Detection of the sentinel node in breast carcinoma using method of a single subcutaneous injection of radiopharmaceutical

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The objective of this work is retrospective evaluation of results of the intraoperative detection of sentinel node in breast carcinoma after a single subcutaneous injection of radiopharmaceutical (RF) within a two-day protocol.

From May/2001 to June/2002, lymphoscintigraphy of the sentinel node (SN) and its subsequent radioguided intraoperative detection (RGS) was performed in 43 women having stage T1–T2, N0 breast carcinoma. The static scans in the anterior and relevant lateral projections were performed using a gamma camera at approximately 30-minute intervals after the subcutaneous administration of 15 MBq ^{99m}Tc Senti-Scint, until the SN was displayed. The localization of the SN was marked on the overlying skin with a water-resistant permanent marker in 1–2 projections. RGS was accessed within 18–24 hours after the injection of the RF and all patients underwent an axillary dissection. The SN was detected in all patients, and in all cases was localized in the ipsilateral axilla. In 26 patients (60%), no metastatic process was found either in the SN or in any other axillary node. However, in one node, deposits of the carcinoma were detected in surrounding fatty tissue with propagation along the vessels and nerve. In 16 patients (37%), metastases in the SN were proved, in 7 cases (16%), a metastatic process was proved at the same time even in further lymph nodes. A number of false negative findings (5.8%) is consistent with the literature data. The method fails in the detection of intramammary localized SNs.

Key words: sentinel node, breast carcinoma, lymphoscintigraphy, Technetium-99m Senti-Scint, intra-operative gamma probe

Demonstration of the metastatic axillary lymph node process represents the most important prognostic factor in early stage breast carcinoma and at the same time it is a key factor for the indication of post-operative chemotherapy. Axillary lymph node dissection and their histopathological examination has recently been, and at some departments still represents, a part of a standard surgery procedure, which is considered to be the only possible method for the correct assessment of a possible metastatic node process. It is, however, known that for up to 70% of the patients axillary lymphadenectomy represents a useless diagnostic burden which not only fails to improve the patient's prognosis but on the contrary, it leads to higher morbidity due to the development of a secondary lymphedema in 15–30% of the patients, or seroma, infection, neurological complications etc. Therefore, a less invasive procedure for axillary staging should be introduced which would eliminate uselessly performed surgical lymphadenectomies. For axillary lymph node staging, some less invasive methods are used – e.g. ultrasonography, MRI and positron emission tomography (PET). However, the results of these methods are not as accurate as a surgical staging. Since the beginning of the 1990s, when a method of intraoperative detection of the SN was developed gradually and at some departments proved to be successful in malignant melanoma [5], this is used more often in breast carcinoma and is becoming a routine method at many departments. There are still new reports available, which describe the use of this method in other types of tumors (e.g. carcinoma of the penis, vulva and squamous head and neck carcinoma). The concept of the detection and subsequent dissection of the sentinel node of the primary tumor assumes that its staging reflects the

possible dissemination of a cancer process into the regional lymph nodes. If early lymphatic metastases are present, they are found in the SN at first [7]. The result of a histopathological examination of the SN affects the extent of subsequent axillary surgery. The surgeon performs dissection of the additional nodes only in situation when the SN metastatic process has been proved. On the other hand, if the finding is negative, further nodal surgery is not indicated. Therefore, dissection of the SN may replace a complete axillary dissection in patients with a N0 tumor. If a SN is not found, axillary exenteration is indicated. Another benefit of this method may be a more accurate histopathological examination of one or two SNs in comparison with the examination of a greater number of nodes after axillary dissection.

The aim of this work is a retrospective evaluation of the results of breast carcinoma intraoperative SN detection after the subcutaneous injection of the radiopharmaceutical (RF) within a two-day protocol, which has been used at our clinic since 2001.

Patients and methods

Lymphoscintigraphy of the SN and its subsequent radioguided intraoperative scanning detection (RGS) were performed from 5/01 to 6/02 in 48 patients with palpable or nonpalpable breast tumors with no clinical signs of lymph node metastases. The patients were aged 39–85 years (mean age 61 years). In all the patients, we used a "two-day protocol", with the injection of the RF and gamma camera imaging on the first day and with the surgery on the second day.

0.1–0.2 ml of 15 MBq ^{99m}Tc Senti-Scint (manufacturer Fodor Joszef NCPH, Fed. J. Curie, NRI Radiob, Budapest) was administered subcutaneously at 1:00–2:00 p.m. on the first day above the projected tumor localization. After the injection of the RF, a gentle massage of the administration site was performed for 1–2 minutes, to quicken lymphatic drainage. 15 images per 60-second (matrix of 64x64) were acquired immediately with the use of single-headed gamma camera Sopha DXT equipped with LEHR collimator. Patients were placed supine with the arm on the affected side under her head. During the acqusition, the gamma-camera detector was oriented at the relevant axilla and the anterior chest wall at an approximately 30 anterior oblique projection. The field of view in all patients included the supraclavicular and parasternal area too. A deposit accumulation, in rare cases showing the afferent lymph vessel, was considered to be the SN. If no imaging of the SN occurred within 15 minutes, the static images in the anterior and relevant lateral projection were repeated at approximately 30-minute intervals until it was displayed. The localization of the SN was marked on the skin in 1–2 projections with water-resistant permanent marker with the help of ^{57}Co point source marker under the gamma camera. In tumors of the upper outer quadrant, the SN could be localized often in the lateral projection only, because in the anterior projection it could be hidden behind the site of the injection. It is beneficial to shield the side of injection with a lead plate during the acquisition.

Surgery was performed 18–24 hours after administration of the RF. In 43 patients with a proven malignant lesion, a radioguided detection of the SN was approached. In more than half of the patients, 4 ml of patent blue was administered intraoperatively around the tumor. First, using a the C-Trak scintillation probe in sterile packing, the SN was localized over the intact skin and extirpated from a short skin cut. Then, the radioactivity of this node was measured *ex vivo* with the help of a the scintillation probe and it was verified that no significant accumulation remained in any other node in axilla. A dissection of nodes level I and II was performed in all patients thereafter. The results of the histopathological examination of the SN were compared to results of the examination of the others dissected axillary nodes.

We monitored the radiation exposure of the surgery staff during the first operations with the help of an EPD Mk2 dosimeter. After completing the operation, an FHT 111 M instrument was used for measurements of the contamination of the material used and of the surgical surfaces which would come into contact with RF.

Results

We were able to image SN preoperatively in all patients. It was localized in all cases in the ipsilateral axilla. No nodes in any other localization were displayed in any patients. In 5 patients with the carcinoma in the upper outer quadrant, the localization of the SN was possible in the lateral projection only because it was covered in the anterior projection by the injection site. In 16 patients, more than one radioactive node was identified. In 48 patients, a total of 65 nodes were displayed; a mean number of 1.3 nodes, maximum number of 3 nodes. In 17 patients, the SN was displayed within 20 minutes, in 18 patients within 2 hours and in 13 patients after more than 2 hours after the injection of the RF. If the RF and a patent blue were used simultaneously for the detection of the SN, all the nodes were colored and radioactive simultaneously.

In 26/43 (60%) patients having proven malignant lesion, metastatic process was detected neither in the SN nor in any other axillary node. However, in one of these patients, we detected cancer deposits in the surrounding fatty tissue, which were penetrating along the vessels and nerves. 16 patients (37%) had metastases proven in the SN, in 7 cases (16% of the total number) metastases were detected even in other nodes at the same time. In one patient, we found four

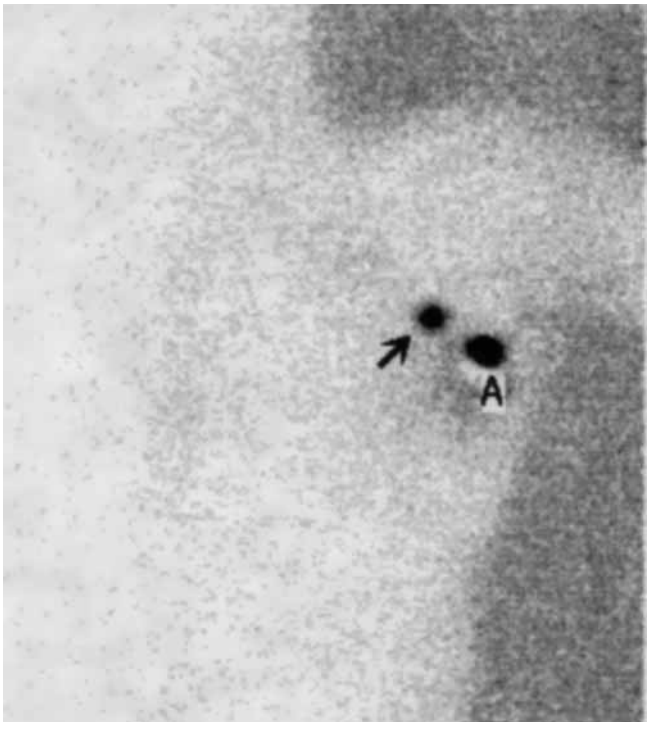

Figure 1. 46-year old female presented with a lump in the left breast. On anterior view one sentinel node is seen in left axilla (arrow), A – is the administration site of the RF. A picture is combined with ^{57}Co transmission.

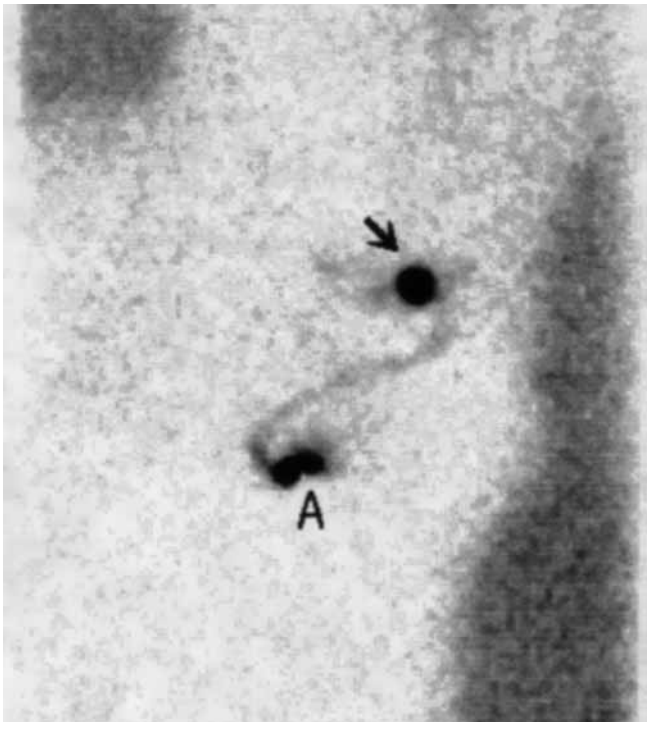

Figure 2. A static image of the SN with the afferent lymphatic vessel in 47-year old patient with a tumor in the lower internal quadrant – anterior projection. The arrow indicates the SN, A is the administration site of the RF. A picture is combined with ^{57}Co transmission.

out of nine nodes of the level I and six nodes of the level II infiltrated with metastases with a negative finding in two SNs.

Discussion

In breast carcinoma different procedures are used for the detection of the SN. There are differencies in the injection site (subcutaneous or intradermal, peritumoral, intratumoral), the type of the RF and dye which are used, the administered activity and administered volume of the RF, acquisition parameters, a one-day or two-day protocol etc. Some departments use a dyes only, other prefer radioguided surgery with preoperative administration of the RF within a one-day or two-day protocol. Approximately 1/3 of the departments perform preoperative lymphoscintigraphy and marking of the SN localisation on the skin with the use of gamma camera; the reliability of this method is 75–98% [7, 8, 10]. Current experience proves that preoperative lymphoscintigraphy and subsequent RGS in combination with the application of a dye is a more accurate method in comparison with the single method – using the combined method provide 98–99% reliability in detection of the SN [4, 6]. NIEWEG et al [7] have shown that preoperative lymphoscintigraphy increased the possibility of successful detection of all SNs. Moreover, lymphoscintigraphy provides information about the site localization and number of nodes; it enables indicating the site for the SN removal and in particular it helps less experienced surgeons to reduce the time for finding the node. We succeeded in the imaging and subsequent preoperative detection of the SN in all patients; in all cases they were localized in the ipsilateral axilla. In almost 75% of the patients, the node was displayed within two hours; however, in three cases, it was displayed more than four hours after the administration of the RF. If the SN is not displayed within 4 hours after the administration of the RF, it is possible, in terms of a two-day protocol, to add the later images (after 5–23 hours), or to repeat the injection of the RF [8]. A later or poorer imaging of the SN can be expected in patients with more advanced metastatic node infiltration, in some elderly patients due to fatty degeneration of the sentinel node and in patients with large breasts [4, 5, 6]. Based on our experience, the problems with imaging of the SN occured mainly in patients with the upper outer quadrant carcinoma, where the SN was covered in the anterior projection by injection site. In these cases, it was possible to image and map the localization of the SN in the lateral projection only. Sometimes it was helpful to retract large breasts medially and downwards to prevent the masking of the SN by the injection side. In most patients, it was very helpful to shield the injection site during acqusition, so as to be able to display the SN with a low impulse frequency.

When performing a lymphoscintigraphy of the SN in

breast cancer, peritumoral or combined peritumoral and subcutaneous administrations of the RF are mostly preferred [3, 6, 12]. In non-palpable tumors, the RF can be administered peritumoraly under sono- or stereotactic control [2]. VERONESI et al [10] described in 1997 for the first time the method of a single subcutaneous injection. This is based on the theory of the unified ectodermal origin of a mammary gland and breast skin. The advantage of subcutaneous and intradermal administrations is quick lymphatic drainage resulting from a rich plexux of lymphatic capillaries in the skin and subcutis. It is known that this method fails in detection of intramammary localized SNs – whereas after subcutaneous administration drainage into these nodes was proved in 2% of the patients only, after peritumoral injection in 16–35% and after intratumoral injection in 23% of the patients [4, 9]. We failed to display the SN outside the ipsilateral axilla in any of the patients.

So far, no integrated opinion concerning the optimal size of the administered particles of the RF has been accepted. It is considered to be a more suitable to use a RF with particles above 100 nm, which are still absorbed into peripheral lymphatic nodes in a sufficient speed, and at the same time are deposited in the SN for a longer time [1, 5–7]. The smaller particles migrate faster from the SN to nodes of a higher level and detection of the SN among these nodes is difficult. The use of ^{99m}Tc Senti-Scint with 95% of the particles sized 200–600 nm resulted in our study in the imaging of 1.3 nodes. Therefore, the use of ^{99m}Tc Senti-Scint seems optimal in the two-day protocol and on the contrary, the use of a RF with a smaller particle size is rather more suitable in the one-day protocol due to the faster lymphatic drainage. According to our experience, it is not necessary when using ^{99m}Tc Senti-Scint to performe a dynamic scintigraphy immediately after administration of the RF. Due to the minimal transfer of the RF into additional nodes, static images at an approximately two-hour or longer interval are sufficient.

Not even the same view concerning the size amount of the administered activity and a volume of the RF has been established. At the different departments, the administered activity ranges between 7–370 MBq, the administered volume between 0.2–8.0 ml. The higher activities and volumes of the RF are preferred in peritumoral or intratumoral injection of the RF [2, 5, 7, 9]. It has been repeatedly verified that a relatively small administered activity (10–15 MBq) was sufficient for the imaging and detection of the SN in a two-day protocol. The advantage of a two-day protocol is a significantly lower radiation exposure of the surgical staff. It is unnecessary to measure the contamination of the material used in the operatin theatre [5]. Comparing the one-day and two-day protocols, similar results were found concerning the success of detection of the SN [12].

The number of false positive findings ranges from 0–40% depending on the method used and the experience of the different authors; in multicentre studies, it is reduced below 5% [5, 7, 10]. A false negative finding is considered to be a node with no proven metastatic process with at least one other metastatic node concurrently. We detected one patient with false negative finding in whom a positivity of nodes of level I and II was proven with a negative finding in two SN. The negative predictive value in our study is 96% and the false positive findings represent 5.8%. The results are therefore comparable to the those achieved in the multicentre studies.

The quantity amount of the RF accumulated in the SN 24 hours after subcutaneous administration ranges – after correction for decay – from 0.005–5% of the administered activity [5]. The radioactivity of the surgical material, which could theoretically be contaminated over the course of the operation, is within a two-day protocol and with an administered activity of 15 MBq, according to our experience and literature data, generally minimal and does not require adherence to any special radiation protection remedies. Similarly, the radiation exposure of the surgical staff and pathologist is minimal within a given protocol. It is possible to perform more than 500 operations per year so as not to exceed a general annual limit of the effective dose for the population (1 mSv).

We are aware of the fact that the method fails in identifications of internal mammary nodes. However, because it is not clear whether the results of the histopathological examination of a node in this localization will affect the treatment and the patients' prognosis, we accept this fact. The objective of this work was not the evaluation of an optimal method for a histopathological examination of the SN.

Our results prove that within the protocol used, it is possible on the basis of a histopathological examination of the SN to predict with high accuracy the status of the axillary nodes and therefore to reduce the morbidity of selected patients resulting from the axillary surgery. In order to minimize the number of false positive findings, it is necessary to follow patient selection for this method carefully.

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