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CURRENT DIAGNOSTIC APPROACHES FOR RADIOIODINE-REFRACTORY THYROID CANCER: THE ROLE OF 18^F-FDG PET/CT

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Aim. Demonstration of a clinical case of radioiodine resistance highly differentiated thyroid cancer and discussion of current diagnostic methods: the role of PET-CT with 18^F-FDG.

Materials and methods. The study design is a retrospective study. A database of patients who underwent treatment in the radionuclide therapy department of the Centre for Nuclear Medicine and Oncology of the Abay Regional Healthcare Institution was formed. This clinical case was taken from this database.

Results and discussion. The clinical case we reviewed confirms the presence of a flip-flop phenomenon in the radioiodine resistance course of thyroid cancer. PET-CT with 18^F-FDG is an important component in the diagnostic algorithm of patients with highly differentiated thyroid cancer, suspected or confirmed radioiodine resistance. The method provides visualization of metabolically active tumor foci due to the accumulation of fluorodeoxyglucose in tissues with increased glycolysis.

Conclusions. PET-CT using 18F-FDG occupies an important place in the diagnosis of radioiodine resistance differentiated thyroid cancer. The method makes it possible to identify metabolically active tumors and metastases that do not accumulate radioactive iodine and indicates the aggressiveness of the process. Despite the existing limitations, PET-CT with 18F-FDG remains an effective tool for making decisions about the expediency of radioiodine therapy and the choice of further treatment tactics.

Key words: highly differentiated thyroid cancer; radioiodine resistance; clinical case; PET-CT

INTRODUCTION

The incidence of thyroid cancer is increasing every year both in the world and in Kazakhstan. According to the indicators of the oncological service of the Republic of Kazakhstan, an increase in this disease was detected in 2023. It is one of the 10 most common cancers in women, accounting for 4.4% (4.2%) [3]. In most cases, the course of well-differentiated thyroid cancer (WDTC) is characterized by a favorable prognosis. Moreover, this disease has a good sensitivity to radioiodine therapy.

After performing organ-preserving operations on the thyroid gland, in cases where, according to the results of the stratification of the risk of recurrence, the patient belongs to the intermediate or high-risk group, total thyroidectomy is indicated for the subsequent use of radioactive iodine [8].

Radioiodine therapy (RIT) allows you to destroy the remnants of thyroid tissue and accumulating radioactive iodine tumor foci. It has a positive effect on overall and disease-free survival in patients with highly differentiated thyroid cancer.

However, it should be noted that a certain group of patients develops resistance to radioiodine therapy during treatment. Cases with one or more of the following signs should be considered as resistance cases of WDTC: the presence of one or more foci of WDTC, visualized on positron emission tomography (PET), but not accumulating I-131 on post-treatment scintigraphy of the whole body; progression of the tumor process after < 12 months against the background of cancer activity of at least 3.7 GBq under the condition of successfully ablated thyroid residue; absence of regression of tumor foci with a total therapeutic activity of radioactive iodine of more than 22 GBq (600 mCi) [4]. Other predictors of radioiodine resistance are: the pres-

ence of BRAF, TERT mutations; an increase in thyroglobulin levels without visible structural progression; significant uptake of 18^{F}-fluorodeoxyglucose (18^{F}-FDG) in PET/CT by metastatic foci; lack of accumulation of I-131 according to SPECT/CT scan during the introduction of therapeutic or diagnostic activity [1].

Radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) is an aggressive form of this disease characterized by limited therapeutic options. In this regard, timely and accurate diagnosis becomes important for determining the optimal treatment strategy. Modern imaging methods play an essential role in the diagnosis, choice of treatment strategy and monitoring of the condition of patients with this pathology. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET), when combined with computed tomography (CT), not only allow for the visualization of tumor lesions but also enable their quantitative assessment, which significantly improves the diagnostic accuracy of radioiodine-refractory differentiated thyroid cancer (RAI-R DTC).

For a correct assessment of tumor dynamics in patients with radioiodine resistance, it is advisable to use the RECIST 1.1 system [6]. It should be noted that for a comprehensive assessment and diagnosis of radioiodine resistance in patients, it is necessary to take into account: the level of thyroglobulin, antibodies to thyroglobulin in the blood serum, the result of post-therapeutic scintigraphy of the whole body, the conclusion of PET-CT with 18^{F}-FDG. Whole-body scintigraphy performed after radioiodine therapy can detect thyroid cancer metastases. PET-CT of the whole body provides an opportunity to detect a discrepancy between the distribution of radiopharmaceuticals I-131 and 18^{F}-FDG. In particular, in the absence of accumulation of I131 for SPECT/CT with radioactive iodine and the presence of increased uptake of 18^{F}-FDG during PET-CT of the whole body, the so-called "flip-flop" phenomenon is observed, reflecting the inverse relationship between the iodine storage capacity of tumor cells and their metabolic activity.

The aim of the study was to demonstrate a clinical case of radioiodine resistance highly differentiated thyroid cancer and to discuss current diagnostic methods - the role of PET-CT with 18^{F}-FDG.

MATERIALS AND METHODS

The study design is a retrospective study. A database of patients who underwent treatment in the radionuclide therapy department of the Centre for Nuclear Medicine and Oncology of the Abay Regional Healthcare Institution was formed. This clinical case was taken from this database.

RESULTS

Patient Zh., 43 years old, has been ill since 2018, when he complained of weakness and the appearance of an formation in the cervical region. He was examined at his place of residence, and surgical treatment was recommended. In 2018, a volume operation was performed - a hemithyroidectomy on the left. Postoperative histological conclusion: follicular cancer. Thyroglobulin is more than 600 ng/ml. In January 2019 and February 2019, 2 repeated surgeries were performed for the progression of the disease in volume: lymphadenectomy of the neck on the left and hemithyroidectomy on the right. In September 2019, he completed 1 course of radioiodine therapy with 3 GBq activity. On the 3rd day after radioiodine therapy, on the background of the physiological distribution of I-131 in the projection of the gastrointestinal tract and salivary glands, focal hyperfixation of the drug in the projection of the thyroid gland bed is determined by 26% of the total body scintigraphy (SVT). No other foci of pathological hyperfixation of the indicator have been identified.

In dynamics, in June 2020, a second volume operation was performed - cervical lymphodissection on both sides. In March 2021, he completed the 2nd course of radioiodine therapy with 3 GBq activity. Scintigraphy of the whole body on the third day after radioiodine therapy against the background of the physiological distribution of I-131 in the projection of the gastrointestinal tract and salivary glands did not reveal data for the presence of foci of hyperfixation of the indicator. In May 2021, a second volume operation was performed – removal of a recurrent thyroid tumor on the left. Postoperative histological conclusion: The morphological picture corresponds to follicular carcinoma of the thyroid gland with invasion of the tumor capsule. In December 2021, he received the 3rd course of radioiodine therapy with an activity of 5610 MBq. Conclusion of whole body post-therapeutic scintigraphy: signs of a focus of weak isotope accumulation in the area of the thyroid isthmus. Recommended: Full body SPECT with I-131 in dynamics. Consultation with a radionuclide therapy doctor. Ultrasound of the neck lymph nodes (level V). Analyzes dated December 2021: antibodies to thyroglobulin - 13.84 IU/ml, thyroglobulin-230 mg/ml.

In dynamics, on November 23, the patient underwent a diagnostic CT scan (fig. 1). Conclusion: The focus of isotope accumulation in the area of the thyroid gland bed has not been revealed (figure 1). Cancer markers from December 2023: thyroglobulin – 528 ng/ml, thyroglobulin antibodies – 19.06 IU/ml. She is consulted by doctors of nuclear medicine. Recommended: follow-up with an oncologist, endocrinologist at the place of residence. A course of radioiodine therapy is currently not indicated.

Further, in dynamics, in March 2025, the patient underwent a full-body PEC-CT scan. Conclusion: The PET-CT picture of a metabolically active nodule formation in the thyroid gland bed with hyperfixation of the thyroid gland corresponds to a recurrence of the underlying disease (figure 2), and consultation with an oncologist is recommended. The metabolically active nodular seals of both lungs are of a secondary nature. Metabolically weakly active subclavian lymph node on the left is reactive, ultrasound monitoring is recommended.

The patient is currently under the supervision of an oncologist at his place of residence.

Ethical issues. The conduct of this study was approved by the Local Ethics Commission of the NCJSC "Semey Medical University" (Extract from the minutes of the meeting №1b dated November 02, 2023). Also, before admission to the hospital, patients signed a written "Informed consent of the patient" for the impersonal dissemination of his medical information.

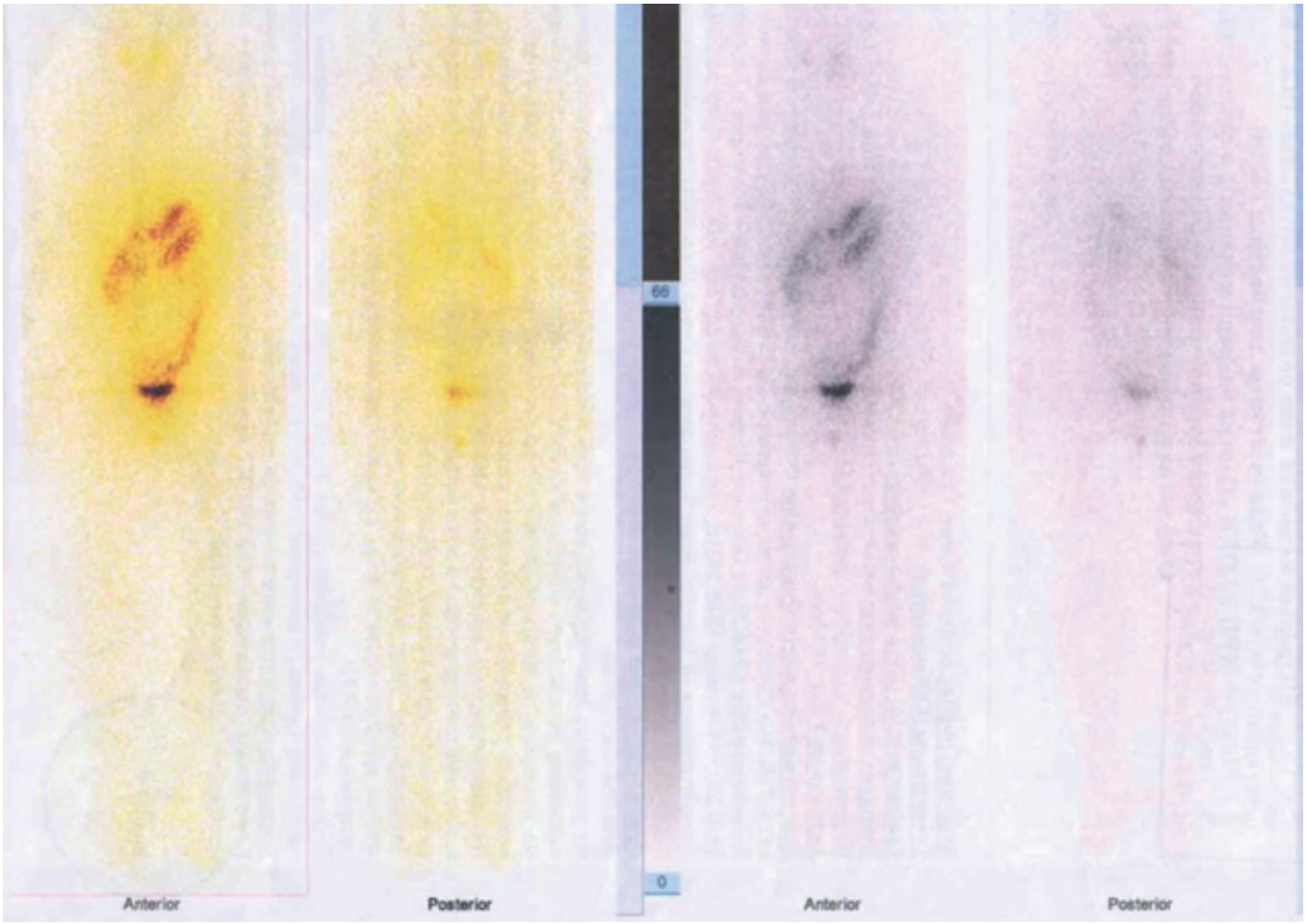


Figure 1 – Conclusion of the SPECT: The focus of isotope accumulation in the area of the thyroid gland bed was not revealed

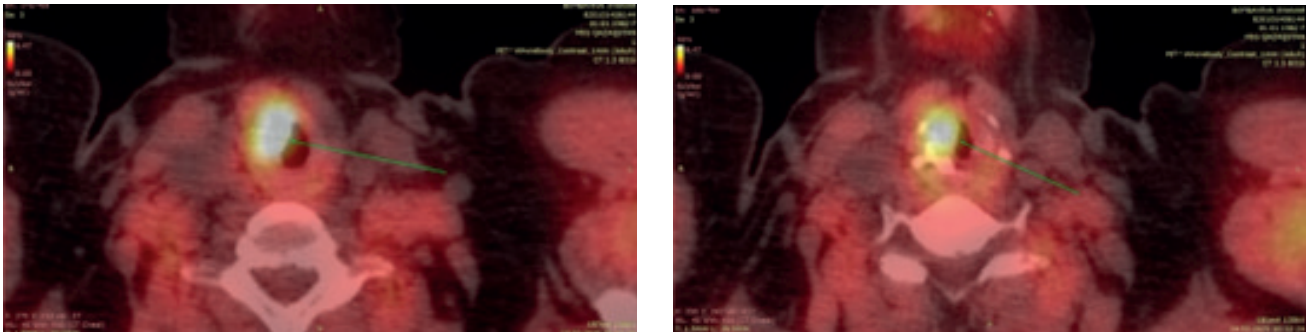
DISCUSSION

Positron emission tomography combined with computed tomography (PET-CT) using 18^{F}-fluorodeoxyglucose (18^{F}-FDG) is included in the diagnostic algorithm for the examination and follow-up of patients with highly differentiated thyroid cancer in the presence of confirmed or suspected radioiodine resistance.

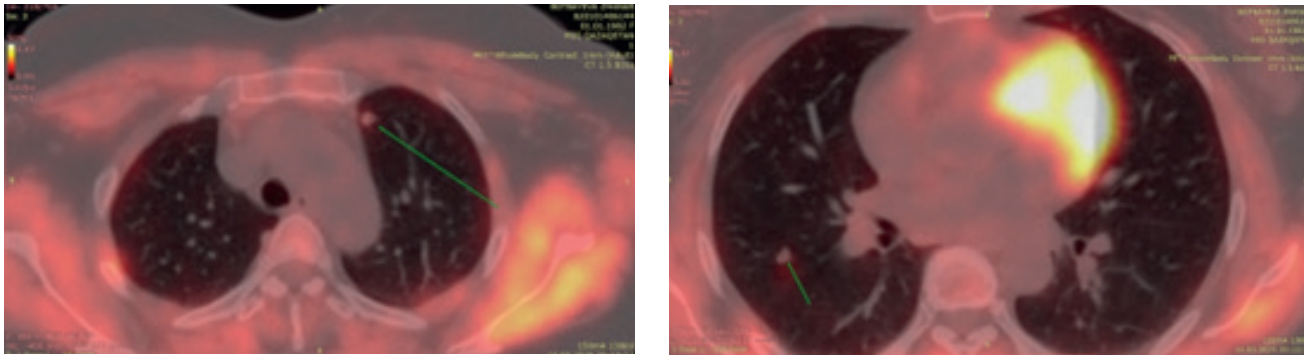
Once inside the cell, fluorodeoxyglucose (FDG) is phosphorylated by the enzyme hexokinase to FDG-6-phosphate. FDG-6-phosphate, in turn, is not a suitable substrate for the enzyme glucose-6-phosphate isomerase and does not undergo a further stage of metabolism. This process leads to its intracellular accumulation, which will be recorded by PET-CT of the whole body. The rate of elimination of phosphorylated FDG is very low. Therefore, in tumor cells with an increased need for glucose, it accumulates to a greater extent than in healthy ones. This makes it possible to differentiate metabolically active metastases or tumors from healthy tissues.

The discrepancy between the accumulation of fluorodeoxyglucose and radioactive iodine was called the flip-flop phenomenon. Thus, PET-CT with 18F-fluorodeoxyglucose has been recognized as an effective diagnostic method for thyroid cancer in patients with radioiodine resistance [5] and is the basis for abandoning radioiodine therapy and searching for other methods of antitumor treatment [10].

In April 2024, a master class was held in the Russian Federation called «Differentiated thyroid cancer. Patient management». The purpose and objectives of this master class were to assess the difficulties associated with the interaction between radiologists of radioiodine therapy centers and clinical oncologists in the field, as well as to develop a unified approach to understanding the stages of treatment of progressive radioiodine resistance differentiated thyroid cancer. Based on the results of this event, limitations of positron emission tomography combined with computed tomography were announced, such as: lack of clear recommendations on the time of re-evaluation; false negative results with a small tumor size; false positive results in inflammatory processes, iatrogenism and foci with high physiological glucose accumulation. However, this diagnostic method has a number of positive qualities in determining radioiodine resistance. It should be taken into account that with PET/CT is advisable to evaluate SUL (standardized uptake lean body mass) – the standardized level of glucose uptake by muscle mass. This indicator has a greater diagnostic value than the SUV. The advantages



A (1, 2)



B (1, 2)

Figure 2 – Conclusion of PET-CT scan. A (1, 2) is a pattern of metabolically active nodular formation in the thyroid gland bed with hyperfixation of the thyroid gland, which corresponds to a recurrence of the underlying disease. B (1, 2), Metabolically active nodular seals of both lungs are of a secondary nature

of using SUL in the assessment of foci are a more uniform distribution of 18^{F}-FDG in muscle mass; SUL does not take into account white fat and correctly assumes the distribution of 18F-FDG, which reaches equilibrium in low-fat tissues. PET/CT results should also be supplemented with an assessment of all the clinical data of patients as a whole [1].

Doctors from Finland published about the successful use of PET-CT with FDG in prostate cancer in their practice in 1987. They described a number of clinical cases of patients with thyroid cancer with multiple distant metastases. The authors concluded that metastases can accumulate only FDG, only I-131, and both FDG and I-131; the accumulation of FDG in metastases increases in parallel with their progression; metastases that accumulate FDG but do not accumulate I-131 may behave more aggressively than metastases that accumulate I-131rather than FDG [9].

Along with this, the benefits of FDG accumulation in thyroid cancer have been studied by other authors in their works. In his work, U.Feine demonstrated the discrepancy between the accumulation of 18^{F}-FDG and radioactive iodine. He called this phenomenon the flip-flop phenomenon. The essence of the phenomenon boils down to the fact that thyroid cancer with low iodine avidity is prone to higher glucose metabolism. Thus, the probability of a positive PET scan increases, which means that this case is probably radioiodine resistance [2, 7].

CONCLUSIONS

Positron emission tomography, combined with computed tomography with 18^{F}-FDG, is an important component in the diagnostic algorithm of patients with highly differentiated thyroid cancer who have suspected or confirmed radio resistance. The method provides visualization of metabolically active tumor foci due to the accumulation of fluorodeoxyglucose in tissues with increased glycolysis. The flip-flop phenomenon, expressed in the inverse dependence of the accumulation of I-131 and 18^{F}-FDG, emphasizes the need to integrate PET-CT in assessing the biological behavior of a tumor in cases where there is no accumulation of radioactive iodine. Despite its high sensitivity, PET-CT has some limitations: false positive results are possible for inflammatory changes, as well as false negative results for small foci. This requires a comprehensive approach to interpreting the results, taking into account the patient's clinical and laboratory data. The clinical data accumulated to date show that FDG-positive, but iodine-negative metastases are characterized by a more aggressive course. As a result, it can be concluded that the results of PET-CT may serve as a basis for abandoning radioactive iodine and choosing alternative therapies, such as targeted or systemic treatment.

Authors' contribution:

L. A. Pak, Zh. B. Mussazhanova – concept and design of the study.

K. K. Kudaiberdinov, M. A. Mussulmanova – collection and processing of the material.

A. M. Rakhmankulova, D. M. Seitkhanova, A. S. Baktiyar – writing the text.

Zh. K. Burkitbayev – editing.

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АКТУАЛЬНЫЕ МЕТОДЫ ДИАГНОСТИКИ РАДИОЙОДРЕЗИСТЕНТНОГО РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ: ЗНАЧЕНИЕ ПЭТ-КТ С 18^F-FDG

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Цель. Демонстрация клинического случая радиойодрезистентного высокодифференцированного рака щитовидной железы и обсуждение современных методов диагностики: роль ПЭТ-КТ с 18^F-FDG.

Материалы и методы. Дизайн исследования – ретроспективное исследование. Сформирована база данных пациентов, прошедших курс лечения в отделении радионуклидной терапии Центра Ядерной медицины и онкологии УЗ Области Абай. Представленный клинический случай был взят из данной базы.

Результаты и обсуждение. Рассмотренный клинический случай подтверждает наличие феномена «**flip-flop»** в течении радиойодрезистентного рака щитовидной железы. ПЭТ-КТ с 18^F-FDG является важным компонентом в диагностическом алгоритме пациентов с высокодифференцированным раком щитовидной железы, подозреваемой или подтвержденной радиойодрезистентностью. Метод обеспечивает визуализацию метаболически активных очагов опухоли за счет накопления фтордезоксиглюкозы в тканях с повышенным гликолизом.

Выводы. ПЭТ-КТ с 18^F-FDG занимает важное место в диагностике радиойодрезистентного дифференцированного рака щитовидной железы. Метод позволяет выявлять метаболически активные опухоли и метастазы, не накапливающие радиоактивный йод и указывающие на агрессивность процесса. Несмотря на имеющиеся ограничения, ПЭТ-КТ с 18^F-FDG остается эффективным инструментом для принятия решения о целесообразности проведения радиойодтерапии и выбора дальнейшей тактики лечения.

Ключевые слова: высокодифференцированный рак щитовидной железы; радиойодрезистентность; клинический случай; ПЭТ-КТ

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РАДИОЙОДҚА ТӨЗІМДІ ҚАЛҚАНША БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ ДИАГНОСТИКАСЫНДАҒЫ ЗАМАНАУИ ӘДІСТЕР: 18^F-FDG ПЭТ-КТ МАҢЫЗЫ

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Зерттеудің мақсаты. Радиойодқа төзімді жоғары сараланған қалқанша безінің қатерлі ісігінің клиникалық жағдайын көрсету және заманауи диагностикалық әдістерді талқылау: 18^F-FDG бар ПЭТ-КТ рөлі.

Материалдар мен әдістер. Зерттеу дизайны ретроспективті болып табылады. Абай облыстық денсаулық сақтауды басқару Ядролық медицина және онкология орталығының радионуклидті терапия бөлімінде емделген науқастардың деректер қоры құрылды. Бұл клиникалық жағдай осы дерекқордан алынған.

Нәтижелер мен талқылау. Берілген клиникалық жағдай радиойодқа төзімді қалқанша безінің қатерлі ісігі кезінде «flip-flop» құбылысының болуын растайды. 18^{F}-FDG бар ПЭТ-КТ радиойодқа төзімділікке күдік бар немесе расталған, жоғары сараланған қалқанша безінің қатерлі ісігі бар науқастарды жүргізудегі диагностикалық алгоритмнің маңызды құрамдас бөлігі болып табылады. Әдіс гликолизі жоғарылаған тіндерде фтордеоксиглюкозаның жиналуына байланысты метаболикалық белсенді ісік ошақтарын визуализациялауды қамтамасыз етеді.

Қорытынды. 18^{F}-FDG бар ПЭТ-КТ радиойодқа төзімді сараланған қалқанша безінің обырын диагностикалауда маңызды орын алады. Әдіс радиоактивті йодты жинақтамайтын және үрдістің агрессивтілігін көрсететін метаболикалық белсенді ісіктерді және метастаздарды анықтауға мүмкіндік береді. Қазіргі кезде кейбір шектеулердің болуына қарамастан, 18^{F}-FDG бар ПЭТ-КТ радиойодты терапияны жалғастыру немесе одан басқа емдеу тактикасын таңдау үшін тиімді құрал болып қала береді.

Кілт сөздер: Қалқанша безінің жоғары сараланған обыры; радиойодты терапияға төзімділік; клиникалық жағдай; ПЭТ-КТ