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Original Article

Sentinel Lymph Nodes Biopsy for Malignant Tumors Using Technefit Radioactive Colloid Technetium ^{99m}Tc

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Abstract

Introduction: Technetium-99m (^{99m}Tc) is a short-lived nanocolloid nuclide widely used by oncologists to diagnose and identify cancer dissemination.

Aim: The aim of the current study was to develop the technique of radiopharmaceutical preparation (RPP) of Technefit^{99m}Tc aimed at examining sentinel lymph nodes (SLN) before surgery.

Materials and methods: We performed a series of trials (33 patients). Based on the information obtained from the portable gamma detector NEO2000 during surgery, a biopsy of the sentinel lymph nodes was carried out when RPP Technefit ^{99m}Tc accumulated in a specific lymph node.

Results: We determined maximum activities, volume, and peculiarities of administration of radioactive colloid Technefit^{99m}Tc in order to examine and perform the biopsy of SLN in the patients with malignant tumors. The most informative results in terms of scintigraphy images of sentinel lymph nodes were revealed in the first trial of the research, with all 5 cases (100%) showing positive results. The first trial included Technefit intradermal-hypodermal injection into one point above the tumor node, RPP activity of 75 to 200 mBq at a room temperature of 21°C, without preliminary anesthesia with Novocain solution.

Conclusion: We determined the most efficient dosages of activities, volume, and characteristics of radioactive colloid administration aimed at the examination and biopsy of sentinel lymph nodes using the radiopharmaceutical preparation Technefit ^{99m}Tc in patients with malignant tumors of different localizations, namely breast cancer and skin melanoma. In some cases, we did not find any signs of considerable lowering of the Technefit ^{99m}Tc activity, which shows that there is a very slow filtration of Technefit ^{99m}Tc through the pores of lymph capillaries.

Keywords

biopsy of sentinel lymph node, breast cancer, colloid radiopharmaceutical preparations, malignant tumors

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PENSOFT.

INTRODUCTION

Technetium-99m (^{99m}Tc) is a short-lived nanocolloid nuclide widely used by oncologists and cardiologists in their research related to diagnostics of inflammatory diseases of skeletal muscles, in patients with tumors, cirrhosis, hepatitis, etc.[1-3] Preferences in terms of choosing colloid radiopharmaceutical preparation (RPP) for clinical practice depend on the peculiarities of their pharmacodynamics and the available clinical experience.

Sentinel lymph node detection is best achieved by using colloid nanomaterials labeled with technetium-99m for scintigraphic or radiometric node localization determination. In this instance, the selection of the indicator is based on the chemical's size. Therefore, a colloid with a particle size of less than 50 nm can accumulate not only in the SLN, but also at nodes of 2nd and 3rd orders.[4] There is a variety of available nanocolloid RPPs particles with a diameter below 100 nm that are commonly used and are considered optimal. However, colloid complexes of small sizes (3–30 nm) predominate in some institutions. One of the most studied is the sulfur nanocolloid used for the identification and biopsy of SLN in several countries.[5-8]

The production of nanocolloid preparations is based on the compounds which form stable hydrosols. The most important factor is considered the nanoparticle size, but not the chemical content.[9] The preferable size of the particles favorable for lymphoscintigraphy is 20 nm to 100 nm. They migrate from the tissues at a speed which does not allow them to penetrate into the blood stream. Particles of sizes less than 20 nm are easily transported into the blood stream, which hinders the visualization of the lymph nodes.[9] Cardiologists can use particles larger than 200 nm to identify the focus of inflammation by marking auto leukocytes.

The radiocolloid Technefit ^{99m}Tc, which has an average colloid particle diameter of more than 200–1,000 nm, is approved for clinical use within the Russian Federation. In the course of the present research, which aimed to develop corresponding techniques, we used a domestic colloid preparation Technefit ^{99m}Tc (legally registered as LS-002365), designed for evaluation of anatomic topographic characteristics of liver and spleen (shape, size, structure) in patients with tumors, cirrhosis, hepatitis, etc. The preparation is intensively absorbed by liver and spleen, and the reticuloendothelial systems. The isotope ^{99m}Tc has a half-life of 6.04 hours. While decaying, ^{99m}Tc emits gamma quanta with the power of 140 keV and output of 90%.

AIM

The aim of this research is to study the possible utilization of the RPP Technefit ^{99m}Tc in order to identify SLNs, followed by biopsy and morphological tests in case of cancer.

MATERIALS AND METHODS

In order to identify the lymph efflux pathways and visualize SNL, we used colloid preparations with a particle diameter of 10 to 200 nm labelled by ^{99m}Tc. We propose the technique, which involves domestic colloid preparation Technefit ^{99m}Tc (registered as LS-002365), which is prepared ex temporo and is based on the standard complex of Technefit ^{99m}Tc and eluate, obtained from the ^{99m}Tc generator. The radioactive colloid Technefit ^{99m}Tc with 75–200 mBq activity is injected around the tumor perimeter:

- In skin melanoma (body and extremities): under the skin 10–15 mm off the tumor visual boundary; in case there are infiltrate tissues around the tumor, then the colloid is administered 10–15 mm off the infiltrate visual boundary.
- In breast cancer: under the skin 1–2 mm off the tumor boundary.

In half an hour and in 2 hours after the administration of the RPP, the 'whole body' scintigraphy is performed in front and back projections. Alternatively, SPECT scintigraphy in 128 projections or SPECT-CT study are also possible. In case the lymph efflux pathways and SNL images are absent within the time frame, it is reasonable to perform an additional study 4 and more hours after the preparation injections.

The method is based on the selective ability of the unchanged reticuloendothelial cells of lymph nodes to capture those colloid particles, marked by radionuclides, which are transported from tissue depot by lymph after their introduction into the tumor, or into the tissues surrounding the tumor and/or into the peritumoral skin structure. Herewith we can obtain the information on the direction of lymph efflux pathways from the tumor to the regional lymph nodes. One or several regional lymph nodes, which are the first on the way of the lymph efflux are called 'sentinel'. They are the first to be invaded by tumor cells, migrating within the lymph flow.

Imaging analysis

The main type of data analysis is visual evaluation of scintigrams. The aim is to identify the area of intensive accumulation of RPP in the projection of injection location, as well as the focuses of the preparation accumulation, corresponding to regional lymph collector. The number and location of lymph nodes, accumulating the radiocolloids are also evaluated. When SLN are identified, they should meet at least one of the following requirements:

- the only lymph node, accumulating the radiocolloids
- the first lymph node, having been visualized
- the lymph node connected with the tumor by the 'path' of lymphatic vessels

All lymph nodes visualized in an anatomic area after a SLN appears in the area, are regarded as the lymph nodes of the second or third order. At the same time, the direction of lymph efflux from the tumor is taken into account alongside with the lymph nodes topography, their shape, contour

readability, contrast stage (normal or increased), lowering or absence of RPP accumulation in symmetrical groups of a lymph node chain, and the presence of the preparation in afferent lymphatic vessels.

Analysis of the findings

SLN biopsy was performed based on the data from the portable gamma-detector NEO2000 in the course of surgery when the RPP Technefit ^{99m}Tc accumulated in a particular lymph node.

The removed SLNs were also evaluated after removal in order to confirm the RPP Technefit ^{99m}Tc accumulation. The specimen underwent urgent histological evaluation followed by standard histological tests for paraffin sections (surgical specimen).

In order to perform indirect radio isotope lymphoscintigraphy, we utilized domestic colloid preparation Technefit ^{99m}Tc (registered as LS-002365) designed for evaluation of anatomic topographic characteristics of liver and spleen.

The RPP was based on the standard complex of Technefit ^{99m}Tc and ^{99m}Tc eluate of Technetium^{99m} generator. Isotope ^{99m}Tc has a half-life of 6.04 hours. It emits gamma quanta with the power of 140 keV and output of 90% in the process of decaying.

For visualization of lymph efflux pathways from lymph nodes, Technefit ^{99m}Tc with the activity of 75–200 mBq was administered as a peritumoral injection **(Fig. 1)**.

Thirty minutes after injection of the radioactive colloid, SPECT test (Siemens E.CAM, Germany) and SPECT-CT test (Mediso AnyScan SC, Hungary, General Electric Discovery NM/CT 670, USA) were carried out with parallel low power collimator. Discriminator window was set up at ^{99m}Tc 140 keV power peak with the width (range) of 25–30%. The main type of data analysis was the visual evaluation of the scintigrams. In the process of analyzing the scintigraphic images, the area of RPP intensive accumulation was identified in the projection of the injection site. In those cases, when the contrasting of SLN did not occur, SPECT and SPECT-CT tests were repeated in 2, 6, 12 hours.

The current study was performed according to the Helsinki declaration (adopted in 1964 and the latest revision in 2013) and ethical approval for the study was obtained by the Ethics Committee of Moscow Research Institute of Oncology n.a. P.A. Herzen (protocol No. 397, 27.03.2014)

RESULTS

We performed 35 tests using the radiopharmaceutical preparation Technefit ^{99m}Tc in 33 early cancer patients, three out of them with early skin melanoma (body and extremities), one with mouth cavity floor cancer and the rest with breast cancer. Breast cancer patient were assessed based on the clinical and pathological TNM system **(Tables 1, 2)**.

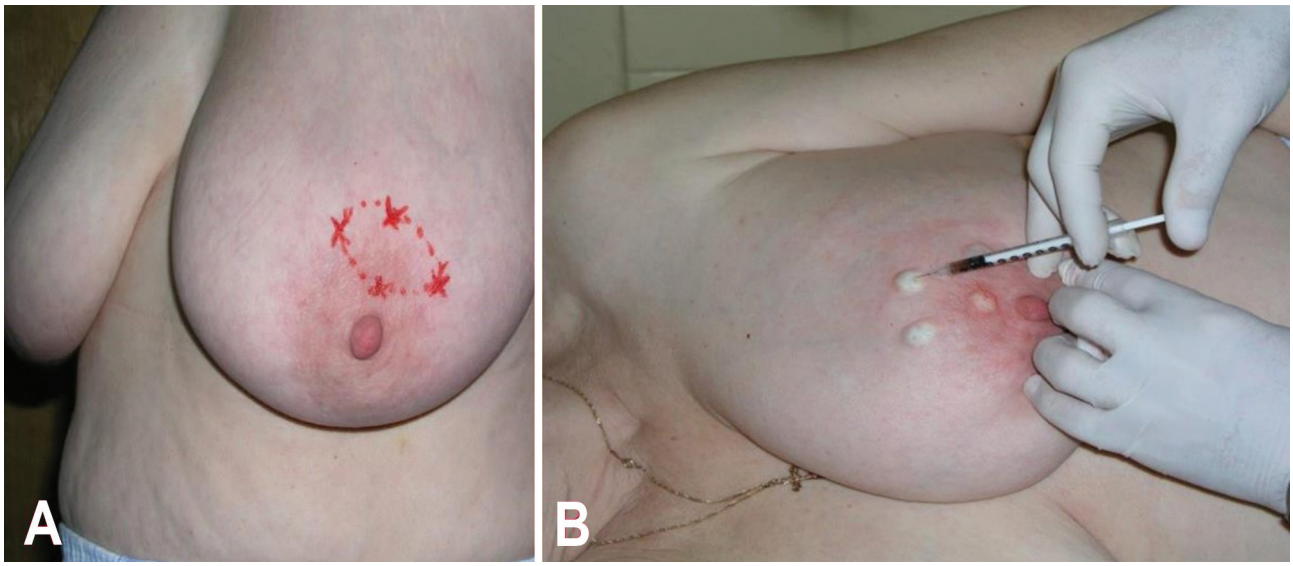

Figure 1. Tumor identification, marking and injection technique. **A**. tumor marking; **B**. - radioactive colloid Technefit ^{99m}Tc peritumoral injection.

Table 1. Breast cancer patient cohorts (31 subjects) as per cTNM tumor process stage

Stage	Stage 0 TisN0M0	Stage I T1N0M0	Stage II T2N0M0
Number of patients (out of the total of 31)	3	18	10
Number of patients in %	9.68	58.06	32.26

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Table 2. Breast cancer patient cohorts (31 subjects) as per pTNM tumor process stage

Stage	0 TisN0M0	I T1N0M0	II A T2N0M0	II A T1N1M0	II B T2N1M0	III A T1N2M0	III A T2N2M0	III C T2N3M0
Number of patients	2	10	11	3	2	1	1	1
Patients in % of 31 patients	6.45	32.26	35.48	9.68	6.45	3.23	3.23	3.23

All patients demonstrated good tolerance of the technique. We did not notice any individual intolerance or allergic reactions in any of the examined patients.

Taking into account the rather big size of colloid particles (200–1000 nm) we performed several practical trials with different variants of administration of Technefit ^{99m}Tc. This was dictated by the necessity to identify the sentinel lymph nodes in patients with different localizations of mammary gland tumors **(Fig. 2)**.

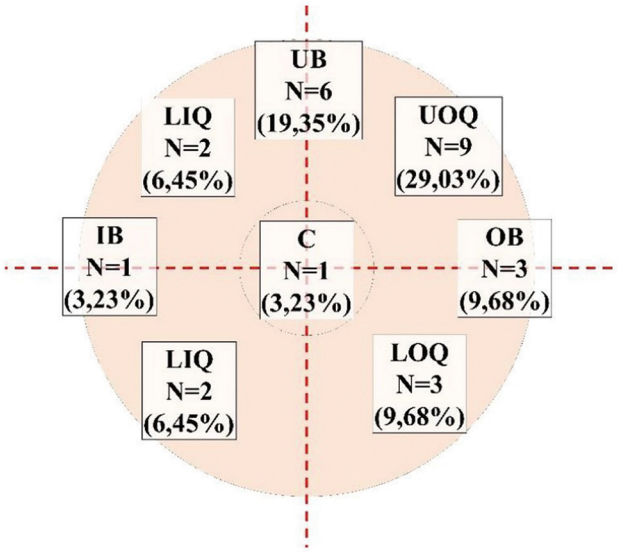

Figure 2. Breast Cancer Patient Cohorts (31 subjects) as per the tumor localization. LIQ: lower inner quadrant, UOQ: upper outer quadrant; LOQ: lower outer quadrant; LIQ: lower inner quadrant; UB: upper border; OB: outer border; IB: inner border; C: central.

We optimized the results of the research by introducing different activity dosages, quantities of administered solution, injection depths, numbers of injection points, usage or non-usage of Novocain solution. Moreover, we used the combination of two RPPs – Technefit ^{99m}Tc and Macrotex and changed the exposition of the study for sentinel lymph nodes, performed in a gamma-chamber from 30 minutes to 17 hours after RPP injection, used a different temperature range for injections and also changed the dispersibility of the solution by shaking it right before the injection. In the course of the study, we performed 10 trials, which included the above-mentioned variations of RPP injections followed by identification of the sentinel lymph nodes. They are presented in **Table 3**.

Analyzing the scintigraphic images, we identified the area of RPP accumulation in the projection of injection point and also the focuses of the RPP accumulation related to the regional lymph collector. We evaluated the number and localization of lymph nodes that accumulated RPP **(Fig. 3)**.

It should be mentioned that the planar lymphoscintigraphy tests did not show the RPP migration from the injection depot into the sentinel lymph nodes after 30 minutes in 17 subjects out of 35 (48%) without any association with RPP quantity and activity **(Fig. 3)**. We did not obtain images of the isotope accumulation in lymph nodes after 17 hours in three subjects (8.57%) after the Technefit ^{99m}Tc injection. In terms of topography, the rest of the subjects showed RPP accumulation in the axillary area. At the same time, in 3 (8.57%) subjects we obtained the images of the accumulated isotope in 2 axillary lymph nodes.

The point of injection depot could cover the picture of the isotope accumulation in sentinel lymph nodes when the activity dose was 75 to 200 mBq. This disadvantage hindered sentinel nodes biopsy performance as it was directly shown during the intraoperative search for those nodes in the lymph efflux area.

The most informative results in terms of scintigraphic images of sentinel lymph nodes were revealed in the first trial of the research, with all 5 cases (100%) showing positive results after. The first trial included Technefit intradermal-hypodermal injection into one point above the tumor node, RPP activity of 75 to 200 mBq at a room temperature of 21°C, without preliminary anesthesia with Novocain solution.

We managed to identify Technetium^{99m} accumulation focuses prior to surgery using a portable gamma detector NEO2000 **(Fig. 4)**. This procedure was followed by surgery for identification and biopsy of SLN.

In every case, we registered high stable non-reducing activity of the Technefit ^{99m}Tc depot in the range of 58 to 80 thousand impulses per second, which was registered by the gamma detector NEO2000 in all the variants of RPPs. This activity was documented 17 hours after RPP administration. This indicates that Technefit ^{99m}Tc filtration through lymph capillary pores is very slow.

We looked for the focuses of the RPP accumulation in the lymph efflux area during surgery, with the help of the gamma detector NEO2000. We registered Technetium activities in the focuses of its accumulation in the surgi-

Table 3. RPP injection trials (35 subjects)

No. of trial	1	2	3	4	5	6	7	8	9	10
Number of tests	5	3	6	4	1 (*)	3	4 (**)	5 (*)	3	1 (*)
RPP quantity (ml)	1.0	1.0	1.0	0.25	1.0	1.0	1.0	1.0	1.0	1.0
RPP injection point	Under the skin and above the node	Peritumoral	Peritumoral	Node border	Under the skin	Peritumoral	Under the skin	Under the skin and peritumoral	Under the skin and peritumoral.	Under the skin
Type of RPP injection	1 point	4 points	4 points	1 point	4 points	4 points	4 points + Novocain	4 points + Novocain	4 points + Novocain	4 points + Novocain
RPP activities dosage	75 100 125 154 200 mBq	100 mBq	150 mBq	150 mBq	200 mBq	200 mBq	2 tests - 200 mBq 2 tests - 100 mBq +100 mBq Macrotex	200 mBq	200 mBq	150 mBq
Time of RPP injection and exposition	8 a.m. not delayed	8 a.m. not delayed	8 a.m. 2 tests; 2 p.m., delayed >17 hours	8 a.m. 1 test; 2 p.m. delayed >17 hours	11 a.m. not delayed	8 a.m. not delayed	8 a.m. not delayed	8 a.m. not delayed	8 a.m. not delayed	8 a.m. not delayed
RPP temperature and dispersibility	21°C	21°C	21°C	21°C after shaking	21°C	21°C and 37°C	21°C	37°C	37°C after shaking	21°C
Lymphography Positive results (in 17 cases)	In 30 min. – 1 hour; Migration into lymph nodes; In 1 case 2 lymph/ nodes	In 2 cases visualization; Sentinel lymph nodes; (1+2 lymph nodes)	In 2 cases; 1 sentinel lymph node in each	In 1 case; In 40 minutes - 1 sentinel lymph node	In 30 minutes; 2 sentinel lymph nodes	none	In 3 cases - in 30 min. 1 hour - migration into 1 axillary l/ node	In 3 cases in 20-30 min. 3 hours - migration into 1 axillary l/n	none	none
Negative results (in 18 cases)	No negative results	In 1 case; No migration	In 4 cases No migration; In 2 cases even after > 17 hours	In 3 cases, No migration	none	In 2 cases; No migration	In 1 case; No migration	In 2 cases; No migration	In 30 min; No migration	In 2 hours; No migration

* skin melanoma (3 cases); ** mouth cavity floor (1 cases)

cal site. The activity range was from 280 to 5000 impulses per second, which was shown on the display of the gamma detector. Such a large range of indices is caused by the different speed of Technefit ^{99m}Tc migration into the lymph nodes. In some cases, the injection depot area covered the picture of the isotope accumulation in SLN and we faced some difficulties identifying the focuses of the isotope accumulation in the lymph nodes. It was caused by Technefit ^{99m}Tc high activities of 75 to 200 mBq. In such cases, the search for the focuses of the isotope accumulation was performed during surgery.

We did not find RPP in lymph nodes in 6 cases out of 35, including those studied outside the surgical site. Therefore, the search failed in 17.1% of the subjects. In 2 of those cases, multiple metastases were found in the lymph nodes. Besides, in 1 (2.85%) of those subjects, a sentinel lymph node was identified in the subclavian cellular tissue, being determined as metastatic by urgent morphologic test and the subsequently multiple metastases were revealed in 8 lymph nodes (N3) during histological examination. The study for the surgical specimens (lymph nodes) demonstrated that in 5 subjects (14.3%) 2 lymph nodes located in axillary cellular tissue were identified as sentinel ones. In 3 subjects (8.6 %), 3 sentinel lymph nodes were found in the axillary area. The rest of the 21 subjects showed 1 sentinel lymph node each, 17 (80.95 %) out of them were located in the axillary, 3 in subscapular, and 1 in the subclavian tissue **(Fig. 5)**.

The identified and marked sentinel lymph nodes were examined outside the surgical site in order to confirm RPP Technefit ^{99m}Tc accumulation. Histological and immunohistochemistry staining is shown in **Table 4**.

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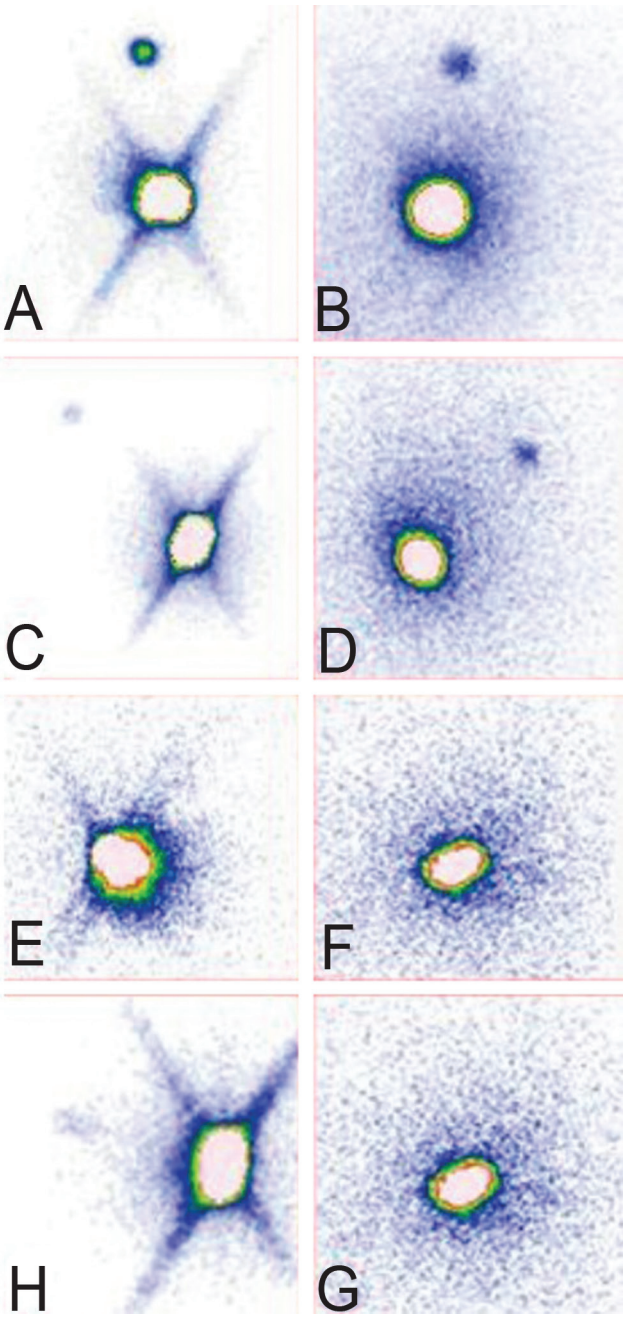

Figure 3. A, **B**. Left breast cancer, lower outer quadrant, 150 mBq of Technefit ^{99m}Tc administered. In 30 minutes after injection, the RPP inclusion into the depot was clearly determined in the planar scintigrams (one axillary SLN at the left); **C**, **D**. Right breast cancer, inner localization, 100 mBq of Technefit ^{99m}Tc administered. In 30 minutes after injections, RPP inclusion into the depot was clearly determined in the planar scintigrams (one axillary SLN at the right); **E**, **F**. Right breast cancer, upper outer quadrant, 150 mBq of Technefit ^{99m}Tc. In 30 minutes and 17 hours after RPP injections into the depot was clearly determined in the planar scintigrams (RPP accumulation in the areas of regional lymph efflux was not found and two axillary SLNs were identified at perioperative period); **H**, **G**. Left breast cancer, the boundary of outer quadrants, 125 mBq of Technefit ^{99m}Tc administered. In 30 minutes after injections, RPP inclusion into the depot was clearly determined in the planar scintigrams (one axillary SLN at the left was clearly identified).

DISCUSSION

SLN biopsies have been studied for different types of cancer such as gynecological cancers, gastric cancer, breast cancer, and melanoma in order to reduce the necessity of lymph node dissection.[10] Multiple randomized trials have shown that SLN biopsy is safe and allows to evade such complications as lymphedema and other postoperative morbidities associated with lymph node dissection.[11,12]

There are several colloid radiopharmaceutical preparations that are used for isotopic lymphography and determination of sentinel lymph nodes. They are different by their methods of preparation and the diameters of the obtained colloid particles **(Table 5)**.

The reported lymph node identification during lymphoscintigraphy is up to 92%-99.8%.[13,14] In a meta-analysis of more than 8000 patients from a systematic review of 69 trials about SLNB, the identification rate of these nodes was 96%.[15] However, in some reports, lymphoscintigraphy may fail to visualize the SLN in 2-28% of cases.[16-20] As we demonstrated in our series of trials, in some cases this may depend on the technical characteristics of RPP administration.

Another major limitation is the number of identified SLN. The median number of sentinel nodes is around 2 but can range from 1 to 15, and approximately 21.9% of them are positive for metastatic carcinoma.[13] The results of the current study also indicate that SLN may be located in different anatomical areas and there may be several SLN. Nevertheless, the AMAROS EORTC trial demonstrated that axillary radiation decreases morbidity and is an acceptable alternative to lymph node dissection for patients with positive SLNs.[21]

The standard for SLNB is the radioisotope technique, but there are several novel techniques developed in the recent years: indocyanine green fluorescence, superparamagnetic iron oxide nanoparticles and contrast-enhanced ultrasound using microbubbles.[22] A major limitation of radioisotope technique is age (≥70 years), obesity (BMI ≥30 kg/m^2) and nonpalpable tumors. However, most of the researcher agree that lymphoscintigraphy is a very robust technique that does not depend on the experience.[23]

One of the major limitation of the current RPP is radiation exposure while SLN identification method in the operating room and pathology which is the equivalent to a mammography and there are still cases when it cannot be adequately used.[24,25]

The limitation of the current study is the small number of cases and a single institution experience. However, due to the nature of the study, we are able to demonstrate several possibilities to inject RPP for optimal identification of SLN.

CONCLUSIONS

We determined the most efficient dosages of activities, volume, and characteristics of radioactive colloid administra-

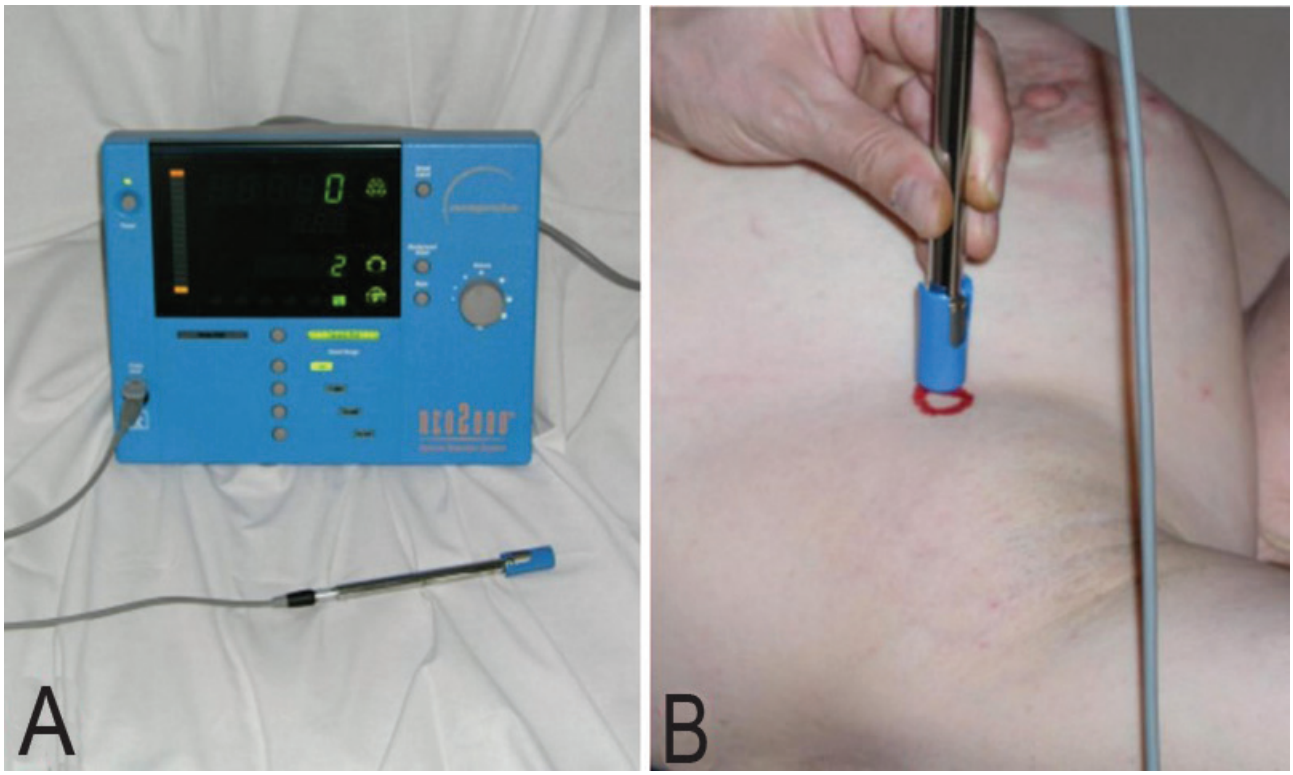

Figure 4. Portable gamma detector NEO2000 and its application. **A**. The device; **B**. Lymph node detection.

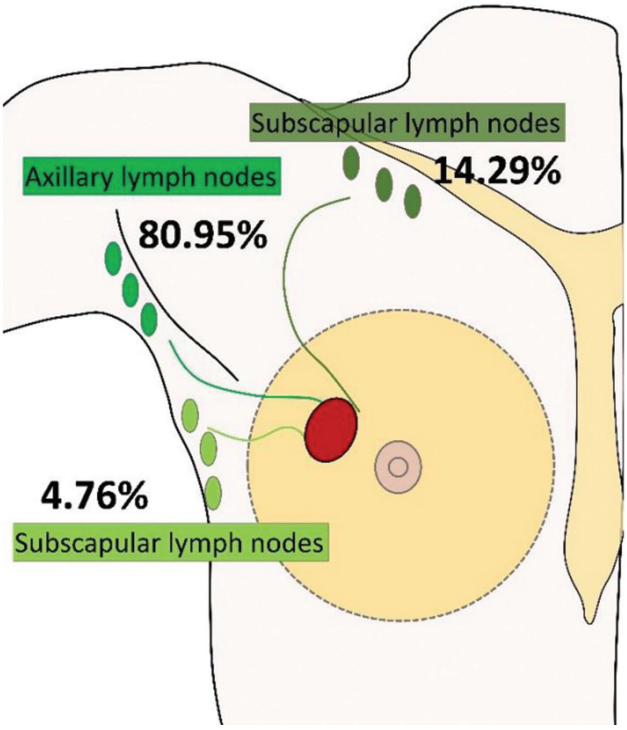

Figure 5. Location of the sentinel lymph node.

tion aimed at the examination and biopsy of sentinel lymph nodes using the radiopharmaceutical preparation Technefit ^{99m}Tc in patients with malignant tumors of different localizations, namely breast cancer and skin melanoma. In some cases, we did not find any signs of considerable lowering of the Technefit ^{99m}Tc activity, which points to the very slow filtration of Technefit ^{99m}Tc through the pores of lymph capillaries.

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Table 4. Results of immunohistochemical tests and tumor subtypes

IHC subtype of BC Total number 31	Luminal A subtype		Luminal B subtype		Luminal B Her-2/neu + subtype		Not luminal Her-2/neu + subtype		Triple-negative subtype	
Number of subjects	15		3		3		3		7	
Percentages of the total	48.3		9.7		9.7		9.7		22.6	
N status	N0	N+	N0	N+	N0	N+	N0	N+	N0	N+
Number of cases	11	4	2	1	1	2	2	1	7	0

Table 5. Data on Technetium ^{99m}Tc-containing nanocolloid preparations produced in Europe

Radiopharmaceutical preparation	Producer	Particle size
Nanocoll	GE Amersham	<80 nm
^{99m}Tc-nanocolloid	GE, Uppsala, Sweden	<80 nm
Nanocis	CIS bio International	~100 nm
Hepatocis	CIS bio International	~500 nm
Microlite	Du Font	~10 nm
Sulfur colloid	CIS bio International	40-10 000 nm

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Competing Interests

The authors have declared that no competing interests exist.

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Биопсия сторожевых лимфатических узлов при злокачественных опухолях с использованием радиоактивного коллоида Technetium ^{99m}Tc

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Резюме

Введение: Technetium ^{99m}Tc— короткоживущий наноколлоидный нуклид, широко используемый онкологами для диагностики и выявления распространения рака. Поэтому целью настоящего исследования была разработка методики применения радиофармацевтического препарата (РФП) Technefit ^{99m}Tc, направленного на исследование сторожевых лимфатических узлов (СЛУ) перед операцией.

Материалы и методы: Мы провели серию испытаний (33 пациента). На основании информации, полученной с портативного гамма-детектора NEO2000 во время операции, была проведена биопсия сторожевых лимфатических узлов при накоплении РФП Technefit ^{99m} Tc в определённом лимфатическом узле.

Результаты: Мы определили максимальные активности, объём и особенности введения радиоактивного коллоида Technefit ^{99m} Tc с целью исследования и проведения биопсии СЛУ у пациентов со злокачественными опухолями. Наиболее информативные результаты с точки зрения сцинтиграфических изображений сторожевых лимфатических узлов были выявлены в первом испытании исследования, во всех 5 случаях (100%) получены положительные результаты. В первом испытании препарат Technefit ^{99m} Tc вводился внутрикожно-гиподермально в одну точку над опухолевым узлом, активность РФП от 75 до 200 mBq при комнатной температуре 21°C, без предварительной анестезии раствором новокаина.

Выводы: Определены наиболее эффективные дозировки активностей, объём и характеристики введения радиоактивного коллоида с целью обследования и биопсии сторожевых лимфатических узлов с использованием радиофармпрепарата Technefit ^{99m} Tc у пациентов со злокачественными опухолями различной локализации, а именно раком молочной железы и меланомой кожи. В ряде случаев не выявлено признаков существенного снижения активности Technefit ^{99m} Tc, что свидетельствует об очень медленной фильтрации Technefit ^{99m} Tc через поры лимфатических капилляров.

Ключевые слова

биопсия сторожевого лимфатического узла, рак молочной железы, коллоидные радиофармпрепараты, злокачественные опухоли