Nuclear Medicine in Breast Cancer Diagnostics: Primary Tumor and Lymphatic Metastasis

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Abstract. The purpose of the study: to assess the possibility of using nuclear medicine techniques at the stages of diagnosis and treatment of breast cancer. Materials and Methods: The study included 290 patients with breast cancer and 70 patients with benign breast tumors. The study was used as a radiopharmaceutical 99mTc-MIBI, 199Tl for imaging tumors and colloid 99mTc-Aloteh for visualization sentinel lymph nodes (SLN), colloid was injected peritumoral in four points to 80 MBq one day prior to the planned operation. Results: The sensitivity of SPECT using both 99mTc-MIBI and 199Tl for breast cancer detection was shown to be rather high, being 98.5% and 98%, respectively. It should be noted that the sensitivity of SPECT in detection of small tumors (less than 1 cm in diameter) and multicentric tumors was not high irrespective of the radioisotope used (60% and 65% with 99mTc-MIBI and 65% and 59% with 199Tl, respectively). The difference in the sensitivity was found between 99mTc-MIBI and 199T for the detection of regional lymph node metastasis (91% vs 70%). SLN were detected in 31 patients. The most commonly SLN were defined in the axillary region of 96.7%. In 22 (70.9%) patients there was no metastasis SLN. The sensitivity of the method was 91.2%, specificity of 100%. Conclusion: The specificity of SPECT with 199Tl was higher than that with 99mTc-MIBI. The data obtained show that SPECT with 199Tl can be recommended for its use as an additional breast cancer detection method in cases when other imaging techniques and histological findings are not accurate enough. The clinical study of 99mTc-Aloteh, a new radiopharmaceutical agent, has shown that the studied colloid has high uptake level in SLN and can be successfully used for visualization of SLN in patients with breast cancer.

INTRODUCTION

According to the recent WHO data more than 10 million newly diagnosed cancer cases occur annually in the world. In many countries cancer ranks the second most common cause of death following cardiovascular diseases.

Nuclear medicine techniques have the advantage over X-ray or magnetic resonance imaging in terms of higher specificity with a similar high sensitivity for cancer detection [1–3]. Moreover, the use of nuclear medicine imaging in detection of laryngeal/hypopharyngeal tumors allows prevention of unnecessary diagnostic invasive procedures.

^{99m}Tc-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) is the most widely used single photon emission computed tomography (SPECT) tracer in detecting malignant disease [4, 5]. However, this tracer with a relatively high sensitivity has rather a low specificity. Therefore, the search for radiopharmaceuticals characterized by a high specificity while maintaining adequate sensitivity is of great importance.

More than 30 years ago the diagnostic value of ^{201}Tl for detecting malignant tumors was studied. It was shown that ^{201}Tl, a biological potassium analogue, accumulated actively in tumors [5]. The findings from animal studies demonstrated that ^{201}Tl had higher tumor accumulation compared to other radiopharmaceuticals [6, 7]. However, a long half-life (72 hours) of ^{201}Tl limited its widespread use, since there was a risk of increased radiation dose to the patient's body and critical organs, especially during re-examinations, for example during chemotherapy.

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It is proposed that ^{199}Tl is a more promising isotope than ^{201}Tl, which is currently used in nuclear medicine. Unlike ^{201}Tl, ^{199}Tl has a simpler and cheaper production method. There are many reports on the use of this isotope for myocardial perfusion scintigraphy. The cellular uptake mechanism of ^{199}Tl is the same as that of ^{201}Tl. However, because of its short half-life (7.4 hours), the radiation dose to the patient's whole body and critical organs is significantly reduced. By using ^{199}Tl, the radiation dose to critical organs is 4–15 times lower than that by using ^{201}Tl. It allows ^{199}Tl scintigraphy to be performed 5 times a year for the same patient [8–11]. The aim of our study was to evaluate the efficacy of SPECT with ^{199}Tl in the detection of breast carcinomas.

The development of the sentinel node concept started at the beginning of the 1990s with evaluation and comparison of the procedures that could be used to detect the sentinel node(s).

If the SLN is free of metastatic disease, all other lymph nodes will also be free of disease [12, 13]. The use of colloid radiopharmaceuticals labeled with technetium-99m appeared to be effective and safe for scintigraphic and/or intraoperative gamma probe identification of SLN 13. Sentinel node biopsy may be a reasonable alternative to avoid extensive axillar lymph node dissection in breast cancer patients with negative SLNs, thereby improving the quality of life of approximately 100,000 patients undergoing lymphodissection for treating breast cancer [12, 14–16]. The two most widely accepted clinical scenarios for SLN biopsy are melanoma and breast cancer. Most modern medical centers worldwide now offer SLN biopsy for these malignancies, yet debate continues regarding whether SLN biopsy should be routinely used in clinical practice [12, 13, 15, 17, 18].

The size of radioactive particles is the most important factor in determining the choice of radiopharmaceuticals. A.J. Schauer et al. 16 reported that a colloid with the particle size of less than 50 nm can be accumulated not only in the SLN but also in the non-SLNs. Particles larger 100 nm slowly migrate from the injection site. A colloid with the particle size of the order of 50-80 nm may be preferable for the SLN detection. Nanocolloids made to date are based on the compounds that form stable hydrosols, and organic substances of different structures are often chosen as starting materials for their production. Another type of such pharmaceuticals is represented by inorganic complexes with 99mTc-rhenium sulfide and antimony, the application of which are limited by their complex manufacturing process and high cost. Our studies showed that stable colloidal compounds can be obtained in a simpler way - by means of adsorption on the reduced 99mTc alumina gamma [19–20]. The original premise for the use of alumina as a “carrier” of 99mTc- label is its relatively low toxicity combined with good adsorption properties, availability and low cost.

A specific feature of this compound is an organic coating of nanoparticles. During passage through the lymphatic system, nanoparticles lose their organic coating and accumulate in SLN without redistribution in the body.

Breast cancer is the most common cancer in women worldwide. Approximately 30,000 new early stage breast cancer cases are diagnosed each year in Russia 21. However, in the patients with early stages of breast cancer regional lymph node metastases are found in only 10–30% of cases. Extended lymph node dissection may increase the risk of postoperative complications 21.

The aim of our study was to evaluate the effectiveness of SPECT with 199Tl in detecting breast carcinoma and the advisability of using a new radiopharmaceutical based on gamma alumina containing technetium-99 m to detect sentinel lymph nodes in the patients with breast cancer.

MATERIALS AND METHODS

A total of 290 patients were included into the study. Out of them, 60 patients with stage T1-4N0-2M0 breast cancer and 30 patients with benign breast lesions were injected with 199Tl, and 160 patients with stage T1-4N0-2M0 breast cancer were injected with 99mTc-MIBI and 40 patients with benign breast lesions.

Single photon emission computed tomography was performed using a double-head gamma-camera (E.CAM 180, Siemens) equipped with parallel high energy collimators for 199Tl and parallel low energy collimators for 99mTc-MIBI. The injection of 199Tl at the dose of 260 MBq or 99mTc-MIBI at the dose of 740 MBq was made intravenously.

In the patients with breast disease the injection was made into the antecubital vein contralaterally to the breast lesion or in the pedal vein. The images of the breast were obtained with the patients lying in the supine position with the arms raised over the head and with the chest, both breasts, axilla and the myocardium, included into the field of view. A total of 32 projection images were recorded into a 64×64 matrix (30 s per projection), without a magnification factor. The scan images were analyzed using the manufacturer software (e.soft, Siemens, Germany).

Three-dimensional images of the chest, sagittal, transverse and coronal sections were obtained. Single photon emission computed tomography scans were visually assessed. The images of contralateral areas were compared and asymmetrically increased radiotracer uptake was considered pathological.

The study included 51 patients with histologically verified breast cancer (T1-2N0-1M0). For SLN visualization, all patients were divided into two groups. Group I consisted of 34 women, who received 4 peritumoral injections of radioactive ^{99m}Tc-Aloteh at a total dose of 80 MBq (20 MBq per quadrant) the day before surgery. Group II comprised 17 women, who were injected with phytate colloid at a total dose of 80 MBq (4 peritumoral injections, 20 MBq per injection) the day before surgery (Figure 1).

All patients underwent single photon emission computed tomography (SPECT) using the dual-head gamma camera (E.CAM 180, Siemens, energy 140 keV, window 15%) in 18 hours after the radiotracer injection. A total of 16 projections were acquired (30 seconds per projection, matrix size 64×64). The scan images were analyzed using the ESoft software (Siemens, Germany). Three-dimensional images of the sagittal, transverse and coronal sections were obtained. To obtain quantitative values, the axial sections were used. The radiotracer accumulation in the SLN with respect to the injection site was evaluated using a quantitative criterion.

For intraoperative detection of sentinel lymph nodes, the hand-held collimated Gamma Finder II® probe was used, which allowed the surgeon to precisely locate gamma radiation source and obtain accurate information about the distribution of the radionuclide in the patient's tissues and organs. The registered gamma radiation level was displayed in numerical values. The lymph node with radioactivity of at least three times more than the background counts was defined as a sentinel lymph node.

The sentinel lymph node was marked and separately sent for express cytological examination. The lymph node was sectioned transversely into 2 mm slices. Depending on the size of the node, 6–10 imprints were made from each slice by gently touching the cut surface of the node to a glass slide. The cytological specimens were stained for 15 s using the kit for rapid staining of blood smears (Leucodiff 200) and examined with a Zeiss Axio Scope (Germany).

RESULTS AND DISCUSSION

Single photon emission computed tomography revealed no abnormal ^{199}Tl uptake in the chest wall and breasts of the patients with benign breast lesions. Despite a small group of patients (n = 30), the specificity of SPECT with ^{199}Tl was 96.7%.

In breast cancer patients, the increased ^{199}Tl uptake was visualized in 58 (96.7%) of the 60 patients. Out of 6 patients with the tumors less than 10 mm 4 showed an abnormal radiotracer uptake. In one case, a large mass detected by mammography and ultrasound appeared as a cluster of microcalcifications. Carrying out SPECT with ^{99m}Tc-MIBI revealed abnormal formations in the projection of the mammary glands in 158 (98.1%) out of 160 patients. The tumors greater than 10 mm were detected by ^{199}Tl and ^{99m}Tc-MIBI SPECT in 100% of cases.

It is well known that a secondary infiltrative ductal breast carcinoma can be difficult to diagnose. In our study, the accuracy in differentiating malignant from benign breast lesions by SPECT with ^{199}Tl was 100%, as well as with ^{99m}Tc-MIBI.

As regard to lymph node involvement, the increased ^{199}Tl uptake in the axillary lymph nodes was observed in 19 out of 28 patients (67.8%) with histologically verified metastases. Only 2 out of 5 patients had abnormal radiotracer uptake in the pectoral and subclavicular lymph nodes. Thus, the ^{199}Tl SPECT sensitivity for the detection of metastatic regional lymph nodes in breast cancer patients was 67.8%.

It was possible to visualize the modified axillary lymph nodes in almost all the cases during the study with ^{99m}Tc-MIBI: in 72 (90.1%) out of 80 patients with verified metastasis pathological inclusion of the ^{99m}Tc-MIBI in axillary region was detected. In addition, pathological changes in the projection of pectoral lymph nodes, subclavian and subscapularis groups were detected in 5 patients. This technique allowed us to differentiate between different levels of lymph nodes. The sensitivity of the SPECT with ^{99m}Tc-MIBI in identifying metastatic regional lymph nodes was 90.1%. The specificity of SPECT with ^{199}Tl was 100%, with ^{99m}Tc-MIBI—80%.

Single photon emission computed tomography with ^{199}Tl showed 100% specificity for detecting breast cancer, when compared to ^{99m}Tc-MIBI with reported specificity varying from 85% to 94% [5, 13].

Despite the abovementioned advantages, ^{199}Tl has also some disadvantages. This cyclotron-produced radiopharmaceutical has a higher cost compared to ^{99m}Tc, the most widely used radioisotope in nuclear medicine. Moreover, our findings have demonstrated rather a low sensitivity in the detection of regional lymph node metastases in breast cancer patients, thus significantly impairing the diagnostic accuracy.

Anyway, ^{199}Tl is a promising radiopharmaceutical for the detection of malignant tumors; however, further studies are required to determine its role in the cancer diagnostic algorithm.

A total of 39 SLNs were identified in Group I patients. The number of identified SLNs per patient ranged from 1 to 2 (the mean number of identified SLNs was 1.08). The most frequent SLN location was the axillary region (97.2%). The metastases in the excised SLNs were detected in 9 patients (26.4%), who subsequently underwent the conventional axillary lymph node dissection. Four patients (11.4%) had metastases not only in the SLN but also in lymph nodes of level II. The presence of SLN metastasis indicated lymphatic dissemination of tumor cells and the formation of clinically undetectable regional lymph node metastases. The sentinel lymph node was free from metastasis in 25 patients (73.6%). We did not observe the phenomenon of the so called "jumping" metastases in these patients.

The ^{99m}Tc-Aloteh uptake in the SLN in 18 hours after the injection was 7–11% (of the radioactivity in the injection site) by SPECT and 17–31% by intraoperative gamma probe detection.

Thus, the sensitivity and specificity of ^{99m}Tc-Aloteh for detecting SLNs in breast cancer patients were 100%.

The intraoperative SLN detection was performed through a small skin incision. Sparing surgical procedures can significantly reduce overall surgery trauma and recovery time.

In Group II, 19 SLNs were identified in 15 patients. The number of SLNs detected per patient ranged from 1 to 2 (the mean number of detected SLNs was 1.04). All detected SLNs were located in the axillary region.

The metastases in the excised SLNs were detected in 5 patients (29.6%), who subsequently underwent the conventional axillary lymph node dissection. In 2 patients (11.8%), the removed SLN and lymph nodes of the level II had a positive histology. In 12 patients (70.4%), the SLN was negative, with no clinical evidence of lymph node metastasis during the follow-up. In this group of patients, there was also no phenomenon of the so called "jumping" metastases.

The percentage of phytate colloid accumulation in the SLN in 18 hours after injection was 1.5–2% by SPECT and 4–7% by intraoperative gamma probe detection.

Thus, the use of phytate colloid for detecting SLNs in the breast cancer patients demonstrated 88.2% sensitivity.

Various techniques of SLN identification are widely discussed in the published literature. Currently, most investigators propose that the blue dye and isotope complement each other, and the detection of SLN is more successful using combined dye- isotope technique, with the sensitivity and specificity approaching 100% [22, 23]. In our study, the use of 99mTc-Al203, a novel molecular imaging agent showed promising results in detecting SLNs with a high sensitivity and specificity.

For histological examination of the identified sentinel lymph nodes, we used the light optical microscopy with hematoxylin-eosin. A number of authors have published immunohistochemistry and flow cytophluorometry for the detection of micrometastases in lymph nodes, allowing a three-fold increase in the detection rate to be achieved [24]. The wide use of the modern methods of histological express analysis will significantly improve the clinical significance of detecting the sentinel lymph nodes in the breast cancer patients.

Thus, the use of the new radiopharmaceutical allows the precise detection of SLNs to be achieved, thereby personalizing the extent of surgery in the patients with primary operable breast and cervical cancers.

CONCLUSION

SPECT with ^{99m}Tc-MIBI and ^{199}Tl-chloride in the patients with breast cancer have a high sensitivity in detecting malignant tumors larger than 1 cm.

In case of small cancers, the use of these methods is not relevant.

It is possible to recommend the use of an SPECT with ^{199}Tl-chloride as an additional criterion in cases where other methods of radiation diagnosis, the results of a morphological study do not give an unambiguous answer.

The novel radiopharmaceutical based on ^{99m}Tc–Aloteh has high accumulation in sentinel lymph nodes, with no evidence of further redistribution along the lymphatic collector, thus significantly facilitating scintigraphic and intraoperative SLN identification.

The sensitivity and specificity of using ^{99m}Tc–Aloteh were 100% for both SPECT and intraoperative identification of sentinel lymph nodes.

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