FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol.12, No 2, 2005, pp. 76 - 80 UC 616-006.6:616.428-076

SIGNIFICANCE OF SENTINEL LYMPH NODE BIOPSY LABELED BY TECHNETIUM TC99M AND PATENT BLUE IN TREATMENT OF PATIENTS WITH THE BREAST CANCER

Milan Višnjić[1], Predrag Kovačević[1], Marina Vlajković[2], Lidija Djordjević[1], Goran Djordjević[1]

[1]*Clinic of Plastic and Reconstructive Surgery, Clinical Center Niš*
[2]*Department of Nuclear Medicine, Clinical Center Niš*

Summary. *The major advance in breast cancer management is sentinel lymph node (SLN) localization and biopsy. The aim of the study was to assess the role of lymphatic mapping and gamma-probe guided lymph node biopsy in breast cancer patients. Thirteen women (mean age 49 years) were analysed. Invasive ductal carcinoma was found in 62%, invasive lobular carcinoma in 15%, and ductal carcinoma in situ in 23%. A total of 0.3 ml (50 MBq) of human albumine labeled by technetium 99m was injected intradermally over the tumor. Dynamic lymphoscintigraphy was performed followed by early and late (16h) static scintigraphy. Blue dye (1%, 3 ml) was injected around the breast mass, 10 minutes before surgery. During the surgery, a gamma probe was used to localize SLN. All SLNs were examined by frozen section, hematoxylin eosin staining and immunohistochemically. The success rate of SLN identification was 100%. Six of the 13 patients (46%) had metastatic disease in the axilla. Of the 6 patients with metastases, the range of involved nodes was from 1 to 3. The SLN(s) was positive in all patients with metastatic disease (sensitivity: 100%), and thus there were no skip metastases (false negatives: 0%). The SLN was the only site of metastases in 4 of 6 patients (66%). Sentinel node biopsy is a highly accurate method for staging and treatment of breast cancer patients.*

Key words: *Breast cancer, sentinel lymph node, technetium Tc99m, patent blue, biopsy*

Introduction

The axillary node status is one of the most powerful prognostic factors for recurrence and survival of patients with primary breast cancer. Nodal status dwarfs other variables based on the primary tumor in prognostic importance including tumor size, estrogen receptor status and ploidy. Multiple regression analysis demonstrates these variables add very little to the prognostic model after lymph node status is considered. The presence of nodal metastases decreases the 5-year survival rate by approximately 40%, compared to patients who are node negative (1). Its dissection has long been the standard procedure for nodal staging in breast cancer. However, axillary nodal dissection may be associated with significant morbidity, including the need for general anesthesia, postoperative lymph edema of the involved extremity, neuropathy of the arm, seroma formation, formation of a painful neuroma, or local wound problems. These complications are associated with increased hospitalizations and considerable discomfort to the patient.

One of the major advances in breast cancer management has been the development of the approach of sentinel lymph node localization and biopsy (2-5). The sentinel lymph node(s) are defined as the first node(s) in the regional lymphatic basin that receive lymphatic drainage directly from the primary tumor. The sentinel lymph node reflects the histologic status of the rest of the nodes in the draining basin. This new approach in axillary staging has proved more conservative and highly accurate with the negative predictive value of almost 100%, especially in early-stage disease (6). Patients can benefit from techniques that make the axillary procedure more conservative and less morbid.

Providing accurate staging for the breast cancer population may contribute to the survival benefit generating by surgical treatment or adjuvant therapy. More accurate staging and effective treatment allow for the identification of a percentage of the breast cancer population that would otherwise be exposed to the potential complications of an extensive surgical procedure or toxicity associated with some chemotherapy or hormone regimens.

The aim of the study was to assess the role of lymphatic mapping and gamma-probe guided lymph node localization in the management of patients with the breast cancer.

Methods for Lymphoscintigraphy

Filtered human serum albumin colloid (HSA) was labeled with 370MBq technetium-99m (99mTc) according to the manufacturer instruction ("SENTI-SCINT", Medi-Radiopharma, Hungary). More than 80% of the labeled

colloid has a particle size in the range of 100-600 nanometers as measured by dynamic light scattering method. The patients were given a total of 0.3 ml (50 MBq) of a radiopharmaceutical intradermally over the tumor at five separate sites. The studies were done using Gamma camera "Siemens" equipped with a low energy all purpose colimator. Dynamic lymphoscintigraphy was performed immediately after the tracer was applicated, followed by early and late (12–16h) anterior and lateral 3 minutes static scintigraphy. The patient's arm was extended above the head to optimize axillary area vizualization. Dynamic images were collected using 64×64, while static images were acquired using 128×128 computer matrix. Using a gamma probe ("Europrobe", France) with an audible guidance system, the axillar region was explored and the area with the highest count rate corresponding to the visualized sentinel lymph node on late lymphoscintigraphy was marked as the place where the sentinel lymph node is the closest to the skin.

At the time of surgery, blue dye was injected intraparenchymally at four sites around the breast mass, 10 minutes before surgery. During the surgery, a gamma probe was used to localize sentinel lymph nodes. All sentinel lymph nodes were examined by frozen section, hematoxylin and eosin staining and if negative were explored immunohistochemically for the detection of micrometastases.

Results

The results present the first experience of the Clinical Center Niš with breast lymphatic mapping, performed from January to April 2005. Enrollment criteria included patients highly suspected of having breast cancer with clinically negative axillary lymph nodes on physical examination, scheduled for either a lumpectomy and axillary node dissection or a modified radical mastectomy. A total of 13 women with a mean age of 49 years (range: 33 to 67 years) were enrolled in the study. Invasive ductal carcinoma dominated the histology of the primary tumors with 62% of the women having this histologic type, 15% of women were with invasive lobular carcinoma, and the others had ductal carcinoma in situ. Sensitivity was calculated by the number of patients in which the histology of the SLN reflected the histology of the remainder of the nodal basin. The unit of analysis was patients and not the number of lymph nodes harvested. All patients had removal of the primary breast cancer by either lumpectomy (31%) or mastectomy (69%), followed in all cases by SLN biopsy and complete lymph node dissection (69%).

A total of 12 SLNs were detected in 11 patients on dynamic and early static lymphoscintigraphy. Early static scintigraphy failed to detect 2 SLNs (14%). Late static scintigraphy demonstrated 14 SLN-s in all 13 patients. No additional SLN was detected in all 13 patients in whom early or late static scintigraphy demonstrated SLNs. All axillary SLNs localised preoperatively were found during the operation by collimated gamma probe detector. Vital blue dye failed to colour one SLN in a patient in whom 2 SLNs were found by lymphoscintigraphy.

The success rate of SLN identification was 100%. In the women in whom mastectomy was done, an average of 6.5 non-SLNs/patient and 1.1 SLNs/patient were obtained. Six of the 13 patients with successful localizations (46%) had metastatic disease to the axilla. Of the 6 patients with metastases, the range of involved nodes was from 1 to 3. The SLN(s) was positive in two patients with metastatic disease (sensitivity: 100%), and thus there were no skip metastases (false negatives: 0%). The SLN was the only site of metastases in 4 of 6 patients (66%).

Report of the Case

A 65-year-old women presented with a left upper outer quadrant breast lump and without any palpable axillary node. Dynamic, early and late lyphoscintigraphy demonstrated two closely related sentinel lymph nodes, of which the lower one was greater in diameter (Fig. 1). Left breast lumpectomy and sentinel nodes excision from the left axilla were performed. Sentinel lymph nodes were both radioactive, but the greater one was not blue coloured (Fig. 2). Histologically, the left

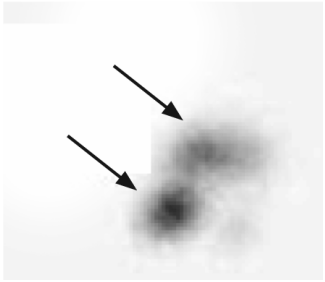

Fig. 1. Late lyphoscintigraphy of the left axilla 16h after intradermal application of 99mTc-HSA demonstrated two closely related sentinel lymph nodes

Fig. 2. Left breast specimen and both sentinel lymph nodes after removal.

breast lumpectomy specimen showed well differentiated ductal carcinoma. Both sentinel lymp nodes were negative on hemotaxin and eosin staining but the smaller one of the removed sentinel lymph nodes was found with micrometastases immunohistochemically (Fig. 3). The patient was subjected to radical mastectomy with complete axillary dissection. The SLN was the only place of micrometastasis and none of the 8 axillary lymph nodes removed during the radical surgery has been found to have metastasis.

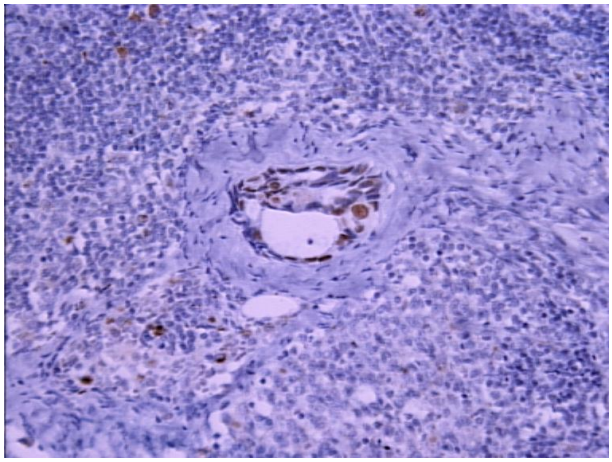

Fig. 3. Micrometastases detected immunohystochemically in one of two sentinel lymph nodes.

Discussion

The risk of metastases depends directly upon the tumor size (7). The development of imaging techniques and screening examinations has made it possible to identify mammary lesions at an early stage so new cases of breast cancer in general present with smaller primary lesions. By contrast, diagnostic non-invasive or minimaly invasive procedures that provide accurate preoperative staging of the lymph node status were not available since the sentinel lymph node concept was introduced. The sentinel lymph node biopsy concept has been developed by Morton et al. as a basis for selecting melanoma patients for regional lymph node dissection (2,3,8). Assuming that lymphogenous metastasis precedes haematogenous metastasis, they demonstrated that early metastasis of melanoma can be localised in the first draining lymph node (sentinel lymph node). Applying this concept to the breast it is likely that any cancer cell which has become detached from the primary tumor will follow the same route as lymph from the site of the primary carcinoma. And conversely, if a careful examination of the sentinel node does not show the presence of cancer cells, the other axillary nodes should also be free of disease.

The axillary sentinel node can be properly identified in 90 to 100% of patients with use of an intraoperative gamma detecting probe and blue dye (9,10,11). The technical success rate for the exam has been reported to be between 66% to 100%. The exam has a reported sensitivity of 83-100% (roughly 95-97%), specificity of 100%, positive predictive value of 100%, negative predictive value of 92-100%, and an accuracy of 95-100% (12,13). The exam has been shown to be highly reproducible (14), accurate (15), and associated with less morbidity compared to axillary node dissection (15).

Lymphatic mapping is a coordinated effort involving a team of physicians--surgeon, nuclear medicine physician, and pathologist. The technique used by the nuclear medicine physician for injecting the radiocolloid directly influences both the ability to image SLNs in the axilla and the surgeon's success in locating the axillary SLN. Breast lymphatics may drain in multiple directions but mainly into the axilla, to a lesser extent into the internal mammary lymph chain, and rarely to the supraclavicular and subclavicular area directly. Till now, there is no standardized technique for sentinel node localization. Wide variations still exist regarding particle size, timing of injection, volume and placement of the injection, use of pre-operative imaging, and operative techniques. There has been some controversy in the literature regarding injection into the skin above the primary site rather than into the breast parenchyma. In general terms, injection techniques may be classified as superficial or deep. Skin-related techniques (periareolar, subareolar, intradermal or subcutaneous) consider the injection of radiopharmaceutical over the primary tumor site. These four injection types are based on the hypothesis that the breast and the overlying skin share lymphatic drainage to a common node because the mammary gland is embriologically derived from the ectoderm (16). Few studies have been performed to determine the optimal radiocolloid for lymphatic mapping, but there are no unequivocal conclusions as to the advantages and disadvantages of the radiopharmaceuticals with various particle size (17,18,19). The ideal radiocolloid would have a proper particle size and stability allowing rapid migration into the lymphatics with deposition and concentration in the SLN. The results of our study suggest that the use of larger colloidal particles 100-600 nm is to be preferred because only one or two sentinel nodes were identified even after 14-16 hours. This allows the surgeon to find the sentinel node easily and quickly. Smaller size colloids are often trapped in several lymp nodes giving a higher false positive rate.

Studies conducted using blue dye only would indicate that this concept can be successfully applied to the management of breast cancer (20). However, with blue dye the SLNs can be missed in up to 30-40% of cases (21). The use of dye has an important drawback, namely, the axillary tissue must be dissected blindly until the blue node is located. This node can be difficult to find since it can be several centimeters from the incision. The advantage of the lymphoscintigraphy imaging technique is that it locates the node and indicates exactly where the skin incision should be made. The small probe detector guides the dissection itself.

The very first results of lymphatic mapping and gamma-probe guided lymph node localization in the management of patients with breast cancer obtained in

our study are promising. The success rate of SLN identification was 100%. Twelve SLNs were detected in 11 patients on dynamic and early static lymphoscintigraphy. Early static scintigraphy failed to detect 2 SLNs (14%). However, late static scintigraphy demonstrated 14 SLN-s in all 13 patients. No additional SLN was detected in the patients in whom early or late static scintigraphy demonstrated SLNs. All axillary SLNs localised preoperatively were found during the operation with a collimated gamma probe detector. Vital blue dye failed to colour one SLN in a patient in whom 2 SLNs were found by lymphoscintigraphy. Six of the 13 patients with successful localizations (46%) had metastatic disease to the axilla. Of the 6 patients with metastases, the range of involved nodes was from 1 to 3. The SLN(s) was positive in two patients with metastatic disease (sensitivity: 100%), and thus there were no skip metastases (false negatives: 0%). The SLN was the only site of metastases in 4 of 6 patients (66%).

Lymphatic mapping using lymphoscintigraphy and blue dye techniques as well as selective lymphadenectomy is a technically feasible and highly accurate method for staging breast cancer patients. The histology of the SLN is reflective of the status of the remaining axillary lymph nodes. The procedure can be performed as an outpatient procedure. Sentinel lymph node biopsy is a more conservative approach to the surgical management of the axilla in breast cancer and provides more information from a detailed examination. The ability to decrease morbidity without compromising patient care is the greatest advantage of lymphatic mapping.

References

1. Bonadonna G. Conceptual and pratcical advances in the management of breast cancer. Karnofsky Memorial Lecture. J Clin Oncol 1989; 7: 1380-1397.
2. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992; 127: 392-399.
3. Morton DL, Bostik PJ. Will the true sentinel node please stand? Ann Surg Oncol 1999; 6: 12-14.
4. Thompson JF, Uren RF. What is a "sentinel" lymph node? Eur J Surg Oncol 2000; 26: 103-104.
5. Nieweg OE, Tanis PJ, Kroon BBR. The definition of a sentinel node. Ann Surg Oncol 2001; 8: 538-541.
6. Veronesi U, Paganelli G, Galimberti V, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet 1997; 349: 1864-1867.
7. Fisher B, Wolkman N, Bauer M, et al. The accuracy of clinical nodal staging and of limited axillary dissection as a determinant of histologic nodal status in carcinoma of the breast. Surg Gynecol Obstet 1981; 152: 765-772.
8. Morton D, Wen D, Cohran A. Management of early-stage melanoma by intraoperative lymphatic mapping and selective lymphadenectomy: an alternative to routine elective lymphadenectomy or "wach and wait". Surg Oncol Clin North Am 1992; 1: 247-259.
9. De Cicco C, Cremonesi M, Luini A et al. Lymphoscintigraphy and radioguided biopsy of the sentinel axillary node in breast cancer. J Nucl Med 1998; 39: 2080-2084.
10. Birdwell RL, Smith KL, Betts BJ, et al. Breast cancer. Variables affecting sentinel lymph node visualization at preoperative lymphscintigraphy. Radiology 2001; 220: 47-53.
11. Linehan DC, Hill AD, Tran KN, et al. Intradermal radiocolloid and intraparenchymal blue dye injection optimized sentinel node identification in breast cancer patients. Ann Surg Oncol 1999; 6: 450-454.
12. Liberman L, Cody HS, Hill AD, et al. Sentinel lymph node biopsy after percutaneous diagnosis of nonpalpable breast cancer. Radiology 1999; 211: 835-844.
13. Mariani G, Moresco L, Viale G, et al. Radioguided sentinel lymph node biopsy in breast cancer surgery. J Nucl Med 2001; 42: 1198-1215.
14. Tanis PJ, Valdes Olmos RA, Muller SH, et al. Lymphatic mapping in patients with breast carcinoma: reproducibility of lymphoscintigraphic results. Radiology 2003; 228: 546-551.
15. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003; 349: 546-553.
16. Borgstein PJ, Meijer S, Pijpers R. Intradermal blue dye to identify the sentinel lymph node in breast cancer. Lancet 1997; 349: 1668-1669.
17. Borgstein PJ, Pijpers R, Comans EF, et al. Sentinel lymph node biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. J Am Col Surg 1998; 186: 275-283.
18. Liu TJ, Wang SJ, Tsai SC. Lymphoscintigraphy using larger colloid particles may enhance visualization of the sentinel node in breast cancer. A case report. Clin nucl Med 2000; 25: 191-192.
19. Pijpers R, Meijer S, Hoechstra OS, et al. Impact of lyphoscintigraphy on sentinel node identification with technetium-99m colloidal albumin in breast cancer. J Nucl Med 1997; 38: 366.
20. Giuliano AE, Dale PS, Turner RR, et al. Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann Surg 1995; 222: 394-401.
21. Paganelli G. Sentinel node biopsy: role of nuclear medicine in conservative surgery of breast cancer. Eur J Nucl Med 1998; 25: 99-100.

ZNAČAJ BIOPSIJE LIMFNIH ČVOROVA STRAŽARA OBELEŽENIH TEHNECIJUMOM I METILENSKIM PLAVIM U TRETMANU PACIJENATA SA KARCINOMOM DOJKE

Milan Višnjić[1], Predrag Kovačević[1], Marina Vlajković[2], Lidija Đorđević[1], Goran Đorđević[1]

[1]Hirurška klinika, Klinički centar Niš
[2]Institut za nuklearnu medicinu, Klinički centar Niš

Kratak sadržaj: *Veliki napredak u tretmanu karcinoma dojke je lokalnizacija i biopsija limfnog čvora stražara. Cilj rada je da se utvrdi značaj limfnog obeleđavanja i biopsije limfnog čvora vođene gama kamerom kod pacijenata sa karcinomom dojke. Ispitivano je trinaest žena (prosečne starosti 49 godina). Invazivni duktalni karcinom nađen je kod 62%, invazivni lobularni karcinom kod 15%, a duktalni karcinom in situ kod 23% pacijenata. Intradermalno iznad tumora je ubrizgana količina od 0,3ml (50 MBq) humanog albumina obeleđenog sa tehnecijumom Tc99m. Rađena je dinamska scintigrafija, a posle nje rana i kasna (16h) statična scintigrafija. Metil plavo (1%, 3 ml) je ubrizgano oko tumora dojke 10 minuta preoperacije. Tokom operacije je korištena gama kamera za loklaizaciju limfnog čvora strađara.Svi limfni čvorovi strađari su smrzavani i bojeni hematoksilin eoyin i imunohistohemijskom tehnikom. Uspešnost identifikacije limfnog čvora strađara je 100%, Šest od 13 pacijenata (46%) je imalo metastaze u aksili. Od 6 pacijenata sa metastazama broj poyitivnih limfnih čvorova bio je 1 do 3. Limfni čvor stražar je bio pozitivan kod svih pacijenata sa meatstazama (senzitivnost 100%). Tako da nije bilo metastaza koje su preskakale limfni čvor stražar (lažno negativno 0%). Limfni čvor stražar je bio jedino mesto metastaze kod 4 od 6 pacijenata.(66%). Biopsija limfnog čvora stražara je jako važan metod za određivanje tradijuma i za tretman pacijenata sa karcinomom dojke.*

Ključne reči: *Karcinom dojke, limfni čvor stražar, tehnecijum Tc99m, metil plavo, biopsija*