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Diagnosis of sentinel lymph nodes in patients with cancer of the larynx and laryngopharynx using a new radiopharmaceutical based on technetium-99m-labeled gamma aluminum oxide

Medvedeva A.A., Chernov V.I., Bragina O.D., Zeltchan R.V., Choyazonov E.L., Chizhevskaya S.Yu., Rybina A.N., Gol'dberg A.V., Cheremisina O.V.

Cancer Research Institute, Tomsk National Research Medical Center (NRMC), Russian Academy of Sciences 5, Kooperativny Str., Tomsk, 634009, Russian Federation

ABSTRACT

Aim. To study the possibility of using a radiopharmaceutical based on aluminum oxide labeled with ^{99m}Tc ($[^{99m}\text{Tc}]\text{-Al}_2\text{O}_3$) for the diagnosis of sentinel lymph nodes (SLN) in tumors of the larynx and laryngopharynx in comparison with a phytate colloid ($[^{99m}\text{Tc}]\text{-phytate colloid}$).

Materials and methods. The study included patients with cancer of the larynx and laryngopharynx ($\text{T}_{2-4}\text{N}_0\text{M}_0$) ($n = 54$). In the prospective group ($n = 30$), $[^{99m}\text{Tc}]\text{-Al}_2\text{O}_3$ was used as a radiopharmaceutical, in the retrospective group ($n = 24$), $[^{99m}\text{Tc}]\text{-phytate colloid}$ was used. All radiopharmaceuticals were introduced endoscopically into the submucosal space along the periphery of the tumor. After 18 hours, single-photon emission computed tomography (SPECT) and intraoperative SLN detection were performed.

Results. In the retrospective group, SLNs were detected in 20 out of 24 patients. A total of 32 lymph nodes were identified in the retrospective group. The median number of detected lymph nodes in one patient was 1.3 [0–3], the intensity of the radiopharmaceutical uptake on scintigrams was 2.2 [0.7–8.1], intraoperatively – 4 [1.6–9.0]. In the prospective group, $[^{99m}\text{Tc}]\text{-Al}_2\text{O}_3$ uptake in the lymph nodes of the neck was determined in 27 patients (90%); in 3 patients, SLNs were not visualized. A total of 57 lymph nodes were identified (in 27 patients). The median number of visualized SLNs was 1.5 [0–5], the intensity of $[^{99m}\text{Tc}]\text{-Al}_2\text{O}_3$ uptake according to SPECT and intraoperative detection was 4.8 [0.7–19.4] and 6 [1.1–22.0], respectively.

Conclusion. The most significant advantage of using $[^{99m}\text{Tc}]\text{-Al}_2\text{O}_3$ as a radiopharmaceutical is its high uptake in SLNs, which leads to an increase in the sensitivity of the method as a whole up to 90 versus 83% when using $[^{99m}\text{Tc}]\text{-phytate colloid}$.

Keywords: radionuclide, colloid, laryngeal cancer, laryngopharyngeal cancer, sentinel lymph node, single-photon emission computed tomography, gamma probe

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee and the Bioethics Committee at Cancer Research Institute, Tomsk NRMC.

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✉ Medvedeva Anna A., medvedeva@mail.ru

Диагностика сторожевых лимфатических узлов у больных раком гортани и гортаноглотки с применением нового отечественного радиофармацевтического лекарственного препарата на основе меченного технецием-99m гамма-оксида алюминия

Медведева А.А., Чернов В.И., Брагина О.Д., Зельчан Р.В., Чойнзонов Е.Л., Чижевская С.Ю., Рыбина А.Н., Гольдберг А.В., Черемисина О.В.

Научно-исследовательский институт (НИИ) онкологии, Томский национальный исследовательский медицинский центр (НИМЦ) Российской академии наук
Россия, 634009, г. Томск, пер. Кооперативный, 5

РЕЗЮМЕ

Цель. Изучить возможность использования радиофармацевтического лекарственного препарата (РФЛП) на основе оксида алюминия, меченного ^{99m}Tc (^{99m}Tc - Al_2O_3), для диагностики сторожевых лимфатических узлов (СЛУ) при опухолях гортани и гортаноглотки в сравнении с фитатным коллоидом (^{99m}Tc -фитатный коллоид).

Материалы и методы. В исследование вошли больные раком гортани и гортаноглотки стадий $\text{T}_{2-4}\text{N}_0\text{M}_0$ ($n = 54$). В проспективной группе ($n = 30$) в качестве диагностического РФЛП использовался ^{99m}Tc - Al_2O_3 , в ретроспективной группе ($n = 24$) – ^{99m}Tc -фитатный коллоид. Все РФЛП вводились эндоскопически в подслизистое пространство по периферии опухоли, через 18 ч проводилась однофотонная эмиссионная компьютерная томография (ОФЭКТ) и интраоперационная детекция СЛУ.

Результаты. В ретроспективной группе СЛУ были выявлены у 20 пациентов из 24. Всего в ретроспективной группе было обнаружено 32 лимфатических узла. Количество выявленных лимфатических узлов у одного больного составило 1,3 [0–3], интенсивность накопления РФЛП на томосцинтиграммах – 2,2 [0,7–8,1], интраоперационно – 4 [1,6–9,0]. В проспективной группе аккумуляция ^{99m}Tc - Al_2O_3 в лимфатических узлах шеи определялась у 27 пациентов (90%), у 3 пациентов СЛУ не визуализировались. Всего было выявлено 57 лимфоузлов (у 27 пациентов). Количество визуализируемых СЛУ составила 1,5 [0–5], интенсивность накопления ^{99m}Tc - Al_2O_3 по данным ОФЭКТ и интраоперационной детекции составила 4,8 [0,7–19,4] и 6 [1,1–22,0] соответственно.

Заключение. Существенным достоинством использования в качестве РФЛП ^{99m}Tc - Al_2O_3 является его высокая аккумуляция в сторожевых лимфатических узлах при опухолях гортани и гортаноглотки, что приводит к увеличению чувствительности метода в целом до 90 против 83% при применении ^{99m}Tc -фитатного коллоида.

Ключевые слова: радионуклидный, коллоид, рак гортани, рак гортаноглотки, сторожевой лимфатический узел, однофотонная эмиссионная компьютерная томография, гамма-зонд

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом по биомедицинской этике НИИ онкологии Томского НИМЦ.

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INTRODUCTION

Surgery is one of the main stages in the treatment of tumors of most localizations. However, surgical intervention often causes a decrease in the quality of life and social adaptation of patients. In this regard, introducing organ-preserving and reconstructive surgeries into clinical practice is extremely relevant. As a result, correct determination of the spread of the malignant process plays an important role in the choice of treatment methods for cancer patients [1–4]. Currently, the sentinel lymph node (SLN) status is considered one of the important prognostic factors for metastasis of some tumors [5–8]. SLN is a lymph node that directly receives lymphatic drainage from a tumor site. R.M. Cabañas was one of the first to coin the term “sentinel lymph node” [9].

Radionuclide diagnosis is actively used in oncological practice, supplementing conventional imaging methods with valuable functional information [10–14]. The use of this method for SLN detection makes it possible to accurately localize SLN both intra- and preoperatively. In 1993, J.C. Alex and D.N. Krag suggested to use intraoperative detection of SLN with a portable gamma-ray scanner by measuring the level of radiation in all lymphatic collectors after administration of a radioactive colloid [15].

In recent years, rapid development of nuclear medicine has been associated not only with technological advancements, but also with introduction of new highly specific radiopharmaceuticals. An ideal radiopharmaceutical for SLN imaging should be characterized by rapid clearance from the injection site and active uptake in the lymph nodes. Researchers believe that such characteristics can be encompassed in the radiopharmaceuticals which are based on ligand – receptor or antigen – antibody binding mechanisms. One of such radiopharmaceuticals is currently [^{99m}Tc]-rituximab, which binds to the CD20 receptor, actively expressed on the surface of B cells. Studies have shown that [^{99m}Tc]-rituximab is to a lesser extent redistributed to the distal lymph nodes, compared with colloidal radiopharmaceuticals, and more actively leaves the injection site [16]. Besides, 99mTc-labeled LymphoseekTM was registered in the United States and is being actively introduced into the clinical practice. This radiopharmaceutical accumulates in the lymph nodes by binding to CD206 on the surface of macrophages [17].

Despite the emergence of targeted radiopharmaceuticals for SLN mapping, research is

ongoing to explore the possibilities of using 99mTc-labeled colloidal preparations which are still the main indicators for SLN visualization. The main criterion for assessing a colloidal radiopharmaceutical is the particle size. A colloid with a particle size of 50–80 nm is considered optimal because it provides fast radiopharmaceutical clearance from the injection site and its high retention in the SLN [18, 19].

The aim of this study was to investigate the possibilities of using a new radiopharmaceutical based on aluminum oxide labeled with ^{99m}Tc ([^{99m}Tc]- Al_2O_3) for the diagnosis of SLN in tumors of the larynx and laryngopharynx in comparison with a phytate colloid ([^{99m}Tc]-phytate colloid) commonly used in Russia.

Both radiopharmaceuticals are colloidal preparations, however, they differ in particle sizes: [^{99m}Tc]-phytate colloid is characterized by a fairly large range of particle sizes – 40–10.000 nm, and [^{99m}Tc]- Al_2O_3 contains colloidal particles ranging from 50 to 100 nm in size. Preclinical and clinical trials of [^{99m}Tc]- Al_2O_3 have shown its safety and functional suitability for imaging of lymph nodes [20–25].

MATERIALS AND METHODS

The study included patients with cancer of the larynx and laryngopharynx $\text{T}_{2-4}\text{N}_0\text{M}_0$ ($n = 54$). The general inclusion criterion was the absence of signs of metastasis in regional lymph nodes at the time of the examination. The study was approved by the local Ethics Committee and the Bioethics Committee at Cancer Research Institute, Tomsk NRMС. All patients signed an informed consent to participate in the study.

In the prospective group ($n = 30$), [^{99m}Tc]- Al_2O_3 was used as a diagnostic radiopharmaceutical, the retrospective group ($n = 24$) was examined using [^{99m}Tc]-phytate colloid. The result of a histologic examination of removed lymph nodes was the reference method for analyzing the diagnostic effectiveness.

Radionuclide diagnosis of SLN includes injection of radiopharmaceuticals, visualization, and intraoperative detection of lymph nodes with their subsequent morphological examination. Radiopharmaceuticals were injected endoscopically into the submucosal space along the periphery of the tumor in the region of the larynx or laryngopharynx at 2 sites (at 12:00 and 18:00 on the conventional dial). The total administered radiopharmaceutical activity was 40 MBq (20 MBq per injection site).

Single-photon emission computed tomography (SPECT) was performed on the E.cam 180 gamma camera (Siemens, Germany) 18–20 hours after the

radiopharmaceutical injection using parallel-hole high-resolution collimators for 140 keV radiation..

SPECT images were assessed visually (identifying the number of areas with focal radiopharmaceutical uptake corresponding to the localization of the regional lymph nodes) and semi-quantitatively (calculating the ratio of the number of impulses in the lymph node with the highest radiopharmaceutical uptake to the number of impulses at the injection site, %).



Fig. 1. Intraoperative assessment of sentinel lymph nodes using a gamma probe

All lymph nodes identified by the gamma probe in the projection of the lymphatic collector were removed. According to intraoperative radiometry, the level of radiopharmaceutical uptake in the projection of SLN was also calculated (in % relative to the injection site). Removed SLNs were subject to immediate cytological examination: with metastasis in the lymph nodes, lymph node dissection was performed.

The normality of data distribution was assessed using the Shapiro –Wilk test. The median and the interquartile range $Me [Q_1 - Q_3]$ were calculated to measure the central tendency in the sample. The Mann – Whitney U test and the Kruskal – Wallis test were used to compare the intergroup differences in the studied results for quantitative variables with non-normal distribution. The sensitivity of the method was assessed according to the formula $TP / (TP + FN) \times 100\%$, where TP is a true positive result, and FN is a false negative result. At the same time, we took into consideration the number of patients with radiopharmaceutical uptake in the projection of the lymph nodes. The reference method for the analysis was the result of the histologic examination of the

During the surgical intervention, intraoperative SLN detection was performed using the Gamma Finder II probe (USA) (Fig. 1). The lymph node with the highest activity, in comparison with other lymph nodes detected by the gamma probe, or the only lymph node detected, was marked as SLN. After removal of the SLN, the area of the lymphatic collector was re-examined using the gamma probe.



surgical material (the presence of lymph nodes in the removed material).

RESULTS

In 7 out of 54 patients, no redistribution of the radiopharmaceuticals from the injection site along the lymphatic collector was noted. No radiopharmaceutical uptake in the projection of the lymph nodes was detected either scintigraphically or intraoperatively using the gamma probe. Unilateral localization of SLN was visualized in 85% of cases ($n=40$), bilateral localization was detected in 7 patients (Fig. 2, 3). At the same time, most often lymph nodes were visualized in the projection of levels III and Va of the neck – 47 and 33%, respectively, less often – in the projection of levels IIa and IIb of the neck – 14 and 12%, respectively.

In the retrospective group, SLNs were detected in 20 out of 24 patients. The results of SPECT and intraoperative detection were in line; all lymph nodes visualized by SPECT were also detected by the gamma probe. The presence of [^{99m}Tc]-phytate colloid in the lymph nodes was not observed in 4 patients (Table 1).

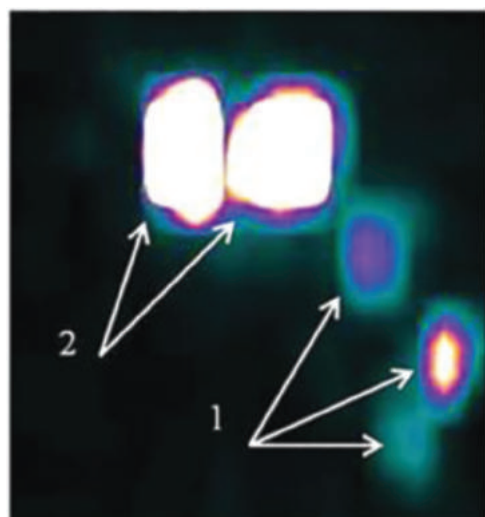


Fig. 2. SPECT image of a patient with laryngeal cancer: 1 – radiopharmaceutical uptake in the projection of the lymph nodes of the neck on the left ($n = 3$); 2 – injection site

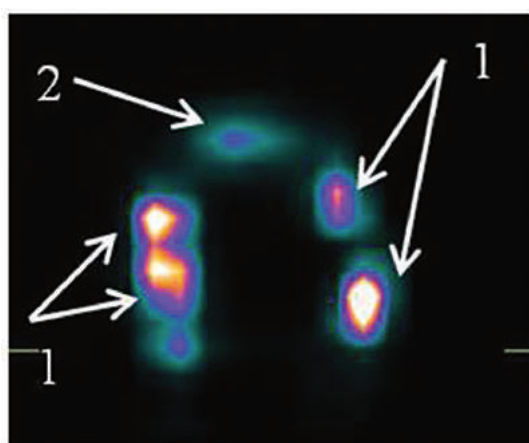


Fig. 3. SPECT image of a patient with laryngopharyngeal cancer: 1– radiopharmaceutical uptake in the projection of the lymph nodes of the neck on both sides ($n = 5$); 2 – injection site

Table 1

Characterization of the results obtained in the retrospective group using [^{99m}Tc]-phytate colloid, $n = 24$		
Result	SPECT, n	Intraoperative detection, n
True positive	20	20
True negative	0	0
False positive	0	0
False negative	4	4

A total of 32 lymph nodes were identified in the retrospective group. The median number of detected lymph nodes in one patient was 1.3 [0–3], the intensity of the radiopharmaceutical uptake according to SPECT and intraoperative detection was 2.2 [0.7–8.1] and 4 [1.6–9], respectively (Table 2).

In the prospective group, [^{99m}Tc]- Al_2O_3 uptake in the lymph nodes of the neck was determined in 27 patients (90%); SLNs were not visualized in 3 patients. Identical results were obtained during intraoperative detection (Table 3). A total of 57 lymph nodes were identified (in 27 patients). The median number of visualized SLNs was 1.5 [0–5], the intensity of [^{99m}Tc]- Al_2O_3 uptake according to SPECT and intraoperative detection was 4.8 [0.7–19.4] and 6 [1.1–22], respectively (Table 2).

Table 2

Comparative analysis of the results of radionuclide diagnosis of sentinel lymph nodes in patients with cancer of the larynx and laryngopharynx using [^{99m}Tc]-phytate colloid and [^{99m}Tc]- Al_2O_3		
Parameter	[^{99m}Tc]-phytate colloid	[^{99m}Tc]- Al_2O_3
Number of visualized lymph nodes, n , $Me [Q_1 - Q_3]$	1.3 [0–3]	1.5 [0–5]
	$p < 0.2$	
Intensity of radiopharmaceutical uptake according to SPECT, %, $Me [Q_1 - Q_3]$	2.2 [0.7–8.1]	4.8 [0.7–19.4]
	$p < 0.027$	
Intensity of radiopharmaceutical uptake according to intraoperative detection, %, $Me [Q_1 - Q_3]$	4 [1.6–9]	6 [1.1–22]
	$p < 0.034$	
Method sensitivity, %	83	90

Table 3

Characterization of the results obtained in the prospective group using [^{99m}Tc]- Al_2O_3 , $n = 30$		
Result	SPECT, n	Intraoperative detection, n
True positive	27	27
True negative	0	0
False positive	0	0
False negative	3	3

According to the results of the histologic examination of the removed lymph nodes, metastasis was detected in 3 patients from the retrospective group and in 3 individuals from the prospective group (all affected lymph nodes corresponded to the side of the primary tumor localization).

DISCUSSION

The comparative analysis of the results obtained indicated significant differences in the nature of the scintigraphic data obtained after the use of radiopharmaceuticals with different sizes of colloidal particles. The most significant advantage of using [^{99m}Tc]- Al_2O_3 is its high uptake in the lymph nodes, which improves visualization of SLNs, facilitates their search during surgery, and increases the sensitivity of the method as a whole up to 90 versus 83% when using [^{99m}Tc]-phytate colloid.

To date, surgery remains the main method for treating cancer of the larynx and laryngopharynx. The volume of surgery is determined by clinical and morphological features of the tumor spread. One of the basic factors that affects the treatment strategy and the prognosis of the disease is assessment of the SLN status. In cancer of the larynx and laryngopharynx, the frequency of metastasis to regional lymph nodes reaches 30% [26].

Many attempts have been made to identify predictors of latent metastases in the lymph nodes, of which the depth of invasion turned out to be the most informative. However, this criterion does not provide absolute confidence in the adequate assessment of the state of the regional lymphatic drainage zones [27]. Therefore, application of the concept of SLNs in tumors of the larynx and laryngopharynx can help reduce unnecessary intraoperative lymphadenectomy and decrease the amount of radiation therapy performed [28–30].

In general, methods for determining SLNs in malignant tumors of the head and neck are more related to oral cavity cancer, and the bulk of the research is devoted to this localization. This is due to a more aggressive course of this pathology, features of lymphatic drainage, and difficulties in detecting metastasis in regional lymph nodes, especially at early stages of the disease. Cancer of the larynx and laryngopharynx is characterized by a lower risk of metastasis to the lymph nodes, however, the problem of organ-preserving surgeries in this localization is quite dire. Therefore, developing methods for proper assessment of tumor spread at the preoperative stage is highly relevant [28, 30–32].

CONCLUSION

A comparative study of the effectiveness of [^{99m}Tc]- Al_2O_3 for visualization of SLN in tumors of the larynx and laryngopharynx in comparison with [^{99m}Tc]-phytate colloid showed that a significant advantage of using [^{99m}Tc]- Al_2O_3 is its higher uptake in SLNs. This phenomenon contributes to an increase in the sensitivity of the method as a whole up to 90 versus 83% when using [^{99m}Tc]-phytate colloid.

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Authors contribution

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Authors information

Medvedeva Anna A. – Cand. Sci. (Med.), Senior Researcher, Department of Nuclear Medicine, Cancer Research Institute, Tomsk NRMIC of RAS, Tomsk, medvedeva@tnimc.ru, <http://orcid.org/0000-0002-5840-3625>

Chernov Vladimir I. – Dr. Sci. (Med.), Professor, Corresponding Member of RAS, Head of the Department of Nuclear Medicine, Cancer Research Institute, Tomsk NRMC of RAS, Tomsk, chernov@tnimc.ru, <http://orcid.org/0000-0002-5524-9546>

Bragina Olga D. – Dr. Sci. (Med.), Oncologist, Senior Researcher, Department of Nuclear Medicine, Cancer Research Institute, Tomsk NRMC of RAS, Tomsk, bragina_od@mail.ru, <http://orcid.org/0000-0001-5281-7758>

Zeltchan Roman V. – Cand. Sci. (Med.), Senior Researcher, Department of Nuclear Medicine, Cancer Research Institute, Tomsk NRMC of RAS, Tomsk, r.zelchan@yandex.ru, <http://orcid.org/0000-0002-4568-1781>

Choyazonov Evgeniy L. – Dr. Sci. (Med.), Professor, Academician of RAS, Director of Cancer Research Institute, Tomsk NRMC of RAS, Tomsk, choyazonov@tnimc.ru, <http://orcid.org/0000-0002-3651-0665>

Chizhevskaya Svetlana Yu. – Dr. Sci. (Med.), Leading Researcher, Department of Head and Neck Tumors, Cancer Research Institute, Tomsk NRMC of RAS, Tomsk, sch@oncology.tomsk.ru, <http://orcid.org/0000-0003-2974-4778>

Rybina Anastasia N. – Cand. Sci. (Med.), Physician, Department of Nuclear Medicine, Cancer Research Institute, Tomsk NRMC of RAS, Tomsk, pankovaan@mail.ru, <http://orcid.org/0000-0002-6488-0647>

Gol'dberg Alexey V. – Cand. Sci. (Med.), Junior Researcher, Department of Radiology, Cancer Research Institute, Tomsk NRMC of RAS, Tomsk, agoldyyy@gmail.com, <http://orcid.org/0000-0001-7829-2515>

Cheremisina Olga V. – Dr. Sci. (Med.), Head of the Endoscopy Department, Cancer Research Institute, Tomsk NRMC of RAS, Tomsk, cheremisinaov@oncology.tomsk.ru, <http://orcid.org/0000-0001-7234-4708>

(✉) **Medvedeva Anna A.**, medvedeva@mail.ru

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