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THE CLINICAL FEATURES OF RADIOIODINE-RESISTANT DIFFERENTIATED THYROID CANCER: PRELIMINARY RESULTS

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Abstract

Introduction. According to global statistics, thyroid cancer is the seventh most common cancer among all types of cancer. Thyroid cancer treatment using radioactive iodine effectively eliminates the remnants of thyroid tissue that accumulate I131. It is worth noting that some patients may experience disease progression even with treatment. Radioiodine-resistant differentiated thyroid cancer is a complex malignancy with limited treatment options, making early diagnosis a key priority for physicians.

Aim: To investigate clinical features of radioiodine resistance in patients with highly differentiated thyroid cancer.

Materials and methods of the study. The study design is a retrospective study. A database of patients from all over Kazakhstan treated in the radionuclide therapy department of the Center for Nuclear Medicine and Oncology of the Abay region from January to December 2023 was formed. 445 medical records were analyzed. A representative sample of 229 patients was selected using Epi Info v5.5.15 software from those records. This sample has high reliability (97%) with an expected frequency of 50% and an error of 5%.

Results of the research and conclusion. In the study, 9.4% of 229 patients showed signs of refractoriness to radioiodine therapy. As a result, 4.5% of patients showed no radioiodine uptake in the areas of regional recurrence. Structural tumor progression was observed in 81%. Also, 9% of patients had tumors after radioiodine therapy without signs of remission. In addition, 4.5% of cases showed “Mismatch between I131 uptake on radioiodine SPECT/CT and 18F-FDG PET/CT”. It is essential to continue research in the direction of studying the resistance of patients to radioiodine therapy in order to clarify the influence of genetic factors on the response to I131 therapy. Further studies of these parameters remain relevant and require in-depth analysis.

Keywords: *Highly differentiated thyroid cancer, radioiodine therapy, radioiodine resistance, molecular genetic testing.*

Резюме

КЛИНИЧЕСКИЕ ОСОБЕННОСТИ РАДИОЙОДРЕЗИСТЕНТНОГО ДИФФЕРЕНЦИРОВАННОГО РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ: ПРЕДВАРИТЕЛЬНЫЕ РЕЗУЛЬТАТЫ

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Введение. По данным всемирной статистики, рак щитовидной железы занимает седьмое место среди наиболее распространенных форм рака. Лечение рака щитовидной железы с использованием радиоактивного йода эффективно ликвидирует остатки тиреоидной ткани, которые накапливают I131. Стоить отметить, что у некоторых пациентов может наблюдаться прогрессирование болезни даже при осуществлении лечения. Радиойодрезистентный дифференцированный рак щитовидной железы представляет собой сложное злокачественное заболевание с ограниченными вариантами лечения, что делает раннюю диагностику ключевым приоритетом для врачей.

Цель: Изучить клинические особенности радиойодрезистентности у пациентов с высокодифференцированным раком щитовидной железы.

Материалы и методы исследования. Дизайн исследования – ретроспективное исследование. Сформирована база данных пациентов со всего Казахстана, проходивших лечение в отделении радионуклидной терапии Центра ядерной медицины и онкологии области Абай в период с января по декабрь 2023 года. Анализу подверглись 445 историй болезней. Из них с помощью программного обеспечения Epi Info v5.5.15 была отобрана репрезентативная выборка из 229 пациентов. Данная выборка имеет высокую надежность (97%) с ожидаемой частотой 50% и погрешностью 5%.

Результаты исследования и выводы. В рамках исследования среди 229 пациентов 9,4% проявили признаки рефрактерности к радиойодтерапии. В результате, 4,5% пациентов не показали поглощения радиоактивного йода в зонах регионарных рецидивов. У 81% наблюдалось структурное прогрессирование опухоли. Также 9% пациентов продемонстрировали наличие опухоли после радиойодтерапии, без признаков ремиссии. Кроме того, 4,5% случаев показали «Несоответствие между накоплением I131 по результатам ОФЭКТ/КТ с радиоактивным йодом и ПЭТ-КТ с 18F-ФДГ». Важно продолжить исследование в направлении изучения резистентности пациентов к радиойодтерапии, чтобы прояснить влияние генетических факторов на ответ терапией I^{131}. Последующие исследования указанных показателей остаются актуальными и требуют углубленного анализа.

Ключевые слова: *Высокодифференцированный рак щитовидной железы, радиойодтерапия, радиойодрезистентность, молекулярно-генетическое исследование.*

Түйіндеме

ҚАЛҚАНША БЕЗІНІҢ РАДИОЙОДҚА ТӨЗІМДІ САРАЛАНҒАН ОБЫРЫНЫҢ КЛИНИКАЛЫҚ ЕРЕКШЕЛІКТЕРІ: АЛДЫН АЛА НӘТИЖЕЛЕРІ

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Кіріспе. Қалқанша безінің қатерлі ісігі әлемдік статистикаға сәйкес, қатерлі ісік ауруларының ішінде жетінші орында тұр. Радиоактивті йодты қолдану арқылы қалқанша безінің обырын емдеу қалқанша без тінінің қалдықтарын және I^{131} жинақталатын ықтимал ісік ошақтарын тиімді түрде жояды. Айта кететін жағдай, кейбір науқастарда емделген күннің өзінде, аурудың одан әрі өршіп кетуі мүмкін. Радиойодқа төзімді сараланған қалқанша безінің қатерлі ісігі – емдеу мүмкіндіктері шектеулі, ерте анықтау дәрігерлердің басты мақсаты болып табылатын күрделі қатерлі ісік түрі болып табылады.

Зерттеудің мақсаты. Қалқанша безінің жоғары сараланған обыры бар науқастардағы радиойодқа төзімділіктің клиникалық ерекшеліктерін зерттеу.

Зерттеудің материалдары мен әдістері. Зерттеудің дизайны - ретроспективті зерттеу. 2023 жылдың қаңтар және желтоқсан айлары аралығында Абай облысының Ядролық медицина және онкология орталығының радионуклидті терапия бөлімшесінде емделген Қазақстан бойынша барлық науқастардың деректер базасы жасалды. Зерттеу аясында 445 ауру тарихы талданды. Олардың ішінен Epi Info v5.5.15 бағдарламалық құралының көмегімен 229 науқастың репрезентативтік үлгісі таңдалды. Бұл үлгі 50% күтілетін жиілікпен және 5% қателік шегімен жоғары сенімділікке ие (97%).

Зерттеу нәтижелері мен қорытындылары. Зерттеу нәтижесінде 229 науқастың 9,4%-ы радиойодты терапияға төзімділік белгілерін көрсетті. Нәтижесінде радиойодқа төзімділігі бар науқастардың 4,5% жергілікті рецидив аймақтарында радиоактивті йодтың қабылданбағанын көрсетті. 81% науқас емдеуден кейін ісіктің құрылымдық прогрессиясын көрсетті. Сондай-ақ, науқастардың 9%-ында радиойодты терапия алғанына қарамастан, ремиссия белгілерінсіз ісіктің болуын көрсетті. Сонымен қатар, 4,5% жағдайда «радиоактивті йодпен ОФЭКТ/КТ және 18F-FDG-мен ПЭТ-КТ нәтижелері бойынша I^{131} қабылдау арасындағы сәйкессіздікті» көрсетті. I^{131} терапиясына генетикалық факторлардың әсерін түсіндіру үшін науқастардың радиойодты терапияға төзімділігін зерттеуді жалғастыру маңызды. Бұл көрсеткіштерді алдағы уақытта зерттеу өзекті болып қала береді және терең талдауды қажет етеді.

Түйінді сөздер: *Қалқанша безінің жоғары сараланған обыры, радиойодты терапия, радиойодқа төзімділік, молекулалық-генетикалық зерттеу.*

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Introduction

According to GLOBOCAN's global statistics for 2022, thyroid cancer is one of the most common types of cancer. This type of cancer is the seventh most common in the world. This disease prevails most frequently in women. On the contrary, thyroid cancer is three times less expected in men [3]. The most familiar histological type of thyroid cancer is differentiated thyroid cancer (DTH) [12]. It can include papillary and follicular cancers. Both variants of thyroid cancer have a favorable course and, with timely treatment, allow patients to achieve high survival rates. According to the approved clinical protocol of the Ministry of Health of the Republic of Kazakhstan, dated 2021, radioiodine therapy is the most effective treatment of highly differentiated thyroid cancer. This type of treatment is based on using the radiopharmaceutical sodium iodide I131. Highly differentiated cells retain the ability to absorb iodine, which makes RIT highly effective. Treatment of thyroid cancer with radioactive iodine has a targeted effect on the affected tissues. The effectiveness of radioiodine therapy is based on its ability to be actively absorbed by thyroid tissues. For successful radioiodine therapy in highly differentiated thyroid cancer (HDTC), it is necessary to perform surgical removal of the thyroid gland - total thyroidectomy - first of all. In addition, it is vital to increase the thyroid hormone (TSH) level in the blood to values exceeding 30 UI/l [1]. Treatment of highly differentiated thyroid cancer with radioactive iodine effectively eliminates residual thyroid tissue and potential tumor foci that accumulate I131. In addition, radioactive iodine therapy has a positive effect on metastatic processes in differentiated thyroid cancer, as the therapy reduces the probability of recurrence and contributes to the improvement of long-term treatment outcomes [2]. Nevertheless, it is worth emphasizing that 70% of patients with metastatic form of the disease have radioactive iodine uptake. At the same time, in the remaining patients, the progression of the disease may be observed, even with the implementation of treatment [9]. Radioiodine-resistant differentiated thyroid cancer (RAIR-DTC) is a complex malignant disease with limited treatment options, which makes early diagnosis a key priority for physicians. Diagnostic methods today [8] play a crucial role in determining the resistance of differentiated thyroid cancer to radioiodine therapy. Subsequently, according to the results of the study, patients are prescribed appropriate treatment and observation.

Methods such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) in combination with computed tomography (CT) or magnetic resonance imaging (MRI) make it possible not only to evaluate but also to quantify lesions in the diagnosis of differentiated thyroid cancer resistant to radioiodine. To diagnose radioiodine resistance in differentiated thyroid cancer, diagnostic methods are used that allow not only to assess but also to quantify the lesions. These include techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) combined with computed tomography (CT) or magnetic resonance imaging (MRI).

Aim: To investigate clinical features of radioiodine resistance in patients with highly differentiated thyroid cancer

Materials and methods. Study design: retrospective study. A database of patients from all over Kazakhstan who underwent treatment in the Radionuclide Therapy Department of the Center for Nuclear Medicine and Oncology of the Abay Regional Healthcare Institution from January to December 2023 was created. *Inclusion criteria* for the study group: patients of both sexes with well-differentiated thyroid cancer who received radionuclide therapy aged 18 to 80 years. *Exclusion criteria:* patients with medullary, poorly differentiated, and anaplastic thyroid cancer. A total of 445 medical records were analyzed. A representative sample of 229 patients was selected using Epi Info v5.5.15 software from these records. This sample has high reliability (97%) with an expected frequency of 50% and an error of 5%.

Ethical review. To conduct a study on this topic, approval was obtained from the Local Ethics Committee of the NCJSC "Semey Medical University" on November 02, 2023, extracted from protocol No.1b. Permission was also taken from the management of the Center for Nuclear Medicine and Oncology of the Abay Region to work with patient case histories. The management is familiar with this work and does not object to further publication of this article in the open press. Informed consent was obtained from patients before admission to the hospital.

Study Results.

In this study, we used generally accepted international criteria [4,15] to define radioiodine resistance in patients with differentiated thyroid cancer. The presence of one or more of the following features indicated the patient's resistance to radioiodine treatment:

- Absence or progressive loss of radioactive iodine uptake during whole-body scanning after therapy;
- Absence of radioactive iodine uptake in primary regional recurrence or distant metastases without radioactive iodine uptake during whole-body scan after therapy;
- Structural tumor progression 12-16 months after radioactive iodine therapy despite the presence of iodine in the post-therapy scan;
- Presence of tumor in patients who have received radioiodine therapy with an activity of 600 millicuries (mCi)/22.2 gigabecquerel (GBq) or more but without evidence of remission;
- Inconsistency between I^{131} and 18F-FDG accumulation, that is, there is a negative result on SPECT/CT with radioactive iodine and a positive result on PET-CT with 18F-FDG.

Patients requiring radioiodotherapy were hospitalized in the specialized radionuclide therapy department of the Centre for Nuclear Medicine and Oncology of the Abay Regional Healthcare Institution. Hospitalization was carried out routinely in accordance with the radiation safety order. Before admission to the hospital, patients underwent a comprehensive examination, including instrumental and laboratory tests, according to the approved protocol of diagnosis and treatment (Figure 1).

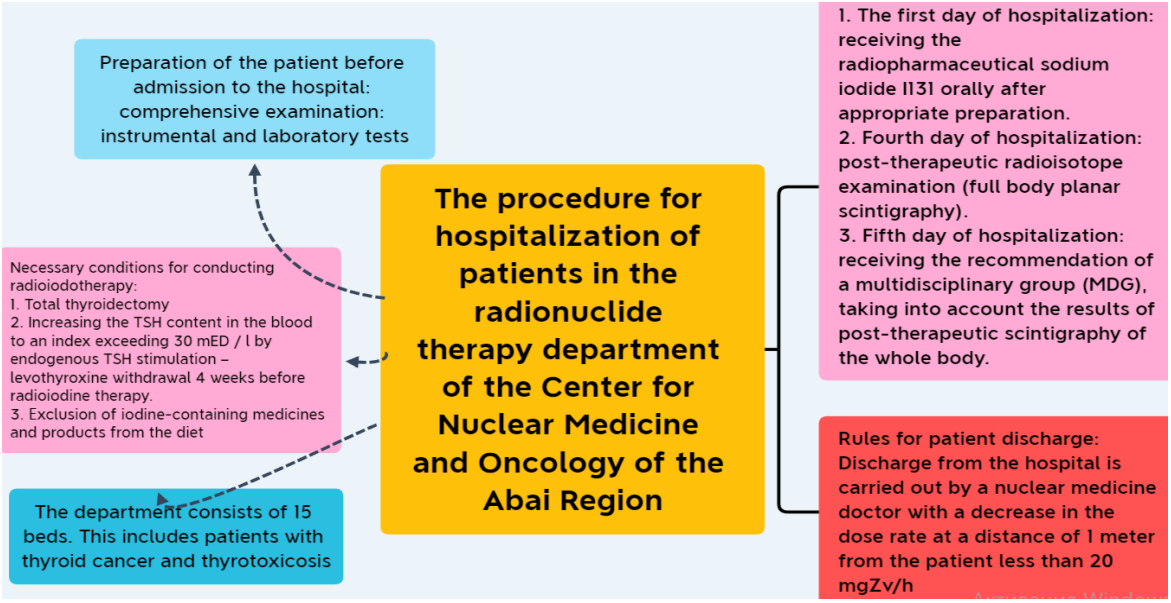

Figure 1. The main characteristics of the department of radionuclide therapy. (This drawing was made using the program XMind).

On the first day of hospitalization, patients received sodium iodide I^{131} radiopharmaceutical orally after appropriate preparation. On the fourth day of hospitalization, a post-therapy radioisotope examination (whole-body planar scintigraphy) was performed. After completion of radioiodine therapy, on the fifth day, patients received recommendations from the

multidisciplinary team (MDT), taking into account the results of post-therapy whole-body scintigraphy.

Between January and December 2023, the following recommendations were assigned to patients who underwent radioiodotherapy by the multidisciplinary team (MDT) (Figure 2):

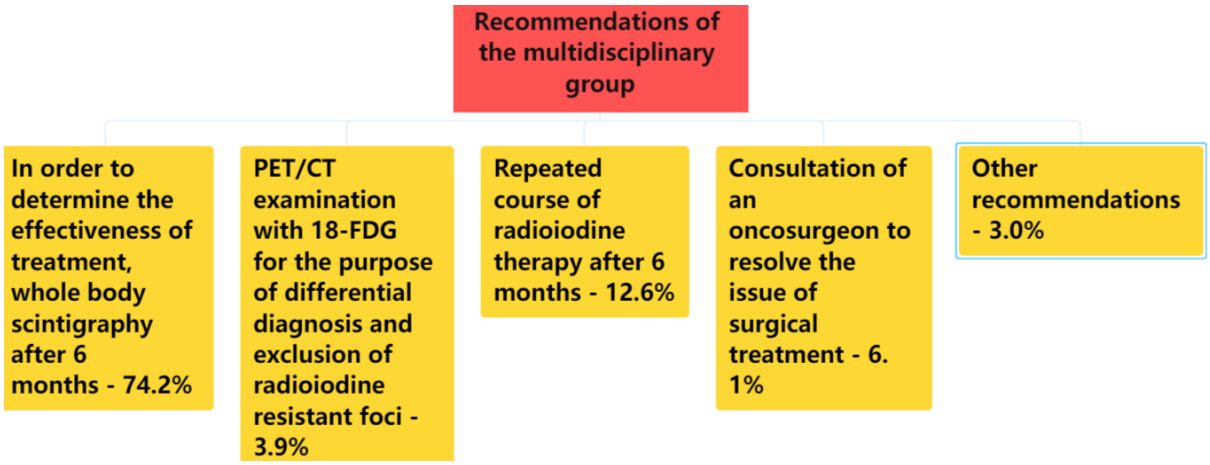

Figure 2: Recommendations of the multidisciplinary team: (This drawing was made using the program XMind).

A retrospective study showed the following results: The study included 229 patients (Table 1*)*. (Of which 65 were men, 164 were women; the average age was 49 years). All patients had undergone total thyroidectomy, and all had histologically confirmed thyroid cancer. In the anamnesis, all had undergone radioiodine therapy in the conditions of the radionuclide therapy department of the Center for Nuclear Medicine and Oncology of the Abay Region.

Table 1.

Basic characteristics of the patients included in the study.

Basic characteristics of the patients included in the study	
Variables	**Values**
Gender	
Male	65 (28,3%)
Female	164 (71,6%)
The average age of the patient	
49 [18-80]	
Histological type of thyroid cancer	
Papillary	133 (58,1%)
Follicular	96 (41,9%)
TNM stage of disease	
I	85 (37,2%)
II	89 (38,9%)
III	49 (21,3%)
IV	6 (2,6%)
Presence of regional or distant metastases	
Yes	66 (28,9%)
No	163 (71,1%)
A recurrence	
Yes	31 (13,6%)
No	198 (86,4%)
Total number of radioiodine therapy courses	
First	161 (70,3%)
Second	33 (14,4%)
Third	20 (8,7%)
Fourth	8 (3,5%)
Fifth	7 (3,0%)

According to preliminary data, out of 229 patients, signs of radioiodine resistance with differentiated thyroid cancer occurred in about 22 (9.6%) patients, the remaining 207 (90.4%) patients remained sensitive to radioiodine treatment.

By analyzing the radioiodine-resistant cases the following data were obtained:

- 4.5% has the relation 'Mismatch between I^{131} accumulation during SPECT/CT with radioactive iodine and PET-CT with 18F-FDG'. Patient G., 27 years old, was observed with the diagnosis of thyroid cancer St I pT1N0M0 since 2017, when surgical treatment in the scope of thyroidectomy was performed. Histological report: Papillary thyroid cancer, classic variant, with foci of invasion into the tumor capsule. In 2020 and 2021 she underwent surgery for the removal of the recurrence of the right lobe of the thyroid gland, and fascial excision of cervical lymph nodes on both sides. On 29.03.2021 in Obninsk, Russian Federation the patient received the first course of radioiodine therapy with activity I^{131} 81 mCi. From 20.12.2021 to 24.12.2021 she received the 2nd course of radioiodine therapy I^{131} with activity 124 mCi. Post-therapeutic SPECT from 23.12.2021 conclusion: SPECT/CT signs: No accumulation of I^{131} isotope in the thyroid bed at the time of the study. Visualized upper paratracheal, lateral cervical nodes of altered shape, without isotope uptake. Single solid nodules in both lungs up to 3-4 mm, without isotope uptake. In the dynamics, the patient underwent PET-CT on 07.12.2022. Conclusion: the picture reveals reliable metabolically active changes in the thyroid gland bed on the right, and in the subclavian region on the left, in the sternum, characteristic of the secondary spread of the main oncological process. It should be noted that the patient's thyroglobulin level was high in dynamics - 223 ng/ml, antibody to thyroglobulin - 10 UI/ml. This phenomenon of discrepancy between I131 accumulation during SPECT/CT with radioactive iodine and PET-CT with 18F-FDG is called the flip-flop phenomenon. Therefore, this case can be attributed to refractoriness to radioiodine therapy [10], [5], [6]

- In 9% of patients had evidence of tumor after radioiodine therapy with activity of 600 mCi or more, but without evidence of remission. Both patients were female, aged 36 and 65 years. Additionally, histological types were

follicular carcinoma and papillary carcinoma, respectively. The patients received 5 courses of radioiodine therapy with activity of more than 600 mCi each. High thyroglobulin and thyroglobulin antibody levels persisted in both patients at follow-up. In the results of post-therapy whole body scintigraphy, there were SPECT/CT signs: multiple nodules of both lungs, with isotope accumulation (mts). In comparison with SPECT/CT of the previous study, no positive dynamics were noted.

- 4.5% of patients demonstrated a lack of radioactive iodine uptake by regional recurrence. Patient I. is 42 years old. On 17.08.2022, a thyroidectomy with cervical lymph dissection on the left was performed. Postoperative histology: Papillary carcinoma of the thyroid gland, in one lobe metastases to the parenchymatous goiter in the other lobe and the isthmus. She further received 1st course of radioiodine therapy with 150 mCi activity. Post-therapy whole body scan revealed an altered inferior jugular node on the right (IV) of rounded shape, 12 mm in size, without drug accumulation. Conclusion: Focus on isotope uptake in the area of the bed of the right thyroid lobe. Visualized altered inferior jugular node on the right side without I^{131} accumulation (susp. mts). A control ultrasound of the thyroid gland revealed regional metastasis and tumor recurrence. In dynamics, the patient underwent surgical treatment.

- In 81% of patients there was structural progression of the tumor 12-16 months after radioiodine therapy, despite the presence of iodine on scintigraphy. Twelve patients had papillary variant and the rest had follicular thyroid cancer. Most patients had progression at 12 months in the dynamics in the form of thyroglobulin and thyroglobulin antibody elevation. And also, on post-therapeutic scanning of the whole body in comparison with previous SPECT/CT there was a progression of the main disease in the form of the appearance of new pathological foci.

The criterion 'Absence or progressive loss of I^{131} uptake on post-therapy scan a few days after RAI therapy' was not encountered in the cases of the above patients.

Discussion

Radioiodine therapy is the main treatment method after surgery for thyroid cancer. It is called the gold standard of treatment in patients with differentiated thyroid cancer [9]. However, about two-thirds of patients with papillary thyroid cancer with distant metastases may be refractory to radioiodine therapy. Resistance to radioiodine therapy is one of the main causes of death in patients. The 10-year survival rate of patients is only 10% [7].

In a study by *Li G., Lei J., Song L., and colleagues*, the refractoriness rates to radioactive iodine were determined. The authors assessed the clinical characteristics of patients who did not respond to radioactive iodine therapy. The authors noted several factors that may influence the development of resistance to radioiodine therapy. These include smoking, tumor type, genetic changes, extrathyroidal extension, the number of lymph node metastases, the rate of lymph node metastasis, and the pN (N1) stage. However, no statistically significant differences were found between such characteristics as tumor size, patient gender, body mass index, and TNM stage [11].

The study by *N.P. Denisenko, G.N. Shuev, and their co-authors* included 181 patients, among whom 37 (20.4%) were men and 144 (79.6%) were women. They analyzed the data of patients admitted to the radiology department of the Clinic named after Professor *Y.N. Kasatkin* from April to December 2021. In their study, they analyzed the role of several genes that can cause radioiodine resistance in patients. They studied single nucleotide polymorphisms of genes such as NFKB1, ATM, ATG16L2 and ATG10. According to the results of the study, resistance to radioiodine therapy was detected in 11 (6.1%) cases out of 181 observations. Unfortunately, the authors failed to identify significant associations between the development of resistance to radioiodine therapy and the carriage of individual polymorphisms $p>0.05$ [2].

In recent decades, there has been a significant advancement in the study of molecular mechanisms contributing to the malignant evolution of differentiated thyroid cancer and the development of resistance to radioiodine therapy [15]. Molecular mechanisms leading to resistance to radioiodine therapy include gene mutations and gene fusions. In addition, the lack of transport of radioactive iodine into thyroid cancer cells and exposure of the tumor microenvironment also contribute to this problem. However, it is not clear whether the above factors are the key reasons why thyroid cancer patients fail to receive the expected benefit from radioiodine therapy [13].

Conclusion

In our study, we analyzed 229 patients, among whom 22 (9.4%) patients showed signs of resistance to radioiodine therapy. As a result, 4.5% of patients with radioiodine resistance did not show radioiodine uptake in areas of regional recurrence. In 81%, there was structural tumor progression within 12-16 months of therapy despite the presence of iodine detected in follow-up scans. Also, 9% of patients demonstrated tumor activity at 600 mCi or higher without evidence of remission. In addition, 4.5% of cases showed 'Inconsistency between I^{131} accumulation by SPECT/CT with radioactive iodine and PET-CT with 18F-FDG'. Most of these patients were women with papillary carcinoma. The above data are critical for tumor risk stratification and assessment of the development of resistance to radioiodine therapy. However, to fully determine cases of resistance to radioiodine therapy, on the one hand, it is necessary to consider the clinical and pathological characteristics and, on the other hand, the molecular characteristics of the disease. It is crucial to continue studies aimed at investigating the resistance of patients to radioiodine therapy to clarify the influence of genetic factors on the response to I^{131} therapy. Follow-up studies on these indicators remain relevant and require in-depth analyses.

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Literature:

1. Клинический протокол медицинского вмешательства. Радиойодтерапия. Протокол №148 Министерства здравоохранения Республики Казахстан от «23» сентября 2021 года.

2. *Денисенко Н.П., Шуев Г.Н., Мухамадиев Р.Х., Перфильева О.М., Казаков Р.Е., Качанова А.А., Милютина О.И., Коненкова О.В., Рыжкин С.А., Иващенко Д.В., Буре И.В., Кириенко С.Л., Жмаева Е.М., Мирзаев К.Б., Аметов А.С., Поддубная И.В., Сычев Д.А.* Генетические маркеры, ассоциированные с резистентностью к радиойодтерапии, у больных раком щитовидной железы. Современная Онкология. 2022/ 24(3):345–350. DOI: 10.26442/18151434.2022.3.201867

3. *Bray F., Laversanne M., Sung H., Ferlay J., Siegel R.L., Soerjomataram I., Jemal A.* Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024 May-Jun. 74(3):229-263. doi: 10.3322/caac.21834. Epub 2024 Apr 4. PMID: 38572751.

4. *Capdevila J., Galofré J.C., Grande E., Zafón Llopis C., Ramón Y Cajal Asensio T., Navarro González E., Jiménez-Fonseca P., Santamaría Sandi J., Gómez Sáez J.M., Riesco Eizaguirre G.* Consensus on the management of advanced radioactive iodine-refractory differentiated thyroid cancer on behalf of the Spanish Society of Endocrinology Thyroid Cancer Working Group (GTSEEN) and Spanish Rare Cancer Working Group (GETHI). Clin Transl Oncol. 2017 Mar. 19(3):279-287. doi: 10.1007/s12094-016-1554-5. Epub 2016 Oct 4. PMID: 27704399.

5. *Chan H.P., Chen I.F., Tsai F.R., Kao C.H., Shen D.H.* Reversing "Flip-Flop" Phenomenon of 131 I and Glucose Avidity in RET-Fusion Positive Radioiodine-Refractory Thyroid Cancer Lesions After Treatment of Pralsetinib. Clin Nucl Med. 2023 Mar 1. 48(3):e147-e148. doi: 10.1097/RLU.0000000000004475. Epub 2022 Nov 11. PMID: 36327463.

6. *Diwanji D., Carrodeguas E., Seo Y., Kang H., Soe M.H., Chiang J.M., Zhang L., Liu C., Behr S.C., Flavell R.R.* Comparative Uptake Patterns of Radioactive Iodine and [18F]-Fluorodeoxyglucose (FDG) in Metastatic Differentiated Thyroid Cancers. J Clin Med. 2024 Jul 6. 13(13):3963. doi: 10.3390/jcm13133963. PMID: 38999527, PMCID: PMC11242608.

7. *Durante C., Haddy N., Baudin E., Leboulleux S., Hartl D., Travagli J.P., Caillou B., et al.* Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006 Aug. 91(8):2892-9. doi: 10.1210/jc.2005-2838. Epub 2006 May 9. PMID: 16684830.

8. *Giovanella L., Deandreis D., Vrachimis A., Campenni A., Petranovic Ovcaricek P.* Molecular Imaging and Theragnostics of Thyroid Cancers. Cancers (Basel). 2022 Mar 1. 14(5):1272. doi: 10.3390/cancers14051272. PMID: 35267580. PMCID: PMC8909041.

9. *Haugen B.R., Alexander E.K., Bible K.C., Doherty G.M., Mandel S.J., Nikiforov Y.E., Pacini F., Randolph G.W., Sawka A.M., Schlumberger M., Schuff K.G., Sherman S.I., Sosa J.A., Steward D.L., Tuttle R.M., Wartofsky L.* 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guiqdelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016 Jan. 26(1):1-133. doi: 10.1089/thy.2015.0020. PMID: 26462967; PMCID: PMC4739132.

10. *Isoda T., BaBa S., Maruoka Y., Kitamura Y., Tahara K., Sasaki M., Honda H.* Impact of patient age on the iodine/FDG "flip-flop" phenomenon in lung metastasis from thyroid cancer. Ann Nucl Med. 2016 Oct;30(8):518-24. doi: 10.1007/s12149-016-1104-9. Epub 2016 Jul 5. PMID: 27380042.

11. *Li G., Lei J., Song L., Jiang K., Wei T., Li Z., Gong R., Zhu J.* Radioiodine refractoriness score: A multivariable prediction model for postoperative radioiodine-refractory differentiated thyroid carcinomas. Cancer Med. 2018 Nov;7(11):5448-5456. doi: 10.1002/cam4.1794. Epub 2018 Sep 27. PMID: 30264548; PMCID: PMC6246937.

12. *Liu Y., Wang J., Hu X., Pan Z., Xu T., Xu J., Jiang L., Huang P., Zhang Y., Ge M.* Radioiodine therapy in advanced differentiated thyroid cancer: Resistance and overcoming strategy. Drug Resist Updat. 2023 May. 68:100939. doi: 10.1016/j.drup.2023.100939. Epub 2023 Feb 8. PMID: 36806005.

13. *Liu Y., Liu C., Pan Y. et al.* Pyruvate carboxylase promotes malignant transformation of papillary thyroid carcinoma and reduces iodine uptake. *Cell Death Discov.* 8, 423 (2022). https://doi.org/10.1038/s41420-022-01214-y

14. *Vaisman F., Carvalho D.P., Vaisman M.* A new appraisal of iodine refractory thyroid cancer. Endocr Relat Cancer. 2015 Dec. 22(6):R301-10. doi: 10.1530/ERC-15-0300. Epub 2015 Aug 25. PMID: 26307020.

15. *Yavuz S., Puckett Y.* Iodine-131 Uptake Study. In: Stat Pearls. Stat Pearls Publishing, Treasure Island (FL); 2023. PMID: 32644709.

References: [1-2]

1. Klinicheski protokol meditsinskogo vmeshatel'stva. Radioiodterapiya. Protokol №148 Ministerstva zdravookhraneniya Respubliki Kazakhstan ot «23» sentyabrya 2021 goda [Clinical protocol of medical intervention. Radioiodine therapy. Protocol No.148 of the Ministry of Health of the Republic of Kazakhstan dated September 23, 2021] [in Russian]

2. Denisenko N.P., Shuev G.N., Mukhamadiev R.Kh., Perfil'eva O.M., Kazakov R.E., Kachanova A.A., Milyutina O.I., Konenkova O.V. i dr. Geneticheskie markery, assotsiirovannye s rezistentnost'yu k radioiodterapii, u bol'nykh rakom shchitovidnoi zhelezy [Genetic markers associated with resistance to radioiodine therapy in patients with thyroid cancer]. *Sovremennaya onkologiya* [Modern Oncology]. 2022. T.24. №.3. pp. 345-350. [in Russian]

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