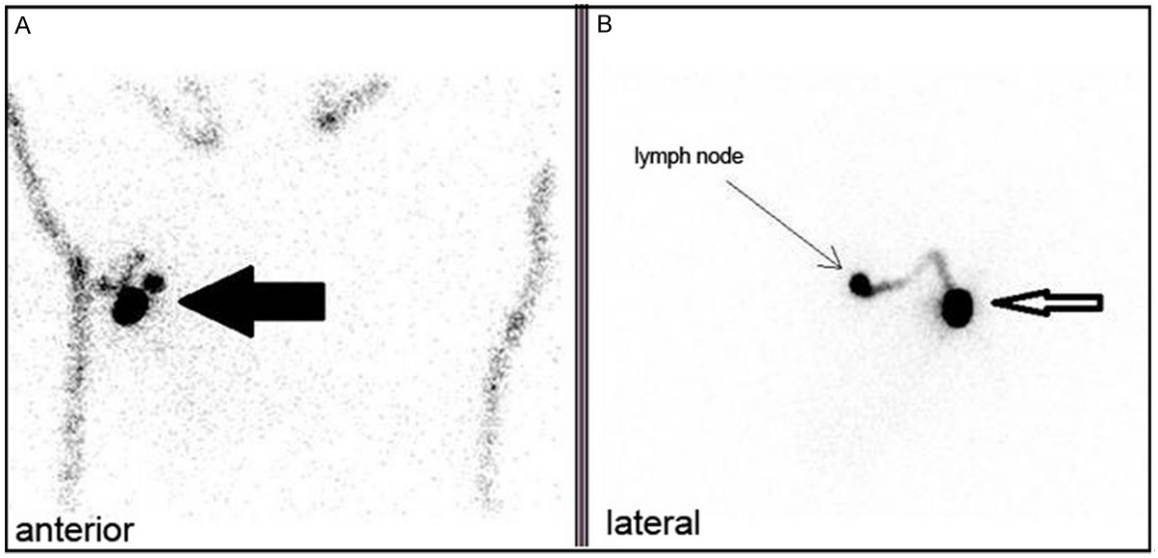

Figure 1. Lymphoscintigraphy for sentinel lymph node detection in breast cancer. A. Anterior projection: note the injection site (large arrow) in the topography of the right breast of the patient; B. Lateral projection: here, the injection site (hollow arrow), the intramammary radiopharmaceutical route and the concentration in the lymph node (thin arrow) can be observed.

incorporate RPs, and these techniques differ primarily in the RPs administration time and site and the acquisition or not of preoperative images. RPs injections can be performed either intraoperatively or preoperatively; the latter are administered hours before the surgical procedure [8].

Materials and methods

A retrospective study was conducted at a single institution during the period from January 2008 to August 2012. The study included an analysis of the medical records of patients.

Inclusion criteria: Patients with a diagnosis of invasive or *in situ* breast carcinoma who underwent surgical treatment (mastectomy or sectionectomy) and SNB; use of RPs for localization and SNB; and mastectomy surgery performed during the period from January 2008 to August 2012, at the Porto Alegre Teaching Hospital (Hospital de Clínicas de Porto Alegre - HCPA).

Exclusion criteria: Patients who underwent prior breast or axillary surgery; and the evolution of surgery for axillary dissection without LN intraoperative histological results.

All cases from 2008 that met the above criteria were selected, as 2008 was the year that intraoperative ^{99m}Tc Dextran-500 injections were introduced for use at the institution. The data were recorded in data collection files for further analysis. The patients were grouped according to the time of ^{99m}Tc Dextran-500 injection for SNB; those who received preoperative RP injections and imaging (lymphoscintigraphy) were called the PO group, and those who received intraoperative RP injections without imaging were called the IO group. In all cases, the surgeons used gamma probe to identify the radioactive focus during intraoperative axillary examinations.

The following characteristics were analyzed: Clinical tumor staging by T value, according to the TNM classification of the 7th edition of the American Joint Committee on Cancer (AJCC); size, histological type and focality of the primary tumor; peritumoral vascular invasion; hormone receptor expression; histological and pathological LN examination results; number and location of the removed LNs and the size of LN metastases. In the PO group, the presence of radioactive LNs, visualized in images, collected from successful intraoperative gamma probe identifications, was also determined.

Preoperative injection

Periareolar subdermal injections of 0.5 to 1.5 mCi (18 to 55 MBq) of ^{99m}Tc Dextran-500 [filtered-sterilized with an 0.22-μm filter (Millex GV Filter Unit 0.22-μm - Durapore PVDF Membrane)] in volumes of 0.2 to 0.5 mL were administered to the tumor-containing quadrant by the nucle-

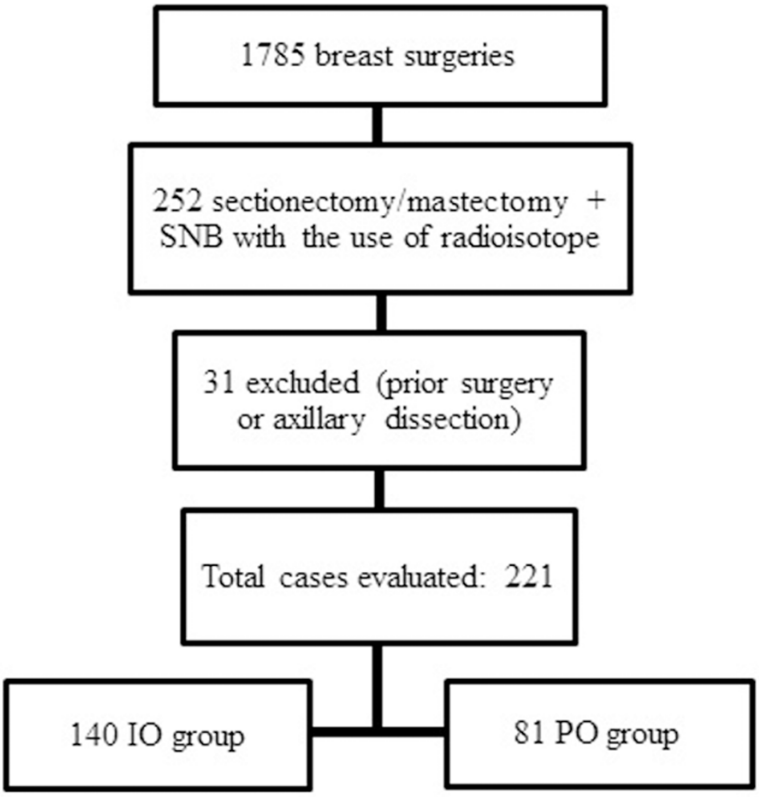

Figure 2. Study flowchart that includes the number of patients in each stage (from January 2008 to August 2012). **SNB: Sentinel Lymph Node Biopsy; IO: Intraoperative; PO: Preoperative.*

ar medicine service. A licensed nuclear physician administered the injections for subsequent lymphoscintigraphy within 2 to 6 hours prior to the surgical procedures.

Lymphoscintigraphy

Images were taken between 30 and 60 minutes after the RP injection. If the LN was not visualized, the patient was instructed to perform mild compression at the site of injection, and delayed images were obtained. Images were obtained during 5 minutes from anterior and lateral or anterior oblique size of the affected side, with a GE Millennium MG gamma camera (Salt Lake City, UT, USA) in a single collimator, 64 x 64 matrix (**Figure 1**). The skin was marked with an indicative dot on the captured LN projection.

Intraoperative injection

After anesthesia, a 5 mL volume of 0.5 to 1.5 mCi (18 to 55 MBq) of filter-sterilized (Millex GV Filter Unit 0.22-μm - Durapore PVDF Membrane) ^{99m}Tc Dextran-500 was injected into the subareolar breast region. On the right breast, the injection position was at 10 o'clock and on the left breast, at 2 o'clock; the injections were always directed medially to the nipple.

Intraoperative gamma probe localization of SN

Axillary region capture measurements were obtained with a radiation detection probe (EuroProbe, Lyon, France) until an area with higher radioactivity counts compared to the surrounding area was identified. This area, called "hot spot", represented the accumulated radiation emission in the SN.

Histology and pathology

Preferably, all SNs were assessed by cytological examination during the surgical examination, with the goal of preserving the specimens in paraffin for diagnosis. In some cases, the SN was frozen and cut during surgery. For the final definitive diagnoses, the resulting paraffin blocks were cut and stained with HE, and a slide was removed and stored for immunohistochemistry. Afterwards, staggered cuts were made at intervals of 200.0-μm until the entire block had been sliced. A slide was removed for immunohistochemistry at each 1,000.0 μm. As a rule, 2 5.0-μm thick tissue slices were placed on each histological slide. During the study, the histological diagnoses were reviewed by a pathologist and compared with the initial diagnoses.

Radiological protection

The radiation doses injected into the breast cancer SNB ranged from 0.5 to 1.5 mCi. Approximately 20% of such a dose is systemically absorbed by the patient [8], and thus the estimated effective dose for the patient is very low. The annual dose limit for the general public is 1 mSv; this limit has been increased to 5 mSv/year for nuclear medicine professionals.

Table 1. Characteristics of the 221 patients included in the study, according to the radiotracer injection time (considering p < 0.005)

	IO Injection N = 140	PO Injection N = 81	*P* value
Mean age	56.2 ± 12.7	56.9 ± 12.0	0.691
Female	139 (99.3)	81 (100%)	0.999
Surgery			0.790
Sectionectomy	92 (65.7)	51 (63.0)	
Mastectomy	48 (34.3)	30 (37.0)	
Laterality			0.843
Left	85 (61.6)	48 (59.3)	
Right	53 (38.4)	33 (40.7)	
Tumor size (cm)	2 (1.3 to 2.6)	2 (1.3 to 2.7)	0.532
Number of foci			0.468
Unifocal	119 (85.0)	65 (80.2)	
Multifocal	21 (15.0)	16 (19.8)	
Histology			0.299
DCIS	3 (2.1)	1 (2.1)	
Ductal Inv	127 (90.7)	69 (85.2)	
Lobular Inv	10 (7.1)	11 (13.6)	
Peritumoral Invasion	47 (37.6)	17 (21.0)	0.067
Nottingham grade			0.157
1	24 (18.3)	19 (27.5)	
2	71 (54.2)	38 (55.1)	
3	36 (27.5)	12 (17.4)	
PR Negative	44 (32.6)	18 (23.4)	0.207
ER Negative	26 (19.3)	12 (15.6)	0.628
Neoadjuvant Treatment	6 (4.3)	7 (8.6)	0.237
Clinical stage (T)			0.319
In situ	3 (2.1)	1 (1.2)	
1	65 (46.4)	46 (56.8)	
2	72 (51.4)	34 (42.0)	

IO: Intraoperative; PO: Preoperatively; DCIS: Ductal in situ; Inv: invasive; PR: Progesterone Receptor; ER: Estrogen Receptor.

This dosage can be compared to the risk of lung cancer death for a smoker [9]. Of the entire dose administered to the patient, approximately 1% migrates to the SNs [10], and 90% of the SNs have doses below 100 μSv [11]. Thus, it can be concluded that the radiation doses to surgeons and pathologists are extremely low and then well below the dose limits for the general public.

Statistical analysis

The data were entered into Excel spreadsheets (Microsoft, Redmond, WA, USA) and then exported to the SPSS v.18.0 software (IBM, Armonk, NY, USA) for statistical analysis. The categorical variables were described as frequencies and percentages and the quantitative variables as means and standard deviations. The categorical variables between the groups were compared with chi-square or Fisher's exact tests, and the quantitative variables between groups were compared with Student's t test for independent samples. The significance level was set at 5%.

Ethics

All authors signed an Ethical Statement for data usage. The study was approved by the Ethics Committee of the HCPA and by the Brazil platform (CAAE: 11920912.4.0000.5327).

Results

During the period from January 2008 to August 2012, 1,785 breast surgeries were performed at the HCPA, of which 252 were mastectomies or sectionectomies that included SNB with radioisotope. Thirty-one individuals were excluded from the analysis because they had received prior surgical manipulations of the axilla or breast or had surgeries that evolved to axillary dissection without intraoperative biopsy. According to chart reviews of the 221 remaining patients, 140 were classified in IO group and 81 in PO group (**Figure 2**). The 2 groups were similar with regard to the following factors: age, gender, clinical staging, type of mastectomy, laterality of surgery, size and number of tumor foci, peritumoral vascular invasion, Nottingham grade, the presence of estrogen and progesterone receptors and neoadjuvant chemotherapy (**Table 1**).

Overall, a total of 478 LN were removed for SNB; 305 were removed in the IO group and 173 in the PO group. The mean of number of LNs removed was 2.20 (± 1.13; range, 1-7 per

Table 2. Characteristics of lymph nodes removed during sentinel lymph node biopsy, according to study group

	IO Injection	PO Injection
Total LN removed	305	173
Mean LN removed	2.20 (± 1.13)	2.07 (± 1.33)
Maximum No. LN removed	7	7
Minimum No. LN removed	1	0
Patients with SN+ for mtx	36 (50)	35.8 (29)
Size of LN mtx		
Emboli	0	3.6 (1)
Micrometastasis	32 (16)	21.4 (6)
Macrometastasis	68 (34)	75 (21)

IO: Intraoperative; PO: Preoperative; LN: lymph node; No.: number; SN+: positive sentinel lymph node; mtx: metastasis.

subject) in the IO group and 2.07 (± 1.33; range, 0-7 per subject) in the PO group ($p = 0.473$). With regards to variation in the sizes of LN metastases in the IO group, 32% (16) were micrometastases and 68% (34) were macrometastases; in the PO group, 3.6% (1) were emboli, 21.4% (6) were micrometastases and 75% (21) were macrometastases (**Table 2**).

The rates of metastasis-positive diagnosis in the SNs during intraoperative examinations were 29.0% and 24.7% in the IO and PO groups, respectively ($p = 0.595$). The final diagnosis in paraffin-fixed positive for metastasis occurred in 50 patients (36%) from the IO group and 29 patients (35.8%) from the PO group (**Table 3**).

The IO group had a concordance rate of 90.6% between the intraoperative and definitive paraffin diagnoses, resulting in a kappa coefficient of agreement of 0.804 ($p < 0.001$). In the PO group, the rate was 87.7%, with a kappa coefficient of 0.735 ($p < 0.001$). A total of 71 (32.3%) patients underwent total axillary dissection. Among them, the mean number of LNs removed was 15.97, with a standard deviation of 7.56 and a range from 2 to 42. In 96.42% of the IO cases, the SN was identified with a gamma probe during surgery, in comparison to 92.59% of the PO cases. The difference between the 2 groups was not significant. The false negative rate was 7.2% in the IO group and 11.1% in the PO group ($p < 0.390$).

In the PO group, lymphoscintigraphy identified the migration of the radiotracer to the internal mammary chain in 2 patients, and 1 of these patients also showed migration to the axillary chain. No LNs were visualized in 6 cases (7.4%), 1 LN was visualized in 41 cases (50.6%) and more than 1 LN in 34 cases (42.0%; **Table 4**). In 50% of the cases in which no radioactive concentration was visualized in the LN by lymphoscintigraphy, radioactive counts were identified intraoperatively with a gamma probe.

Discussion

The involvement of the axillary lymphatic chain is critical for the staging, prognosis and treatment of patients with breast cancer [12]. After considering that only 30-40% of patients with breast cancer have axillary metastases [13-15] as well as more recent studies in which ≥ 70-80% of patients with early-stage breast carcinomas have shown no metastatic LN involvement [14], axillary lymphadenectomy has been recognized as excessive for use in all patients. In the present study, LN metastasis was observed in 36% of the IO and 35.8% of the PO group patients. Similar results were published by Martelli et al [15], who observed a metastatic LN involvement rate of 33.7% among 172 patients.

The initial study on SNs in breast cancer, in which radiotracers and gamma-ray detectors were used perioperatively, was performed by Krag et al. [16] in 1993. That study used a ^{99m}Tc bound sulfur colloid, and the authors observed an 81% rate of SN identification and a 100% prediction rate for the axillary LN status. Although the techniques have improved since their introduction, there remains concern about the number of false-negative cases. In a meta-analysis, Kim et al. [14] reported a mean false-negative rate of 8.4% among the studies assessed, with a median of 7% and a range from 0 to 29.4%. This false-negative rate is critical, because it delays the start of neoadjuvant treatment and subjects the patient to additional intervention with a second surgical procedure.

Because only patients with a metastatic SN that was confirmed by intraoperative histological examination underwent axillary dissection (32.3% in total) in the present study, the rate of false negatives (IO = 7.2%; PO = 11.1%) refers to the histological method in comparison to the anatomopathological method and not to the

Table 3. Number of metastasis-positive lymph nodes found during transoperative and final examinations (in paraffin), according to study group

	IO Group	PO Group	*P* Value
LN with MTX in the Transoperative examination*	40 (29.0%)	20 (24.7%)	0.595
LN with MTX in the Definitive (paraffin) examination*	50 (36.0%)	29 (35.8%)	0.999

*2 losses. Data presented by the absolute frequency and relative percentage frequency and compared with a chi square test with Yates convention. IO: Intraoperative; PO: Preoperative; LN: lymph node; MTX: metastasis.

Table 4. Number of lymph nodes visualized on the lymphoscintigraphy images in the preoperative group

No. of LN visualized by Lymphoscintigraphy	No. of patients (only in the PO group)
0	6 (7.4%)
1	41 (50.6%)
More than 1	34 (42.0%)

No.: number; LN: lymph node; PO: Preoperative.

success of the technique with respect to correct SN identification.

The main indications to SNB are cases of invasive, primary breast cancers with tumors no more than 5 centimeters in diameter and a clinically negative axilla [15, 17, 18]. The analysis of surgeries performed at our institution revealed that the practice of SNB in patients with invasive T1 and T2 tumors, and *in situ* (Tis) in some cases, agrees with the consensus by the American Society of Breast Surgeons [18], which has restricted the method to stage T3 tumors in clinical trials.

A variety of RPs have been used for SNB in the past 30 years [13, 19]. In Brazil, we basically use ^{99m}Tc phytate and ^{99m}Tc Dextran-500. Xavier et al. [20] compared ^{99m}Tc phytate to ^{99m}Tc Dextran-500 in 40 patients who were subjected to lymphoscintigraphy with both RPs and observed that the Dextran-500 tagged more LNs in a higher number of cases than the phytate solution. The Dextran-500 showed good results when injected intraoperatively in a pioneer study that was conducted in Brazil by Delazeri et al. [21]: the SN identification rate was 98% with only the use of a gamma probe (without lymphoscintigraphy). The present study made a unique comparison, as there are no reports of studies in Brazil that have compared the findings for the 2 ^{99m}Tc Dextran-500 injection techniques (intra- and preoperative).

One of the main advantages of preoperative injections is the ability to obtain images for mapping the breast lymphatic route towards the SN (lymphoscintigraphy), that was introduced in 1958 (17) and is still widely used. Lymphoscintigraphy identifies and confirms the hot focal area, the number of radioactive LNs, the presence of migration to non-axillary LN (supra or infraclavicular, or internal mammary chain), as well as the lack of radioactive material concentration in the LN.

Lymphoscintigraphy is essential when there is drainage to the internal mammary chain [22, 23], to help to plan the radiotherapeutic and chemotherapeutic approaches [5]. The real value of the removal of LN from internal mammary remains controversial [24, 25]. In the present study, of all of the LNs visualized on the images, only 2 (2.6%) were within the internal mammary chain, and in 1 case, there was also drainage and concentration in the axillary chain. In the IO group, there were no such cases described in the medical records. There are, however, literature reports on the identification of non-axillary LN with only intraoperative gamma probe in more than 10% of investigated cases [26].

Newman [12] summarized data from representative studies about lymphatic mapping and SN in breast cancer patient and concluded that intraoperative gamma probe is more sensitive than lymphoscintigraphy. In this article, the study by Borgstein et al [27] is cited because, when analyzing 14 patients in whom the SN was not visualized by lymphoscintigraphy, in approximately half of the cases it was instead detected with a radiation counter (gamma probe) during surgical axillary manipulation. In the present study, there was no detectable lymphatic concentration by lymphoscintigraphy in 6 cases and, out of these cases, 3 (50%) were detected with an intraoperative gamma probe. Omitting lymphoscintigraphy would be justified in these cases based on studies that show that these examinations do not increase the SN detection rate, like McMasters et al. [28] have

showed when studying 588 patients with breast cancer, where 348 had done lymphoscintigraphy and no difference was detected in SLN identification, neither a number of SLNs resected.

To decrease the risk of axilla understaging, it is necessary to remove all detected radioactive LN, which in practice are those that have a radiation level of at least 10% of that observed in the hottest LN during the *ex vivo* count, second advocated Dutta et al. [29]. In a meta-analysis of SNB and lymphoscintigraphy, Kim et al. [14] reported that among patients with metastasis-positive SN, 53% have other affected LN. The SN programs with lower rates of false negatives report the average removal of 2 LNs per dissection [30]. In the present study, the mean numbers of LN removed were 2.20 (± 1.13) for the IO group and 2.07 (± 1.33) for the PO group, in agreement with the literature.

The first study of intraoperative RPs injections was published by Layeeque in 2004 [24]. The method consisted of an intraoperative, subareolar injection of RPs and blue dye in, with a total of 88 patients and 96 procedures: 97% of procedures had successful identification; all SNs were hot; 91 (of 93 procedures with blue dye) were blue and hot; the mean time from radioisotope injection to incision was 19.9 minutes. He concluded that intraoperative subareolar injection of radioisotope rapidly drains to the SNs and allows immediate staging of the axilla.

Like our study, others similar were published, with similar results. But in the current study we injected ^{99m}Tc Dextran-500, while the most studies use ^{99m}Tc-sulfur colloid. Dauphine et al. [31] analyzed the results of SN identification in 200 patients, of whom 120 received preoperative RP injections and 80 received intraoperative injections. The following results were obtained: SNs were identified in 96% of the PO and 100% of the IO cases; radioactive LNs were identified in 95% of the PO and 97% of the IO cases; and SNs were found to be metastasis-positive in 25% of the PO and 35% of the IO cases. In a more recent study, Vu et al [32] analyzed 739 SNB (647 had preoperative injection of radiocolloid and 92 had intraoperative injection), and found similar rates from SN identification, the average number of SN removed and the overall rates of positive SN, between the two groups.

In a retrospective study, Stell et al. [33] analyzed 214 patients, of whom 102 received preoperative injections of ^{99m}Tc sulfur colloid and 112 patients received intraoperative injections. The authors found no significant differences in the main results of SN surveys between the groups and concluded that the intraoperative injection was an advantageous and oncologically safe procedure.

Radiocolloid injections performed in the operating room while the patient is under anesthesia decrease delays in operating room scheduling by presenting better logistics, as it is unnecessary to relocate patients to the nuclear medicine service. Furthermore, this method eliminates injection pain, reduces the anxiety associated with PO injections, and reduces costs [31, 33-34].

Conclusion

This study has validated the intraoperative injection technique as a safe and statistically similar method as compared to the previously used technique (preoperative injection). The results of this study indicate the equal efficacies of intraoperative and preoperative ^{99m}Tc Dextran-500 injections for SN detection in breast cancer, creating another alternative for the performance of this examination in a less costly and more rapid manner.

Disclosure of conflict of interest

None.

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