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THE FREQUENCY AND EFFICACY ASSESSMENT OF RADIOIODINE THERAPY FOR DISTANT METASTASES OF THYROID CANCER

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Abstract

Introduction. In Kazakhstan, as well as globally, the incidence of thyroid cancer is increasing. In 2023 the incidence rate rose by 13.1% compared to the previous year. Radioactive iodine therapy (I-131) is the primary treatment method for highly differentiated thyroid cancer (HDTC) following surgical tumor removal. However, in some patients distant metastases may develop, worsening the prognosis and necessitating an assessment of the effectiveness of radioiodine therapy in such cases.

Objective: To study the incidence of distant metastases and evaluate the effectiveness of radioiodine therapy (I-131) in patients with thyroid cancer.

Materials and Methods. A retrospective analysis of medical records was conducted for 443 patients diagnosed with HDTC who underwent treatment in the radionuclide therapy department from January to December 2023. Among them, 33 patients (7.4%) were diagnosed with distant metastases. The localization of metastases, therapeutic doses of I-131, and clinical outcomes were assessed based on medical documentation.

Results. Among the 443 patients studied, 7.4% had distant metastases of thyroid cancer. As a result, metastatic lesions were localized in the lungs in 54.5% of cases, in the bones in 12.1%, and in distant lymph nodes in 15.2%. Complete remission was achieved in 44% of patients, while disease stabilization was observed in 50%. In 6% of cases, radioiodine therapy did not produce a significant effect. Additionally, 3% of patients had rare metastatic sites, including the brain and ovaries. These findings highlight the need for further research into factors influencing the effectiveness of radioiodine therapy. Further studies in this area are necessary to optimize treatment strategies for patients with metastatic disease.

Conclusion. The incidence of distant metastases in HDTC was 7.4%, with the lungs being the most frequently affected site. Radioiodine therapy demonstrated high effectiveness in treating patients with metastatic disease, particularly in cases of pulmonary metastases. The obtained data underscore the importance of early diagnosis and timely therapy to improve the prognosis in patients with metastatic lesions.

Keywords: *Differentiated high grade thyroid cancer, radioiodine therapy, distant metastases, treatment methods, treatment effectiveness, I-131 therapy outcomes.*

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Резюме

ЧАСТОТА ВСТРЕЧАЕМОСТИ И ОЦЕНКА ЭФФЕКТИВНОСТИ РАДИОЙОДТЕРАПИИ ПРИ ОТДАЛЁННЫХ МЕТАСТАЗАХ РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ

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Введение. В Казахстане, как и в мире, наблюдается рост заболеваемости раком щитовидной железы. В 2023 году уровень заболеваемости увеличился на 13,1% по сравнению с предыдущим годом. (I131) является основным методом лечения высокодифференцированного рака щитовидной железы (ВДРЩЖ) после хирургического удаления опухоли. Однако у части пациентов возможно развитие отдалённых метастазов, что ухудшает прогноз и требует оценки эффективности радиойодтерапии в таких случаях.

Цель. Изучить частоту встречаемости отдаленных метастазов и оценить эффективность метода лечения радиоактивном йодом (I131) у пациентов с раком щитовидной железы

Материалы и методы. Проведён ретроспективный анализ историй болезней 443 пациентов с диагнозом ВДРЩЖ, прошедших лечение в отделении радионуклидной терапии с января по декабрь 2023 года. Среди них у 33 (7,4%) были диагностированы отдалённые метастазы. Локализация метастазов, терапевтические дозы I131 и клинические исходы оценивались на основе медицинской документации.

Результаты. В рамках исследования среди 443 пациентов у 7,4% были выявлены отдалённые метастазы рака щитовидной железы. В результате, у 54,5% пациентов с метастазами поражение локализовалось в лёгких, у 12,1% – в костях, у 15,2% – в отдалённых лимфатических узлах. Полная ремиссия была достигнута у 44% пациентов, тогда как у 50% зафиксирована стабилизация заболевания. В 6% случаев наблюдалось отсутствие значимого эффекта от радиойодтерапии. Кроме того, у 3% пациентов были выявлены редкие локализации метастазов (головной мозг, яичник). Полученные результаты подчеркивают необходимость дальнейшего изучения факторов, влияющих на эффективность радиойодтерапии. Дальнейшие исследования в этом направлении необходимы для оптимизации стратегий лечения пациентов с метастатическим поражением.

Заключение. Частота отдаленного метастазирования ВДРЩЖ составила 7,4%, при этом наиболее часто поражаются лёгкие. Радиойодтерапия продемонстрировала высокую эффективность в лечении пациентов с метастатическим поражением, особенно в случаях лёгочного метастазирования. Полученные данные подчеркивают важность ранней диагностики и своевременного проведения терапии для улучшения прогноза у пациентов с метастатическим поражением.

Ключевые слова: *Высокодифференцированный рак щитовидной железы, радиойодтерапия, отдаленные метастазы, методы лечения, эффективность лечения, результаты терапии I-131.*

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Түйіндеме

ҚАЛҚАНША БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ АЛЫС МЕТАСТАЗДАРЫНЫҢ КЕЗДЕСУ ЖИІЛІГІ ЖӘНЕ РАДИОЙОДТЕРАПИЯНЫҢ ТИІМДІЛІГІН БАҒАЛАУ

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Кіріспе. Қазақстанда және әлемде қалқанша безінің қатерлі ісігіне шалдығу көрсеткіші өсуде. 2023 жылы сырқаттанушылық деңгейі алдыңғы жылмен салыстырғанда 13,1%-ға артты. I^{131} хирургиялық ісікті алып тастағаннан кейін жоғары сараланған қалқанша безінің қатерлі ісігін (ЖСҚБҚ) емдеудің негізгі әдісі болып табылады. Алайда, кейбір науқастарда алыстағы метастаздар дамуы мүмкін, бұл болжамды нашарлатады және мұндай жағдайларда радиойодтерапияның тиімділігін бағалауды қажет етеді.

Мақсаты. Қалқанша безінің қатерлі ісігі бар науқастарда алыстағы метастаздардың жиілігін анықтау және радиоактивті йод (I^{131}) көмегімен емдеу әдісінің тиімділігін бағалау.

Материалдар мен әдістер. 2023 жылдың қаңтар-желтоқсан айларында радионуклидтік терапия бөлімінде ем алған ЖСҚБҚ диагнозы қойылған 443 науқастың ауру тарихына ретроспективті талдау жүргізілді. Олардың 33-інде (7,4%) алыстағы метастаздар анықталды. Метастаздардың орналасуы, I^{131} терапиялық дозалары және клиникалық нәтижелер медициналық құжаттама негізінде бағаланды.

Нәтижелер. Зерттеу барысында 443 науқастардың 7,4%-ында қалқанша безінің қатерлі ісігінің алыстағы метастаздары анықталды. Метастаздардың орналасуы келесідей бөлінді: 54,5% – өкпеде, 12,1% – сүйектерде, 15,2% – алыстағы лимфа түйіндерінде. Толық ремиссия 44% науқаста тіркелді, 50%-ында аурудың тұрақтануы байқалды, ал 6%-ында радиойодтерапияның айтарлықтай әсері болмады. Сонымен қатар, 3% науқастарда сирек локализацияланған метастаздар (бас миы, аналық без) анықталды. Алынған нәтижелер радиойодтерапияның тиімділігіне әсер ететін факторларды терең зерттеу қажеттігін көрсетеді. Осы бағыттағы қосымша зерттеулер метастатикалық зақымдануы бар науқастардың емдеу стратегияларын оңтайландыру үшін қажет.

Қорытынды. Қалқанша безі қатерлі ісігінің алыс метастаздарының генерализациясының жиілігі 7,4%-ды құрады, көбінесе өкпе метастаздану аймағы ретінде анықталды. Радиойодтерапия өкпелік метастаздар жағдайында жоғары тиімділік көрсетіп, науқастардың жалпы емделу нәтижелерін жақсартуға ықпал етті. Алынған деректер метастаздық зақымдануы бар науқастардың болжамын жақсарту үшін ерте диагностика мен уақытылы терапия жүргізудің маңыздылығын айқындайды.

Түйінді сөздер: *Жоғары сараланған қалқанша безінің қатерлі ісігі, радиойодтерапия, алыс метастаздар, емдеу әдістері, емдеудің тиімділігі.*

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Introduction:

Thyroid Cancer

The prevalence of thyroid cancer has risen across numerous countries and regions. The primary reason for this is the rising prevalence of the main form of differentiated high grade thyroid cancer (DHGTC). According to data from the International Agency for Research on Cancer, 821,214 new cases were recorded in 2022. This malignant disease ranks 7th worldwide in terms of prevalence [9].

On a regional level, the incidence rate varies according to GLOBOCAN data for 2022: 2,612 new cases of thyroid cancer were registered in Egypt [10], 52,169 cases in the USA [11], 4,229 cases in Argentina [12], 16,419 cases in Japan [13], 9,618 cases in France [14], and 3,769 cases in Australia [15]. The age-standardized incidence rate averages 3.1 cases per 100,000 people among men and 10.1 cases per 100,000 among women [16].

Along with the global trend an increase in the incidence of thyroid cancer has been observed in the Republic of Kazakhstan. In 2023 the growth rate of thyroid cancer (TC) incidence was 13.1% compared to the previous year [4]. This issue is particularly evident in regions with unfavorable environmental conditions and iodine deficiency. Notably, women are diagnosed with thyroid cancer five times more often than men, with 917 cases compared to 167 cases, respectively [9].

Currently, several key factors contributing to TC development have been identified, including mutations in the BRAF, PTEN, APC, DICER1, MNG, NRAS, KRAS, and TERT genes. Additionally, ionizing radiation exposure and hereditary syndromes such as Gardner syndrome, Cowden syndrome, and multiple endocrine neoplasia types 2A and 2B are recognized as risk factors [17].

Thyroid Cancer Metastasis and Its Prognostic Significance

Metastasis to regional lymph nodes occurs in approximately 30–40% of cases of papillary thyroid cancer (PTC) [8]. Distant metastases in highly differentiated thyroid cancer (HDTC) can develop over a wide range of time intervals following the primary thyroid surgery. However, the presence of such metastases is a dominant negative prognostic factor.

Based on the time of occurrence, metastases can be classified into several types. Synchronous distant metastases refer to metastases detected within 12 months after the initial diagnosis of HDTC. Metachronous metastases are characteristic of malignancies with both early and late onset, classified as early (1–5 years after the initial diagnosis) and late (≥5 years after the initial diagnosis) [7]. The most common sites of distant metastases include the lungs, pelvic bones, femur, skull bones, and ribs [1,6]. According to data from the Surveillance, Epidemiology and End Results (SEER) program for 2021, the most frequent metastatic sites in PTC are: lungs (53.4%), bones (28.1%), liver (8.3%), brain (4.7%) [18].

Radioiodine Therapy as an Effective Treatment for Thyroid Cancer Metastases

Radioiodine therapy (I-131) is a highly effective postoperative treatment for highly differentiated thyroid cancer (HDTC). Its primary objectives include:

Destruction of residual thyroid tissue

Elimination of thyroglobulin-producing substrate

Detection and subsequent treatment of metastases [2,5].

Clinical studies have demonstrated that adequate uptake of radioactive iodine significantly improves 5-year and 10-year survival rates and leads to a notable reduction in tumor marker levels [3].

According to a study conducted at the Medical Radiology Research Center (MRRC) of the Russian Academy of Medical Sciences, a complete treatment response was achieved in 71.7% of patients. The high effectiveness of radioiodine therapy has been observed in patients with thyroid cancer metastases in the mediastinum, as well as in those with X-ray-negative and small pulmonary metastases [18]. In patients with differentiated thyroid cancer (DTC) and pulmonary metastases, partial or complete remission was achieved in 95% of cases following radioiodine therapy [17]. Currently, in the Republic of Kazakhstan, the first and only radionuclide therapy (RNT) department operates within the Center for Nuclear Medicine and Oncology under the Abay Regional Health Administration. Therefore, this study remains highly relevant today.

Objective: To study the incidence of distant metastases and evaluate the effectiveness of radioactive iodine (I-131) therapy in patients with thyroid cancer.

Materials and Methods

The study design is a retrospective analysis of patient medical records. According to the conducted analysis, from January to December 2023, a total of 443 patients diagnosed with highly differentiated thyroid cancer (HDTC) underwent treatment in the Radionuclide Therapy Department. A database was created based on patient medical records, including cases with various metastasis localizations. Out of 443 patients, 33 were diagnosed with distant metastases in different organs. Upon admission to the Radionuclide Therapy Department, patients complete an informed consent form for data processing.

Descriptive Analysis All continuous variables, such as patient age and administered doses of I-131, were summarized using means (M), standard deviations (SD), medians (Me), and interquartile ranges (IQR). Categorical variables, including the presence and localization of distant metastases, treatment response, and histological subtypes, were presented as absolute (n) and relative frequencies (%).

Effectiveness of Radioiodine Therapy

The therapeutic response to radioiodine therapy was categorized into three groups: stabilization, disease progression, and complete remission. The proportion of patients in each response category was compared using the **Z-test for proportions** to determine if there was a significant difference in treatment outcomes. The test statistic was calculated as:

$$Z = \frac{p_1 - p_2}{\sqrt{p(1-p)\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}$$

A 95% confidence interval (CI) was calculated for each treatment effect category to assess the variability in outcomes.

Comparison of Metastatic Sites.

The distribution of metastases was assessed using frequency analysis. Differences in the distribution of metastatic sites were evaluated using the **Chi-square test (χ2\chi^2χ2)** for categorical variables to determine whether metastases were more likely to occur in a specific organ. The hypothesis tested was:

- **Null Hypothesis (H0H_0H0)**: There is no significant difference in the distribution of metastases across different organ sites.
- **Alternative Hypothesis (HAH_AHA)**: The distribution of metastases differs significantly between organs.

The test statistic was calculated as:

$$\chi^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

A p-value <0.05 was considered statistically significant.

The statistical analysis provided robust evidence of the prevalence and distribution of distant metastases in HDTC and the effectiveness of I-131 therapy. The results were validated using appropriate statistical tests, ensuring reliability and clinical significance.

Ethical issues. This consent explicitly states that patients agree to the use of their data and research results for educational and scientific purposes to enhance the quality of medical care. Additionally, all patient data is anonymized to ensure confidentiality and compliance with ethical standards in medical research. The Head of the Radionuclide Therapy Department was informed about the progress and conduct of the study and has no objections to the publication of the data in open access.

Results

Radioactive iodine therapy was administered under the condition of complete surgical removal of the thyroid gland and an elevated thyroid-stimulating hormone (TSH) level exceeding 30 mIU/L, achieved by discontinuing Euthyrox or L-thyroxine.

The I-131 activity dose was determined based on the required therapeutic effect:

- 3700 MBq (100 mCi) for residual tissue ablation after thyroidectomy without metastases or infiltration into surrounding tissues.
- 5550 MBq (150 mCi) for cases with regional lymph node metastases and/or infiltration into surrounding tissues.
- 7400–11100 MBq (200–300 mCi) for distant metastases in the lungs and bones.

Of the studied patients, 87.5% have papillary carcinoma, and 12.5% have follicular carcinoma (table 1):

Table 2.

Localization of distant metastases of thyroid cancer.

Histological Types	Cases	Percentage of the Total Number of Cases
Papillary carcinoma	28	87.5%
Follicular carcinoma	4	12.5%

A total of 443 patient records were analyzed, and 33 patients (7.4%) were found to have distant metastases in various organs (table 2):

- Lungs – 18 patients (54.5%)
- Bones – 4 patients (12.1%)
- Lungs and bones – 4 patients (12.1%)
- Distant lymph nodes – 5 patients (15.2%)
- Brain – 1 patient (3.0%)
- Ovary – 1 patient (3.0%)

Analysis of the Presented Data

From the total 443 patients, 33 (7.45%) were diagnosed with distant metastases. This means that approximately one in fourteen patients had metastatic involvement beyond the primary thyroid tumor site. A more detailed analysis reveals the following.

Table 2.

Localization of distant metastases of thyroid cancer.

Localization of distant metastases of thyroid cancer	Cases	Percentage of the Total Number of Cases
Lungs	15	46.9%
Brain, spine, lungs	1	3.1%
Lungs, spine	2	6.3%
Lungs, pleura	2	6.3%
Lungs, sternum	1	3.1%
Femur, sacrum	1	3.1%
Lungs, soft tissues of the nasopharynx and oropharynx on the left.	1	3.1%
Ovary	1	3.1%
Femur, pubic bone, sacrum	1	3.1%
Paratracheal lymph nodes	4	12.5%
Ribs	1	3.1%
Humerus	1	3.1%
Lungs, rib, ilium	1	3.1%
Supraclavicular lymph nodes	1	3.1%

Main Metastatic Sites:

- Lungs: 15 patients (46,9%) among those with distant metastases. This confirms the well-known clinical pattern that the lungs are the most common site of distant metastases in differentiated thyroid cancer (DTC).
- Bones: 4 patients (12.1%). Additionally, another 4 patients (12.1%) had combined metastases in both bones and lungs, indicating a more advanced and aggressive disease course in this subgroup.
- Distant lymph nodes: 5 patients (15.2%), suggesting an additional route of tumor dissemination beyond the neck and mediastinum.
- Brain: 1 case (3.1%). Brain metastases from thyroid cancer are rare, and this single case reflects the low frequency of such localization.
- Ovary: 1 case (3.1%). Ovarian metastases are also considered a rare form of hematogenous spread in thyroid cancer.

Frequency of Organ Involvement

The lungs are the most commonly affected organ, accounting for approximately 55% of all metastases. When considering patients with combined metastases (lungs + bones), the total number of lung-involved cases reaches 22 out of 33, representing 66.7% of all metastatic cases.

Bone metastases occur in 4 patients (12.1%) as an isolated finding and in 4 additional cases (12.1%) alongside lung metastases. Thus, the total number of bone metastasis cases is 8, making up 24.2% of all metastatic patients.

Other sites (lymph nodes, brain, and ovary) constitute a smaller proportion but are important for understanding the diverse dissemination pathways of thyroid cancer.

In our study sample, the majority of thyroid cancer cases remain non-metastatic, which aligns with the typical clinical course of highly differentiated thyroid carcinomas (papillary and follicular types), known for their prolonged localized growth.

Among the 33 patients with metastases, the lungs are the primary target for tumor spread, confirming the classical metastasis pattern of thyroid cancer.

The presence of isolated cases of brain and ovarian metastases highlights the variability and unpredictability of cancer dissemination in certain patients.

Table 3.

Effect of radioiodine therapy.

Effect of radioiodine therapy	Cases	Percentage of the Total Number of Cases
Stabilization	25	78.1%
Progression	6	18.8%
Full effect	1	3.1%

Discussion

Research results show distant metastases function as an important prognostic factor for disease advancement and patient survival in highly differentiated thyroid cancer (HDTC). Our study found that distant metastases occurred in 7.4% of HDTC patients which matches earlier epidemiological findings showing a low yet clinically meaningful occurrence rate of metastasis in HDTC. The lungs were the primary site for metastasis at 54.5%, with bones and distant lymph nodes following at 12.1% and 15.2% respectively. Prior research confirms that pulmonary metastases represent the primary metastatic site in differentiated thyroid cancer affecting more than half of the metastatic patient population

Radioiodine therapy (I-131) stands as a vital component for managing metastatic HDTC. Complete remission from radioiodine therapy occurred in 44% of patients while another 50% experienced disease stabilization and a mere 6% showed no significant response to the treatment. Existing scientific studies confirm that radioiodine therapy proves highly effective against iodine-avid metastatic conditions especially within lung lesions. The stabilization rates observed emphasize that patients with ongoing metastatic disease require ongoing monitoring together with repeated therapeutic treatments.

Notably, a small subset of patients (3%) exhibited metastases in uncommon locations, such as the brain and ovaries. These rare metastatic patterns indicate the necessity for individualized treatment approaches, including multimodal strategies involving surgery, external beam radiation therapy, and targeted systemic therapies when radioiodine uptake is insufficient.

The histological distribution of cases in our study also corresponds with global trends, with papillary carcinoma representing the majority (87.5%) of cases. Given that papillary thyroid carcinoma (PTC) is generally associated with a favorable prognosis, the presence of distant metastases represents a shift towards a more aggressive disease course. This emphasizes the importance of early detection strategies, including serum thyroglobulin monitoring and advanced imaging techniques such as PET-CT for high-risk patients.

Research moving forward needs to include genomic analysis for improved patient stratification regarding their potential response to radioiodine therapy.

Our research confirms that radioiodine therapy plays an essential role in treating metastatic HDTC especially in patients with lung metastasis. The study results highlight the necessity of early detection along with prompt intervention to enhance patient survival rates. The optimization of personalized treatment approaches and improvement of

survival rates for metastatic thyroid cancer patients requires future prospective studies that include molecular and genetic profiling.

Conclusion

The analysis demonstrates that among 443 patients, only 33 (7.45%) were diagnosed with distant metastases, with the lungs being the most common metastatic site. Bone metastases are less frequent, though they coexist with lung involvement in nearly one-third of cases. Other metastatic sites (brain, ovary) are rare but may indicate a more aggressive or distinct disease course.

These findings reflect the typical characteristics of thyroid cancer—a relatively favorable prognosis due to the low metastasis rate and a clear tendency for lung involvement when the disease spreads.

Additionally, the study confirms the effectiveness of radioactive iodine therapy (RAI) in patients with highly differentiated thyroid cancer (HDTC) and distant metastases. The rate of disease dissemination was 7.4%, with lung metastases being the most prevalent.

The obtained data emphasize the importance of early diagnosis and timely administration of RAI therapy, which helps achieve disease stabilization in 50% of patients and complete treatment response in 44%.

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Conflict of interest

The authors of this article confirmed the absence of a conflict of interest.

Authors' Contributions:

Sergazina A.O. *- The primary author of the article developed the research concept, conducted data analysis, wrote the full manuscript, and formatted it.*

Pak L.A., Esbolatova N.S., Dushimova Z.D. *- Respected heads of specialized departments, whose extensive clinical experience and expert recommendations have made a significant contribution to shaping the scientific concept of the study and interpreting the obtained data.*

Rakhmankulova A.M. *- Actively participated in the preparation of the "Materials and Methods" and "Results" sections, as well as edited the text and assisted in formatting the article in accordance with GOST requirements and scientific publication standards.*

Kudaiberdinov K.K., Bekenova Zh.T., Rysbekov B.N. *- Participated in the collection and systematization of clinical data, discussion of interim research results, and preparation of the final materials.*

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