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Sentinel lypmh node biopsy in early breast cancer: preliminary results of the combined technique of CT lymphography and blue-dye

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ABSTRACT

Aim: The aim of this study was to evaluate the efficacy of CT lymphography in sentinel lymph node biopsy for early stage breast cancer and to investigate its contribution to the conventional blue-dye method.

Material and Method: A total of 47 patients with early stage breast cancer underwent preoperative CT lymphography for lymph node mapping before sentinel lymph node biopsy with blue-dye method. The lymph nodes identified by CT lymphography and/or blue-dye method were examined for metastatic involvement. The sentinel lymph node detection rates of CT lymphography and blue-dye method were compared using t-tests.

Results: The sentinel lymph node detection rate with blue-dye method (87.2%) was significantly higher than with CT lymphography (66.0%) (P=0.027). However, the combined method (blue-dye method and/or CT lymphography) increased the detection rate (95.7%) (P=0.267). Benign sentinel lymph nodes were detected more often with CT lymphography (P=0.366), while metastatic sentinel lymph nodes were detected more often with blue-dye method (P=1,000). Upper outer quadrant tumors were detected less successfully with CT lymphography and more successfully with blue-dye method (P=0.220 and P=0.674, respectively). The success rate of CT lymphography in younger patients (less than 50 years old) was higher compared to older patients (P=0.001).

Conclusion: CT lymphography was found to be insufficient as a standalone method for sentinel lymph node biopsy. However, it could be used as a complementary method to blue-dye method to increase the success of sentinel lymph node detection.

Keywords: Breast cancer, CT lymphography, lymph nodes, sentinel lymph node, sentinel lymph node biopsy

INTRODUCTION

Axillary metastatic lymph nodes (LNs) can be detected using ultrasound (US) and magnetic resonance (MR) imaging (1-4). However, a negative result on US or MR does not exclude axillary node metastases due to their low negative predictive values. The accuracy of US, which also depends on the size and number of LNs, has been reported to range between 68% and 80% (4). In a meta-analysis of 23 studies, Zhou et al. (5) reported a pooled sensitivity of 77% and a pooled specificity of 90% for MR in detecting metastatic axillary LNs. Similarly, recent studies using FDG (6,7,8) and SPECT CT (9,10) to detect metastatic axillary LNs were promising but not accurate enough. Therefore, surgical staging of the clinical and radiologic node-negative axilla is still necessary in the treatment of early breast cancer.

Axillary LN dissection (ALND) is highly effective in staging and controlling local disease in breast cancer. However, due to the high risk of neurovascular and lymphatic complications and high morbidity, it has been replaced by sentinel LN biopsy (SLNB), which is a less invasive and highly accurate technique. A negative SLNB enables avoiding unnecessary ALND in patients with no metastatic axillary LNs (11-14). In cases where sentinel lymph nodes (SLN) cannot be detected and sampled, ALND has to be done.

Besides relatively new techniques such as MR (11,15) and US lymphography (16,17), SLNB is mostly performed using blue-dye (BD) and radioisotope lymphography (RIL) methods. The combination of BD and RIL methods for determining the SLNs is more effective than either

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method applied alone (18,19). However, RIL is not widely used in our country, mostly due to a lack of equipment. Therefore, in most centers, including our institution, SLNB is performed only with BD in daily routine practice.

In the early 2000s, SLN localization with CT lymphography (CTL) was introduced and widely used by Japanese physicians with highly accurate results (14,20-24). However, it is not a widely practiced method in Europe and the USA. In this paper, the authors present their preliminary results of a combined technique with BD and CTL methods for SLN localization.

MATERIAL AND METHOD

This prospective study was approved by Kocaeli University Non-interventional Clinical Researches Ethics Committee (Date: 20.07.2016, Decision No: KÜ-GOKAEK 2016). Before the procedure, each patient was informed about the indication, technique, and possible complications of CTL, and written informed consent was obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between July 2017 and June 2020, patients with histopathologically proven breast cancer were evaluated for SLNB by the departments of General Surgery and Radiology. Histopathological diagnoses were confirmed by core-needle biopsy. Patients with pathologic axillary lymph nodes or distant metastases, inflammatory breast cancer, prior neoadjuvant chemotherapy, or known iodinated contrast allergy were excluded from the study. A clinically node-negative axilla was determined by the absence of palpable lymph nodes, the absence of sonographically suspicious lymph nodes, and/or the absence of metastatic lymph nodes confirmed by US-guided biopsy. The patients underwent CTL for axillary lymph node mapping in our CT unit before breast surgery, including SLNB with the BD method. The time interval between the CTL procedure and surgery was 45 minutes to 7 hours.

The CTL procedure was performed using the "Aquilion 64 helical CT scanner (Toshiba)". Pre-contrast CT images were obtained from the upper thoracic region to the axilla with the patient in a supine position and arms in a cranial direction. The technical parameters of the CT scan were as follows: "120 kV, 250 mA; slice thickness, 2mm; field of view, 350 x 450 mm; matrix, 512x512; table speed, 1.53 mm/0.5 s". The axial images were reconstructed with 0.5 mm pitch and 0.3 mm slice thickness.

Local anesthesia was administered using 8 mL of lidocaine hydrochloride 1%, with a 26-gauge needle at the 3, 6, 9, and 12 o'clock positions (2 mL each) subcutaneously on the areola. Then, 2 mL of iodinated contrast (Iohexol, Omnipaque®, 350mg/200 mL) was administered at the same positions on the areola subcutaneously, using a 26-gauge needle. To facilitate drainage of the contrast to the lymphatic ducts (LDs) and LNs, the breast was gently massaged from the areola towards the axilla for 60 seconds. The procedure was performed by two radiologists working at the same time to avoid any delay in contrast injection and massage. Three sets of CT scans were performed in the 1st, 3rd, and 5th minutes after contrast injection.

The images were automatically transferred to the workstation, and densities of the LNs were measured by carefully placing the range of interest to avoid the peripheral structures. 3D maximum intensity projection (MIP) images were used to define the LDs (**Figure 1**). The SLN was identified as the LN(s) to which the contrast medium in the LD(s) reached. If more than one enhanced LN was present, the SLN was detected by tracing the LDs. In cases where the ductal system was poorly visualized, the densities (HU) of the LNs on pre- and post-contrast images were measured, and the LN with the earliest contrast enhancement was considered as the SLN.

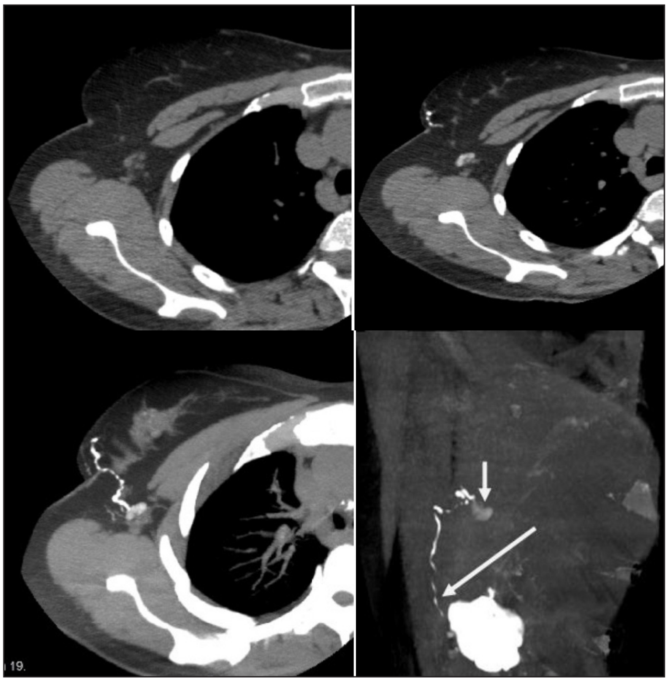

Figure 1. a-d. A 44-year-old female has invasive ductal carcinoma. She undergoes a CTL procedure, with precontrast (a) and 3rd minute postcontrast (b) axial images taken. An axial MIP (c) and 3D MIP (d) images are also obtained. The images show the contrast-enhanced lymphatic duct (long arrow) and the sentinel lymph node (short arrow).

After determination of the SLN(s), a metallic marker was placed on the skin over the determined LN(s) as a guide. The projection of the LN(s) onto the skin was marked over the CT plane light with a permanent pen, and the breast surgeon team was informed about the results. The CTL procedure lasted 20 to 45 minutes.

In the operating theater, 8 mL of methylene blue (Blumet, 100mg/10mL) was injected SC at the periareolar 3, 6, 9, and 12 o'clock positions (2 mL at each site) with a 26-gauge needle. After 5 minutes of massaging, all the blue-stained LNs in the axilla were excised. The LN(s) marked by CTL were also excised, even if they were not stained blue. Each excised LN was carefully noted to indicate which technique was used for its determination (BD, CTL, or both). In case of metastatic involvement reported by the Pathology Department, ALND was performed in the same setting.

Statistical Analysis

The CTL and BD techniques were compared for overall SLN detection rates as well as detection rates based on the presence of metastatic involvement in the LN(s), tumor location, and age of the patients. The statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) for Windows 20.0 program. The t-test was used to evaluate the data, with $p<0.05$ being considered statistically significant.

RESULTS

A total of 47 women (mean age: 50; range: 28-77) underwent CTL before breast surgery, including SLNB. Of these, 45 patients had early-stage (T1 or T2) invasive breast cancer, and 2 patients had ductal carcinoma in situ (DCIS) and underwent mastectomy. The histopathological diagnoses were invasive ductal carcinoma (n=42), invasive lobular carcinoma (n=3), and DCIS (n=2).

The 45 invasive cancers had a mean tumor diameter of 1.98 cm, ranging from 0.6 to 5.0 cm. The two patients with ductal carcinoma in situ had tumors measuring 10.5 cm and 1.5 cm, and SLNB was performed in both cases due to planned mastectomy. The location of the lesions was in the right breast in 25 patients, with 16 in the upper outer quadrant, 5 in the lower outer quadrant, 3 in the upper inner quadrant, and 1 retroareolar. In the left breast, 22 patients had lesions, with 12 in the upper outer quadrant, 3 in the lower outer quadrant, 3 in the upper inner quadrant, 1 in the lower inner quadrant, and 3 retroareolar.

During the surgery, 26 patients without metastatic axillary LNs underwent breast surgery and SLNB, while 21 patients had to undergo ALND, with 19 of them having metastatic SLNs. Two patients required ALND because SLN could not be detected by either method.

A comparison of the two methods in 47 patients showed that in 27 (57.5%) patients, the same lymph node (LN) was identified with both CTL and BD. In 12 (25.6%) patients, CTL failed to identify any LN while BD was successful. On the other hand, 6 (12.7%) patients had no LN detected by BD, but CTL found SLNs in 4 (8.5%) of them. In 2 of these 4 cases, the SLNB confirmed that the detected LNs were benign, thus avoiding unnecessary ALND thanks to CTL. However, in 2 (4.3%) patients, BD and CTL marked different LNs, and subsequent pathological examination showed that only the LNs identified by BD had metastatic involvement. As a result, the LNs identified by CTL in these 2 patients were not considered sentinel. Finally, in 2 (4.3%) patients, neither method was able to detect any LN, and ALND revealed benign axillary LNs.

The rates of detecting the SLNs using two different methods, BD and CTL, as well as the overall detection rate using either method or both, are presented (**Table 1**). These rates were compared based on the presence of metastatic involvement in the lymph nodes. The results showed that the rate of SLN detection was significantly higher with BD compared to CTL, with a P-value of 0.027. However, the higher detection rate when using at least one of the methods (BD and/or CTL) compared to BD alone was not statistically significant, with a P-value of 0.267.

Table 1. Comparison of the detection rates of SLNs according to metastatic LN involvement in CTL, BD and with at least one of the methods (BD and/or CTL).

	Benign (n=28)	Malignant (n=19)	Total (n=47)	P
CTL	20 (71.4%)	11 (57.9%)	31 (66.0%)	
BD	24 (85.7%)	17 (89.5%)	41 (87.2%)	0.027 (BD vs CTL)
BD and/or CTL	26 (92.9%)	19 (100.0%)	45 (95.7%)	0.267 (BD vs BD+CTL)

CTL: CT lymphgraphy; BD: Blue-dye method

According to the presence of metastatic LNs, the differences in detection rates of both methods were not statistically significant. With CTL, the detection rate of benign SLNs was higher than that of metastatic SLNs (P=0.366). With BD, the detection rate of malignant SLNs was higher than that of benign SLNs (P=1.00).

According to the detected LNs and LDs, CTL successfully identified SLNs in 31 (66.0%) of 47 patients. Of these 31 patients, both LDs and SLN were successfully imaged in 12 (38.7%) patients with CTL. In 19 (61.3%) patients in whom LDs could not be visualized, the first contrast-enhanced LN in the axilla was considered as the SLN. A total of 37 LNs were marked in 31 patients with CTL (1 in 28 patients, 2 in 2 patients, and 3 in 1 patient). In 16 of the 47 (34.0%) patients who underwent CTL, no LN could be marked because the contrast did not reach the axilla. A total of 46 LNs were blue-stained in 41 patients with BD (1 in 37 patients, 2 in 3 patients, and 3 in 1 patient). In 6 (12.8%) of the 47 patients who underwent BD, no LN was stained. In 4 of the 6 patients in whom no LN could be identified with the BD method, CTL was able to detect SLNs.

According to tumor location, the SLN detection rate of CTL and BD methods were 17 (60.7%) and 25 (89.3%) of 28 upper outer quadrant tumors and 5 (62.5%) and 7(87.5%) of 8 lower outer quadrant tumors, respectively. The performances of the two methods were similar in the retroareolar (3 of 4, 75.0%) and in the upper inner (5 of 6, 83.3%) and the lower inner (1 of 1, 100%) quadrants. The success of CTL in upper outer quadrant tumors (60.7%) was lower than the rest of the tumors (14 of 19, 73.7%), but this difference was not statistically significant (P=0.220). On the other hand, the success of BD in upper outer quadrant tumors (89.3%) was higher than the rest of the tumors (84.2%), with no statistical significance (P=0.674). Two SLNs that could not be detected by either method were in patients with DCIS in the left lower outer quadrant and invasive lobular carcinoma in the right upper outer quadrant. These patients underwent ALND after which no metastatic involvement was noted.

According to age, CTL was successful in 18 (90.0%) of 20 patients under 50 years of age and 13 (48.2%) of 37 patients 50 years and over. The higher rate of success in younger patients was statistically significant (P=0.001). The BD method was successful in 18 (90.0%) of 20 patients under 50 years of age and in 23 (85.2%) of 27 patients 50 years and over. The higher rate of success in younger patients was not statistically significant (P=0.378).

DISCUSSION

In our research, the success rate of detecting SLNs with the CTL method was 66.0%, which was lower than previous reports by Minohata et al. (24) who reported a 98.5% success rate, and Takahashi et al. (21) who reported a 96% success rate. The detection rate of SLNs with BD in our study was 87.2%, similar to previous reports. In a meta-analysis of 18 studies, Li et al. (25) reported a detection rate of 75-100%. The combination of CTL and BD methods improved the detection rate of SLNs from 87.2% to 95.7% in our study. Although this increase was not statistically significant (P=0.267), the results were similar compared to previous reports. Minohata et al. (24) reported that the SLN detection rate was 95% with only the BD method, but 99% with the addition of CTL. Similarly, Takahashi et al. (21) reported an increase in the detection of SLNs from 92% to 99% with the combination of CTL to the conventional BD technique.

Our study found that the SLN detection rate with CTL was higher in benign LNs (71.43%) compared to metastatic SLNs (57.9%), which was consistent with previous reports. Takahashi et al. (21) and Minohata et al. (24) also reported lower detection rates in metastatic LNs. The possible explanation for this failure in metastatic LNs may be the blockage of lymphatics by tumor cells or the development of alternative lymphatic pathways (26).

Our study found that with BD, benign SLNs were successfully detected by 85.7% and metastatic SLNs by 89.5%, which was not compatible with previous reports. Takahashi et al. (21) and Minohata et al. (24) reported a better rate of detection in benign SLNs than metastatic SLNs with BD.

Motomura et al. (23) used the size criteria for the differentiation of benign and metastatic LNs. A node larger than 5 mm in short-axis diameter on CTL was considered metastatic. Nakagawa et al. (14) described a typical pattern of metastatic LNs and LDs on CTL. According to this study, a stain defect in the LNs, as well as dilatation and stagnation of lymphatics, were signs of metastases. They reported 92.5% sensitivity, 88.6% specificity, and 89% accuracy with the criteria they defined. In a 12-year study, Yamamoto et al. (22) reported that SLNB disclosed 12% and 40% of micro- and macrometastasis, respectively, in LNs with filling defects. In LNs without any contrast filling defects, SLNB disclosed 5% and 7% micro- and macrometastasis, respectively. Due to the high rate of false negative and positive results, filling defects in LNs detected by CTL was not a reliable diagnostic criterion for the presence of metastasis. In our series, we ignored the presence of filling defects since the aim of CTL was to localize the SLN(s), not to differentiate benign and metastatic LN(s) (**Figure 2**).

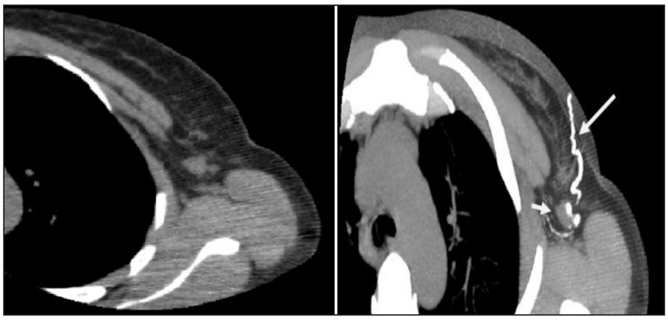

Figure 2. a-b. A 46-year-old female presents with invasive ductal carcinoma. SLN pathology is negative for metastasis. An axial precontrast image shows two radiologically benign lymph nodes (a). An axial postcontrast MIP image shows a filling defect in the larger lymph node (short arrow) and a contrast-filled lymphatic duct (long arrow) (b).

Identification of LDs enable a more accurate localization of SLNs (22). With the RILtechnique, LDs cannot be clearly identified as in BD or CTL methods. Yamamoto et al.(22) could image both LNs and LDs in 96% of the patients with CTL. In our study, both LDs and SLNs could be imaged in 12 (38.7%) patients with CTL, whereas in 19 (61.3%) patients only SLNs were imaged. The authors need more experience to develop their technical skills, since the success rate of SLN detection was lower in our initial cases.

Both CTL and BD methods could not perform a statistically significant difference, according to the location of tumors. CTL showed lesser success in the upper outer quadrant tumors (73.7%), compared to otherlocations

(60.7%).Similarly in a study with CTL, Minohata et al. (24) reported a lower detection rate of SLNs in upper outer quadrant tumors (96%),than other quadrant tumors (100%),without statistical significance(P=0.24). Success rate of BD in the upper outer quadrant (89.3%) was higher than in other locations(84.2%) in our study. However, Minohata et al. (24) reported that SLNs of tumors located in the upper outer quadrant (98%) could be detected less than other quadrant tumors(100%) with the BD method (P=0.29).

Minohata et al. (24) reported that CTL was more successful in patients older than 50-years-old (P=0.24). In our study both BD (P=0.378) and CTL (P=0.001) were more successful in younger patients. In the same study, they reported no statistically significant association between body mass index (BMI), tumor size, and success of CTL, either. In our study we did not study a possible correlation with BMI and tumor size.

There are different, relatively new radiological techniques other than CTL which may be an alternative to BD in SLNB. With MR lymphography using superparamagnetic iron oxide as contrast agent,97-100% detection rate of SLNs were reported (11,15).With US lymphography using sonographic contrast agents Sonazoid(Perfluorobutane) (17) and Sonovue (sulfur hexafluoride) (27), detection rates of 95% to 98% were reported. But these techniques need to be validated by larger series.

The limitations of this study is the relatively small number of patients and the relatively limited experience of the CTL operators. Breast surgeon team in the study group has been practising SLNB with BD technique for the last 14 years. However CTL procedure has been practiced since 2015 by the radiologists. SLNB with CTL has become popular since early 2000's especially in Japan. In our country it is not a frequent technique. In our institution, we have got promising results with our 3-year-experience.

CONCLUSION

The CTL is insufficient as a stand-alone method to determine SLNs, but may be a complementary method that increased the success of SLN detection when applied together with BD method. With increasing experience, it will provide better results for more accurate localization of SLNs. Studies with larger patient series will shed light on the subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kocaeli University Non-interventional Clinical Researches Ethics Committee (Date: 20.07.2016, Decision No: KÜ-GOKAEK 2016).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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