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OUR EXPERIENCE WITH SENTINEL LYMPH NODE DETECTION AND BIOPSY IN BREAST CANCER AND MALIGNANT MELANOMA

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A b s t r a c t

The aim of this study was to establish whether it is necessary to employ three methods or whether it is sufficient to use one or two methods for sentinel lymph node detection in breast cancer and malignant melanoma patients.

There are described methods of scintigraphic detection, utilisation of surgical gamma probe and isosulfan blue dye in patients with these malignant tumours.

Sentinel nodes were examined by one, two, or all three methods in 83 breast cancer patients and 149 melanoma patients. No nodes were found by any of the three methods in 2 patients with breast cancer and 6 patients with malignant melanoma. Generally, by scintigraphy, 193 lymph nodes (average 2.3 in 1 patient) were imaged in the group of breast cancer patients, and 268 lymph nodes in malignant melanoma patients (average 1.8 in 1 patient).

In the group of patients with breast cancer, scintigraphy failed to display the sentinel lymph node in 6 patients – success rate of lymphoscintigraphy was 92.8 %. The detection rate of the lymph node using the gamma probe was 88.5 %.

The success rate of lymph node detection using blue dye was 86.4 %.

A combination of scintigraphy, blue dye, and probe proved a sentinel lymph node in 97.6 % of all patients examined (in 81 of 83 patients).

In the group of patients with malignant melanoma, the success rate of lymphoscintigraphy was 94.6 %, the success rate of lymph node detection using blue dye was 75.8 %, the success rate of the sentinel lymph node detection using the gamma probe was 85.2 %, and generally we proved a sentinel lymph node in 96 % of all patients examined (in 143 of 149 patients).

Lymph node metastatic involvement was demonstrated in 36 patients (43.4 % of all) with breast cancer and in 14 patients with malignant melanoma (9.4 % of all).

It follows from the finding data that parallel use of scintigraphy, surgical gamma probe, and isosulfan blue dye is the most effective for sentinel lymph node detection.

K e y w o r d s

Sentinel lymph node, Lymphoscintigraphy, Surgical gamma probe, Isosulfan blue dye, Breast cancer, Malignant melanoma

INTRODUCTION

Evidence of sentinel lymph node in some types of malignant tumours – particularly in breast cancer and malignant melanoma patients – is important in order to determine the complex therapeutical strategy, prognosis, and staging. If, after surgical removal and histopathological examination, it proves that the sentinel lymph node is not affected by metastasis, it is possible to avoid removal of whole groups of lymph nodes and thus to avoid bothering the patient with unnecessarily extensive procedures, often associated with high morbidity.

MATERIAL AND METHODS

After peritumoral and subdermal application of radiopharmaceuticals we examined all patients using scintigraphy by means of a scintillation camera with recording the location of the lymph node by a cross on the skin. Operation of the tumour, removal of the sentinel lymph node, and removal of lymph nodes in the axilla (for the time being, axillary lymphadenectomy has been carried out in all breast cancer patients; we are still within the learning curve) followed on the same day in malignant melanoma patients, and on the second day after scintigraphy (two-day report), or less frequently on the same day (one-day report) in breast cancer patients. Proper localisation of the lymph node by the surgeon was facilitated firstly by the cross on the skin, secondly by dyeing the lymph node with blue dye applied near the tumour immediately before the operation, and also by using a surgical gamma probe capable of sensitive detection of radioactivity in the sentinel lymph node. The removal of the sentinel lymph node was subject to histological and immunohistochemical examination.

We performed scintigraphic detection of sentinel lymph node by means of three radiopharmaceuticals as follows:

NANOCIS (^{99m}Tc-colloid rhenium sulphate – nanocolloid) by Cis bio international, Gif-sur-Yvette, Cedex, France; SENTISCINT (^{99m}Tc-human serum albumin colloid) by FJC National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary; and NANOCOLL (^{99m} Tc-nanocolloid of human serum albumin) by Nycomed Amersham Sorin, Saluggia (Vercelli), Italy. The radiopharmaceuticals were applied in doses of 80–100 MBq by 4 peritumoral punctures and by 1 subdermal puncture above the tumour in breast cancer, and by 4 subdermal punctures around the tumour in malignant melanoma. The volume and activity in 1 puncture is 0.1–0.2 ml and 15–20 MBq. Immediately after application the nurse would gently knead the puncture for about 1 minute using a wad in forceps to accelerate the discharge of the radiopharmaceutical through the lymphatic system.

The puncture spot is covered with lead plates and fixed with a plaster (this coverage of the puncture spot would facilitate the subsequent scintigraphic evidence of the sentinel lymph node) (*13*). After the application, the patient is laid down under the detector of a scintillation camera (MEDISO TH Nucline, Budapest, Hungary) with a high-resolution collimator focusing on the area of interest; scintigraphy is carried out in anterior, lateral, and posterior position. If the sentinel lymph node is displayed, the occurrence spot is marked with a self-adhesive label on the computer monitor (for better orientation upon marking); subsequently the doctor in co-operation with the nurse would find the spot of occurrence of the lymph node using a spot cobalt source. The skin surface, under which the lymph node is located, is marked with a felt-tip pencil cross first and subsequently by dye. In breast cancer we perform a five-minute static scintigraphy in anterior and lateral position 1 hour after the application. If the node does not show up within 1 hour from the application of the radiopharmaceutical, static scintigraphy follows 2 hours after the application. If lymph node location is not successful this time either, the patient would be invited to appear on the next day, and the scintigrams are performed in the same projections 20–22 hours after application of the radiopharmaceutical. In malignant melanoma we perform dynamic scintigraphy for 20–30 minutes immediately after application and then a targeted five-minute static scintigraphy in anterior, lateral or even posterior projections, if necessary. After

displaying and marking the lymph node the doctor evaluates the study and the patient leaves with a description and scintigrams for surgery – removal of primary tumour and sentinel lymph node(s) and, for the time being, also for axillary lymphadenectomy.

In the operation theatres of five clinic centres of two hospitals, the surgeons have used isosulfan blue dye (Patent Blue V or Blue Patenté V, Laboratoire Guebert, Aulnay-sous-Bois, France) (2 ml of blue dye is applied during the surgical procedure either around the lesion, or around the excision spot. The sentinel lymph node is coloured first. The whole process is very quick because the dye penetrates the surrounding tissue within several minutes), and surgical scintillation probes of three types: a gamma probe DI SURPRO by Delong Instruments, Brno, Czech Republic, a surgical gamma probe NAVIGATOR GPS by Radiation Monitoring Devices, Inc., Watertown, Massachusetts, USA, and a gamma probe Neo2000 by Neoprobe Corporation, Dublin, Ohio, USA. For the material taken – the sentinel lymph node – a histopathological examination follows, consisting of a cytological examination of the lymph node from impression cytology carried out in the surgical room, and a histological examination (fixation of node in formol, covering with paraffin, serial cutting, dyeing with haematoxylin eosin, Schiff s reagent). To prove micrometastases, an immunohistochemical examination follows – in melanoma the proof of antigen associated with melanoma HMB-45 and S-100 protein (*4*), and in breast cancer the proof of cytokeratin and epithelial membrane antigen (*22*). Axillary nodes after axillary lymphadenectomy are examined in the same way.

RESULTS

Group of breast cancer patients

To prove sentinel lymph nodes, we examined 82 women and 1 man with the diagnosis of breast cancer (aged 60.4 years on average) from June 2002 to May 2003.

The one-day report (scintigraphy and operation on the same day) was carried out in 5 patients, while the two-day report was carried out in 78 patients.

Scintigraphic examination was carried out in all of them.

In 83 examined patients a total of 193 lymph nodes were displayed (2.3 node per patient on average); scintigraphy failed to display the sentinel lymph node in 6 patients (the success rate of lymphoscintigraphy was 92.8 % then).

A hit after 1 hour from the application occurred in 53 patients (63.9 %), in 2 hours in 16 patients (19.3 %), in 20–22 hours in 8 patients (9.6 %); no hit occurred in the remaining 6 patients (7.2 %).

Axillary and parasternal lymph nodes were displayed in 11 cases, only parasternal lymph nodes in two cases, and axillary lymph nodes (or together with the nodes directly in the breast tissue or supra- or infraclavicular nodes) in the remaining cases (*Fig. 1*).

Using the gamma probe, 78 patients were examined and 141 lymph nodes detected (1.8 lymph node per patient on average), while no lymph node was detected in 9 patients (11.5 % of the patients). The lymph node hit rate using the gamma probe was 88.5 %.

The surgeon examined 81 patients with isosulfan blue dye; 129 lymph nodes were dyed (1.6 lymph node per patient), and no lymph node was dyed in 11 patients (13.6 %). The lymph node hit rate using the blue dye was 86.4 %.

In four patients we used only scintigraphy with blue dye (agreement – detection

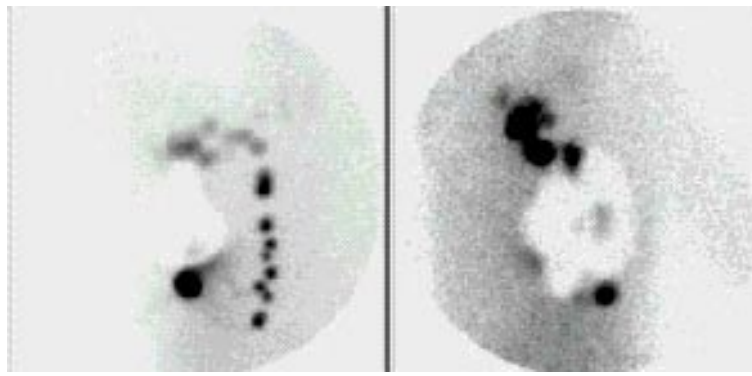

Fig. 1
Static scintigraphy 1 hour after radiopharmaceutical application in a patient with cancer in right breast.
Left: anterior projection, right: right lateral projection. The amount of parasternal lymph nodes and several axillary nodes is displayed.

both by scintigraphy and blue dye – in 2 patients, in whom affection of multiple lymph nodes by metastasis was detected, and agreement – without detection both by scintigraphy and blue dye also in 2 patients, in one of whom affection of multiple lymph nodes by metastasis was detected).

A combination of scintigraphy, probe, and blue dye was used in 77 patients (all the three methods corresponding with detection of lymph node in 59 cases, discovery by scintigraphy and blue dye in 5 cases, by scintigraphy and probe in 7 cases, by scintigraphy only in 2 cases, by blue dye only in 2 cases, by blue dye with probe in 2 cases).

In 2 patients (i.e. only in 2.4 %), the sentinel lymph node was not detected by any of the methods, which means that the combination of scintigraphy, blue dye and probe proved sentinel lymph nodes in 97.6 % of all patients examined.

In the set of 83 patients with breast carcinoma a node metastasis was detected in 36 patients, i.e. in 43.4 % of the operated patients. Out of these 36 patients with metastasis-affected nodes there were 2 patients with affected axillary lymph nodes without any affection of the sentinel lymph node, which means that skip metastasis was proved in 5.6 % (2 in 36). Only sentinel lymph nodes were affected in 21 patients (in these, there was only a micrometastasis in 5 of them), affection of both sentinel and axillary lymph nodes was proved in 13 (in this, micrometastasis in sentinel lymph node was detected in 1 case).

What was the situation with detection of sentinel lymph nodes with metastasis?

Scintigraphy with blue dye was used in two patients, both methods having been unsuccessful in the detection of the node in one patient.

All the three methods were combined in the other 33 patients; the lymph node was detected by all the three methods in 25 cases, by scintigraphy only in 2 cases, by scintigraphy and blue dye in 4 cases, and by scintigraphy and probe in 2 cases.

Group of malignant melanoma patients

To prove sentinel lymph nodes we examined 161 patients from November 2000 to March 2003; out of them 149 patients were with a diagnosis of malignant melanoma (62 men aged 58.9 on average and 87 women aged 53.8 on average). Twelve patients were excluded from the set because after histological examination either benign skin lesions or basocellular skin cancer were detected.

Melanoma thickness according to Breslow in the set of our patients ranged from 0.2 to 13 mm.

Localisation of melanoma in our patients:

Head	4
Upper limb	29
Ventral part of thorax	16
Back	54
Lower limb	44
Vagina	2

In a total of 149 examined patients, scintigraphic examination displayed 268 lymph nodes (1.8 node per patient on average); the scintigraphy failed to display the sentinel lymph node in 8 patients (the success rate of lymphoscintigraphy was 94.6 % then).

In 141 patients, in which scintigraphy proved a lymph node, 119 patients had a unilateral, 21 patients bilateral, and 1 patient trilateral lymph drainage.

Eighty-eight patients were examined by means of a gamma probe, while 107 lymph nodes were detected (1.2 nodes per patient on average) and no lymph node was found in 13 patients (14.8 %). The success rate of the lymph node detection using the gamma probe was 85.2 %.

The surgeon examined 124 patients using isosulfan blue dye; 113 lymph nodes were dyed (0.9 nodes per patient), no lymph node was dyed in 30 patients (4.2 %). The success rate of lymph node detection using blue dye was 75.8 %.

In patients we used only scintigraphy with blue dye in 47 cases (agreement – detection both by scintigraphy and blue dye – in 32, divergence – detection by scintigraphy and no detection by blue dye – in 15) and scintigraphy with probe in 10 cases (both methods coincident with detection of lymph node in 9 cases, in 1 case detection by probe only), all three methods in 79 patients (unsuccessful scintigraphy and probe, successful blue dye in 1 patient, detection by scintigraphy without detection by blue dye and probe in 11 cases, proof by scintigraphy and blue

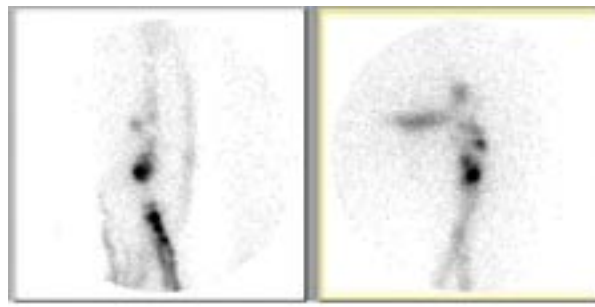

Fig. 2
Static scintigrams 30 minutes after radiopharmaceutical application in a patient with malignant melanoma of left heel.
Left: posterior projection – lymph nodes in popliteal socket
Right: anterior projection – inguinal lymph nodes

dye and unsuccessful probe in 1 case, detection by scintigraphy and probe without detection by blue dye in 4 patients and coincidence of all the three methods – all positive in 62 patients), and in 13 patients by scintigraphy only (including 6 non-detections of the lymph node).

No lymph node was found in 6 cases (generally we proved sentinel lymph node in 96 % of all patients examined – in 143 out of 149 patients). Unfortunately, these 6 operated patients were subjected to scintigraphic examination only.

The lymph nodes were affected by metastases in 14 patients; of this number in 12 patients only sentinel lymph nodes were affected, and in 2 patients other nodes besides the sentinel one were affected (*Fig. 2*).

Standard regional dissection of lymph nodes was subsequently carried out in these patients.

In patients with affected lymph nodes a combination of scintigraphy, blue dye and probe was used in 9 cases; all the three methods were successful in 7 cases, in 1 case detection by blue dye only was successful, and in 1 case by scintigraphy and blue dye. In 1 patient only scintigraphy was used (with display of the affected sentinel lymph node), a combination of scintigraphy and blue dye in 4 cases – the affected lymph nodes were displayed both on scintigrams and by blue dye in all 4 cases.

DISCUSSION

For complex therapeutic strategy, determination of prognosis and staging of the patients, especially with breast cancer and malignant melanoma, it is advantageous to know into which groups of lymph nodes the drainage of lymph from the tumour is directed. The first node draining the lymph flow from the primary tumour, and which as the first one is the most likely to be affected by metastases, is called

sentinel node. The conception of sentinel node was introduced by *Cabanas* in 1977 in penis cancer (*3*). The concept was later used in skin melanoma (*14*), and immediately afterwards in breast cancer (*8).* At first, the sentinel lymph node was located and removed by dye-navigated surgery (*14, 15*). The procedure was optimised by the application of a radiopharmaceutical around the tumour with subsequent lymphoscintigraphy using an operation gamma probe (*1, 11*).

In breast carcinoma the proving method of sentinel node is intended for patients without clinical suspicion of any axillary node affection.

At the time of detection of skin melanoma, most patients are without clinical suspicion of metastatic affection of regional lymph nodes. The probability of lymph metastases grows in tumours with medium (0.76 – 4 mm) thickness. Usefulness of elective dissection of lymph nodes is not quite sure in these patients. Some authors advocate the strategy of "monitoring and waiting", preferring the use of detection and biopsy of the sentinel node to an extensive dissection of nodes (*23*). This strategy is supported by extensive randomised studies, which detected no usefulness of regional lymphadenectomies for the patients (*19, 25*).

Prior to sentinel lymphadenectomy, most surgical centres currently use scintigraphic detection (orientation by means of a cross mark on the skin), isosulfan blue dye, and radionavigated surgery (gamma radiation from the radiopharmaceutical applied before scintigraphy at the nuclear medicine department and localised in the sentinel node is detected in the operation room during sentinel lymph node biopsy by a specially manually controlled gamma probe with a small detector sensitively detecting radioactivity) (*10, 24).*

This procedure in malignant melanoma is carried out on the day of scintigraphic examination, because scintigraphic display of a sentinel lymph node, unlike the situation in breast cancer, is a quick event. If the operation is to be carried out on the day following scintigraphy, it is necessary to apply a higher dose of 100 MBq of the radiopharmaceutical to be able to detect the lymph node.

To implement this combined scintigraphic examination with biopsy, a narrow co-operation between the nuclear medicine department and the surgical centre is necessary. It is necessary to pass 30 to 50 operations (learning curve) and to deal with the technique regularly in order to manage the operation technique. The technique must also be managed by the pathologist (*7*). Routine removal of parasternal lymph nodes (along v. mammaria interna) has not been carried out yet in breast cancer. Parasternal nodes are the alternative ways for metastatic cells, especially for tumours in the medial breast part (*9*). If parasternal sentinel lymph nodes are displayed, it should be the indication for planning radiotherapy on this area (*21*). A combination of peritumoral and subdermal application of the radiopharmaceutical results from the knowledge regarding the fact that after subdermal administration, lymphoscintigraphy would display the sentinel lymph node earlier and with a higher uptake of the radiopharmaceutical as compared with peritumoral injection (*6, 16*), while upon peritumoral administration, on the

contrary, there is a higher chance of displaying the parasternal lymph nodes (*18*).

Based on our experience obtained so far we may state that lateral projection is the most conclusive method for scintigraphic detection of axillary lymph nodes, anterior projection for display of parasternal nodes, posterior projection is necessary to prove the lymph node in popliteal socket in lymphoscintigraphy, anterior projection for display of an inguinal node. Failure to prove a sentinel lymph node may be caused by numerous factors, mostly by its significant affection by metastasis and also previous operation of the tumour. Therefore, the examination of a sentinel node is not suitable in the event of clinical suspicion of affection of the node by a tumour and after a performed operation procedure on breast, axillary or inguinal nodes. Formerly it was reported that the procedure was not suitable after performed chemotherapy of breast cancer either; recently detection of sentinel lymph nodes has been tested in these cases, too (*5*). In the event of failure of lymphoscintigraphy and gamma probe, proximity of tumour and sentinel lymph node may play a big role, too. Then it is necessary to recognise also the mistakes in identification of the sentinel lymph node and detection of micrometastasis in a properly detected sentinel lymph node, which may be influenced by various factors (technical failure of surgeon, biological factors, and failure during histopathological examination) (*20, 26*). With a negative finding in the sentinel lymph node (without metastasis) there is a high probability that the other nodes in the given basin are not affected either (except for skip metastasis, when the tumour cells skip the sentinel node and settle in the subsequent lymph node or nodes), and thus the patient may avoid an extensive removal of other lymph nodes connected with significant undesirable symptoms (*25*). The evidence and biopsy of sentinel lymph nodes are important for determination of complex therapeutical strategy, determination of prognosis and staging; in many cases it is possible to avoid removal of whole groups of lymph nodes and prevent the patient from being loaded with unnecessarily extensive procedures often connected with high morbidity. This detection method of sentinel lymph node is therefore very precious, apart from its contribution to the determination of staging and prognosis of the disease. This procedure has its economic advantages, too. During our work we did not compare the various manners of administration of radiopharmaceuticals – intradermal, subdermal, peritumoral, intratumoral, subareolar. We did not evaluate the advantages and disadvantages of the three types of gamma probes used, either (they were used in various departments) and the three types of radiopharmaceuticals (the prevailing majority of examinations were carried out by means of NANOCIS, the other two radiopharmaceuticals were used in a small number of patients only).

According to the literary data there are no unequivocal conclusions as to the advantages and disadvantages of the radiopharmaceuticals with various size of particles (*2, 12, 17*).

CONCLUSIONS

It follows from the data determined that simultaneous use of all the three methods – scintigraphy, isosulfan blue dye, and intraoperative gamma probe – is the most beneficial manner. Detection and biopsy of sentinel lymph nodes in patients with breast cancer and malignant melanoma require close co-operation of the nuclear medicine, surgical and pathological departments.

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DETEKCE A BIOPSIE SENTINELOVÝCH UZLIN U KARCINOMU PRSU A MALIGNÍHO MELANOMU

S o u h r n

Autoři se zabývají problematikou průkazu sentinelové uzliny u pacientů s karcinomem prsu a maligního melanomu. Popisují metody scintigrafického průkazu, využití operační gama-sondy a isosulfanové modři. Jednou, dvěma nebo všemi třemi metodami byly sentinelové uzliny zjišťovány u 83 nemocných s karcinomem prsu a u 149 pacientů s maligním melanomem.

U karcinomu prsu nebyla sentinelová uzlina zachycena ani jednou metodou u 2 nemocných. Celkově se scintigraficky zobrazilo 193 uzlin (průměr 2,3 /1 pacienta). U maligního melanomu nebyla sentinelová uzlina prokázána u 6 nemocných ani jednou metodou. Celkově se scintigraficky zobrazilo 268 uzlin (průměrně 1,8 uzliny/1 pacienta).

Nádorové postižení jedné nebo více uzlin bylo prokázáno u 36 nemocných s karcinomem prsu (tj. u 43,4 % nemocných) a u 14 pacientů s maligním melanomem (u 9,4 % pacientů).

Byl porovnán záchyt sentinelové uzliny těmito různými metodami. Ze zjištěných údajů vyplývá, že pro detekci sentinelové uzliny je nejpřínosnější použít současně scintigrafii, operační gama-sondu (radiační navigovanou chirurgii) a isosulfanovou modř.

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