DOI: https://doi.org/10.17816/DD532728

Современный взгляд на основные аспекты подготовки пациентов с дифференцированным раком щитовидной железы к радиойодтерапии: научный обзор

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АННОТАЦИЯ

Рак щитовидной железы — наиболее распространённая опухоль эндокринной системы, составляющая 1–3% всех злокачественных новообразований (по состоянию на 2021 год). В 90% случаев выявляют дифференцированные формы — папиллярный и фолликулярный варианты — обладающие относительно благоприятным прогнозом.

Комбинация хирургического лечения и последующей супрессивной гормональной терапии, радиойодтерапии, обеспечивают благоприятный прогноз у пациентов с высокодифференцированным раком щитовидной железы. Тем не менее сохраняется вероятность недостаточного ответа на радиойодтерапию, что может быть ассоциировано со многими факторами, включая этап подготовки к её проведению. На сегодняшний день сохраняется актуальным вопрос о выборе оптимального метода подготовки пациента к терапии радиоактивным йодом.

В публикации представлен обзор научной литературы, посвящённой аспектам подготовки пациента с высокодифференцированным раком щитовидной железы к проведению терапии радиоактивным йодом. Освещены и обобщены принципы подготовки пациентов на основании рекомендаций ведущих экспертных сообществ и публикаций по данной теме, приняты во внимание нежелательные явления, ассоциированные с радиойодтерапией, качество жизни пациентов, эффективность и отдалённые результаты лечения.

Основная цель обзора — составить целостное представление о методах подготовки пациента с высокодифференцированным раком щитовидной железы к проведению радиойодтерапии, осветить существующие проблемы и перспективные направления исследований с целью модернизации лечения в сторону персонализированной терапии.

Был проведен поиск научных статей и обзоров, опубликованных до конца января 2023 года, в базах данных National Library of Medicine, The Cochrane Library и Google Scholar по следующим ключевым словам: подготовка к радиойодтерапии, тиреотропин альфа, отмена тиреоидных гормонов, побочные эффекты, йод-ограниченная диета, сиалоаденит, первичный гипотиреоз, качество жизни, тиреоидэктомия, дифференцированный рак щитовидной железы, эффективность радиойодтерапии — в их различных комбинациях. Использовались рекомендации по высокодифференцированному раку щитовидной железы следующих научных сообществ: Российские клинические рекомендации по высокодифференцированному раку щитовидной железы, American Thyroid Association, European Thyroid Association, The National Comprehensive Cancer Network, European Association of Nuclear Medicine, British Thyroid Association, European Society for Medical Oncology. Критериями исключения были статьи, не доступные в полном объёме, не на английском или русском языках, систематические обзоры на аналогичную тему. Всего было отобрано и проанализировано 124 источника, выделены общие тенденции современного подхода к подготовке пациентов к терапии радиоактивным йодом и актуальные проблемы, освещены концепции оптимизации подготовки к радиойодтерапии в рамках персонализации терапии, сформированы результаты и выводы.

Ключевые слова: дифференцированный рак щитовидной железы; терапия радиоактивным йодом; йод-ограниченная диета; тиреотропин альфа; методы подготовки; нежелательные явления.

Как цитировать:
Рейнберг М.В., Слащук К.Ю., Трухин А.А., Аврамова К.И., Шеремета М.С. Современный взгляд на основные аспекты подготовки пациентов с дифференцированным раком щитовидной железы к радиойодтерапии: научный обзор // Digital Diagnostics. 2023. Т. 4, № 4. С. 543–568.
DOI: https://doi.org/10.17816/DD532728

Рукопись получена: 08.07.2023 **Рукопись одобрена:** 05.09.2023 **Опубликована online:** 10.10.2023

DOI: https://doi.org/10.17816/DD532728

Preparation for radioiodine therapy in patients with differentiated thyroid cancer: a modern perspective (a review)

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ABSTRACT

Thyroid cancer is the most prevalent tumor of the endocrine system, accounting for 1%–3% of all malignant neoplasms as of 2021. Differentiated forms, papillary and follicular, with a relatively favorable prognosis, are detected in 90% of cases. The combination of surgical treatment, subsequent suppressive hormonal therapy, and radioiodine therapy provides a favorable prognosis in patients with differentiated thyroid cancer. However, an insufficient response to radioiodine therapy may be possible, which may be associated with multiple factors, including the preparation step for radioiodine therapy. To date, the question of choosing the optimal method of patient preparation remains relevant. This paper presents a review of the scientific literature on the preparation of patients with differentiated thyroid cancer for radioiodine therapy. The principles of preparation are based on the recommendations of leading expert societies, and publications related to this topic are highlighted and summarized, including the adverse events associated with radioiodine therapy, quality of life, efficacy, and long-term results of treatment. The main purpose of this review was to provide a comprehensive insight into the methods of preparing a patient with differentiated thyroid cancer for radioiodine therapy, highlight existing problems and promising areas of research, and modernize treatment toward personalized therapy. Scientific articles and reviews from the National Library of Medicine, Cochrane Library, and Google Scholar databases, published up to the end of January 2023, were searched by the keywords listed below in their various combinations. Recommendations from the following scientific communities were used: Russian Clinical Guidelines for Differentiated Thyroid Cancer, American Thyroid Association, European Thyroid Association, National Comprehensive Cancer Network, European Association of Nuclear Medicine, British Thyroid Association, and European Society for Medical Oncology. Articles not available in full, not in English or Russian, or systematic reviews of a similar topic, were excluded. In total, 124 sources were selected and analyzed, general tendencies of modern approaches to preparation for radioiodine therapy and actual problems were highlighted, concepts of optimization of preparation for radioiodine therapy within the framework of personalized therapy were covered, and results and conclusions were presented.

Keywords: differentiated thyroid cancer; radioiodine therapy; low-iodine diet; thyrotropin alpha; methods of preparation; side effects

To cite this article:

Reinberg MV, Slashchuk KYu, Trukhin AA, Avramova KI, Sheremeta MS.Preparation for radioiodine therapy in patients with differentiated thyroid cancer: a modern perspective (a review). *Digital Diagnostics*. 2023;4(4):543–568. DOI: https://doi.org/10.17816/DD532728

Received: 08.07.2023 **Accepted:** 05.09.2023 **Published online:** 10.10.2023

DOI: https://doi.org/10.17816/DD532728

目前对分化型甲状腺癌患者放射性碘治疗准备工作主要方面的看法：文献综述

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简评

甲状腺癌是内分泌系统中最常见的肿瘤。它占所有恶性肿瘤的1%–3%（截至2021年）。在90%的病例中，可发现分化型甲状腺癌（乳头状癌和滤泡状癌）。它们的预后相对较好。

对于高分化甲状腺癌患者来说，手术治疗和随后的激素抑制治疗、放射性碘治疗相结合的预后良好。不过，放射性碘治疗仍有可能出现反应不充分的情况。这可能与许多因素有关，包括准备阶段。迄今为止，如何选择最佳的放射性碘治疗准备方法仍是一个重要问题。

该出版物对有关高分化甲状腺癌患者接受放射性碘治疗的准备问题的科学文献进行了综述。根据主要专家团体的建议和有关该主题的出版物，我们对患者准备工作的原则进行了介绍和总结。文章还考虑了（1）与放射性碘治疗相关的不良反应；（2）患者的生活质量；（3）疗效；（4）治疗的长期结果。

这篇综述的主要目的是提供一个全面的视角，介绍为高分化甲状腺癌患者接受放射性碘治疗做准备的方法，强调现有的问题和有前途的研究方向，以便使治疗现代化，实现个性化治疗。

在National Library of Medicine、The Cochrane Library和Google Scholar数据库中检索了截至2023年1月底发表的科学文章和综述。检索时使用了以下关键词：为放射性碘治疗做准备、促甲状腺素α、停用甲状腺激素、副作用、禁碘饮食、涎腺炎、原发性甲状腺功能减退症、生活质量、甲状腺切除术、分化型甲状腺癌、放射性碘治疗的疗效。采用了以下科学界关于高分化甲状腺癌的建议：俄罗斯高分化甲状腺癌临床指南、美国甲状腺协会、欧洲甲状腺协会、American Thyroid Association、European Thyroid Association、The National Comprehensive Cancer Network、European Association of Nuclear Medicine、British Thyroid Association、European Society for Medical Oncology。排除标准为：未提供全文的文章；非英语或俄语文章；类似主题的系统综述。共选择并分析了124个资料来源。本文强调现代放射性碘治疗患者准备工作的总体趋势和当前存在的问题，指出在治疗个性化框架内优化放射性碘治疗准备的概念，最后得出结论。

关键词：分化型甲状腺癌；放射性碘治疗；禁碘饮食；促甲状腺素α；准备方法；不良反应。

引用本文：

Reinberg MV, Slashchuk KYu, Trukhin AA, Avramova KI, Sheremeta MS. 目前对分化型甲状腺癌患者放射性碘治疗准备工作主要方面的看法：文献综述. *Digital Diagnostics*. 2023;4(4):543–568. DOI: https://doi.org/10.17816/DD532728

收到：08.07.2023 **接受：**05.09.2023 **发布日期：**10.10.2023

INTRODUCTION

Thyroid cancer (TG) has five histological types:

- Papillary (80%–85%)
- Follicular (10%–15%)
- Medullary (5%)
- High grade (1%)
- Anaplastic (0.1%–0.2%)

The first two types are low-grade cancers with relatively good outcomes. The global incidence rate of malignant neoplasms is between 1% and 3% of all new diagnoses.

Among thyroid nodules, up to 5% of cases (according to some data, up to 20%) are cancerous [1], whereas the average annual growth rate in incidence is 3%. Since 2011, the incidence has increased by 36%, whereas the mortality rate has remained low [2]. This is mainly due to improvements in diagnostic methods, including the increased availability and quality of ultrasonography.

Despite a good response to surgical treatment and radioiodine therapy (RIT), 20% of patients may experience a relapse of the disease, and in this case, an unfavorable prognosis is observed in 8% of cases [1]. In Russia in 2021, 996 patients per 100,000 population died from thyroid cancer. From 2011 to 2021, a statistically significant increase was found in the "crude" incidence of malignant thyroid neoplasms in children aged <15 years (40%) [2].

Patients with highly differentiated thyroid carcinoma (HDTC), including those at high risk of recurrence, have a generally favorable overall survival profile, and approximately 90%–95% were responders to radioactive iodine therapy [3]. The prognosis is somewhat worse in patients with distant metastases, incomplete response after the first course of radiotherapy, and advanced disease. According to various sources, the 10- and 5-year overall survival rates of such patients are approximately 30% and 55%, respectively [3, 4]. The tumor-specific survival rate is approximately 30%–65% [5]. A. Hassan et al. [6] reported 5-year disease-free survival rates of 52% in intermediate-risk patients and 17% in high-risk patients. Currently, no consensus has been established on the reasons for the incomplete response to RIT and thyroid cancer progression, which may be due to various factors, including the methodology and principles of preparing the patient for RIT. Finding the reasons for an incomplete response to therapy and developing methods to improve the quality of life and treatment approaches remain urgent problems.

RIT refers to a radical method of treatment for HDTC and is part of combination therapy in patients with predominantly intermediate and high risks of disease relapse (according to the criteria of scientific communities [7-11]). The goal of radionuclide therapy is the ablation of residual thyroid tissue after thyroidectomy and the removal of tumor tissue and metastases that can accumulate iodine-131 (I-131).

The effectiveness of RIT depends on various factors, including the histological type of the tumor, size of the primary tumor and/or metastases, presence of locoregional and/or distant metastases, patient's age at the time of diagnosis, hormonal status of the thyroid gland at the time of HDTC detection, and RIT strategy. One of the important criteria is compliance with the conditions of preparation for RIT to optimize the uptake of I-131 by thyrocytes of residual tissues or thyroid cancer cells. Adequate thyroid-stimulating hormone (TSH) and low-iodine levels in the body are believed to be necessary for the adequate uptake of radiopharmaceuticals by tumor cells. These conditions are achieved through thyroid hormone withdrawal, injection of recombinant human thyrotropin alpha (rhTSH), and adherence to a low-iodine diet before RIT. However, no consensus has been reached on the timing and intensity of compliance with these recommendations regarding their effects on the long-term outcomes of therapy. In world practice (Table 1), the accepted standard for preparing for RIT includes the following steps:

- Discontinuation of levothyroxine sodium (LT4) for 3–6 weeks or
  - Replacing LT4 with liothyronine (LT3) for 2 weeks followed by a 2-week withdrawal
  - Use of rhTSH in patients at low and intermediate risk of relapse/progression
- Low-iodine diet for 1–4 weeks (with achievement of iodine concentration in single and/or daily urine <50–100 μg/L).

Taking into account current trends, the contribution of each point of preparation for RIT must separately consider the patient's quality of life, development of side effects, and effectiveness of RIT.

THYROID HORMONE WITHDRAWAL

As the first method of preparation for RIT, the LT4 regimen was discontinued 6 weeks before the initiation of RIT; however, this regimen led to severe hypothyroidism and related side effects. Subsequently, various variations were used to improve the quality of life without compromising the effectiveness of RIT. A. Golger et al. and T. Davids et al. concluded the sufficient adequacy of a 3-week withdrawal of LT4 in most patients [14, 15]. Alternatively, the option of replacing LT4 with LT3 for 2 weeks and then withdrawing LT3 for the same period can be used. However, according to some studies, this method does not provide additional benefits regarding the quality of life of patients [16, 17] and can sometimes potentiate the side effects of LT3 [18]. The limited availability of triiodothyronine preparations on the Russian market and the above factors may make this preparation option less convenient for patients.

Despite the proposed methods, 4 weeks of LT4 withdrawal or 2 weeks of LT3 withdrawal are sufficient for the development of clinically significant hypothyroidism, accompanied by associated side effects that significantly reduce the quality of life of patients. In addition, patients

Table 1. Comparative characteristics of requirements and methods for radioiodine therapy in various scientific communities

Recommendations	Preparation strategy	Low-iodine diet	rhTSH	TSH before RIT	Iodine concentration
Russian clinical guidelines [7]	Discontinuation of LT4 for 4 weeks or rhTSH (2 injections)	2 weeks	Unspecified	>30 mIU/L	Unspecified
European Association of Nuclear Medicine [8]	Discontinuation of LT4 in 3–4 weeks or LT4/LT3/rhTSH (2 injections)	1–2 weeks	In low- or intermediate-risk patients or off-label in patients with distant metastases	>30 mIU/L	Adequate: <100 μg/L Optimal: <50 μg/L
American Thyroid Association [9]	Discontinuation of LT4 in 3–4 weeks or LT4/LT3/rhTSH (2 injections)	1–2 weeks	In low- or intermediate-risk patients	>30 mIU/L	Adequate: <100 μg/L Optimal: <50 μg/L
European Thyroid Association [10]	Discontinuation of LT4 in 3–4 weeks or LT4/LT3/rhTSH (2 injections), preferably rhTSH	A diet may be prescribed; however, its benefits have not been clearly proven. It is recommended to discontinue iodine-containing medications	Not recommended in patients with distant metastases	>>30 mIU/L	Adequate: <100 μg/L Optimal: <50 μg/L
European Society for Medical Oncology [11]	Discontinuation of LT4 in 4–5 weeks or rhTSH (2 injections)	Unspecified	Unspecified	>30 mIU/L	Unspecified
British Thyroid Association [12]	Discontinuation of LT4 in 4 weeks or LT4/LT3/rhTSH (2 injections)	1–2 weeks	Not recommended in patients with distant metastases and massive tumor spread beyond the thyroid capsule	>30 mIU/L	Unspecified
The National Comprehensive Cancer Network [13]	Discontinuation of LT4 in 4–6 weeks or rhTSH (2 injections)	10–14 days	Unapproved in patients with distant metastases	>30 mIU/L	< 100 μg/day

DOI: https://doi.org/10.17816/DD532728

on suppressive therapy may tolerate symptoms of hypothyroidism less. Signs of hypothyroidism affecting the quality of life were reported to progress 2 weeks after cessation of suppressive therapy in most patients [19]. When analyzing the questionnaires, a deterioration in the quality of life was also noted 2 weeks after cessation of LT4 intake [20].

The issue of reducing the withdrawal time of LT4 to 2–3 weeks is being actively discussed. It can be effective in achieving the target TSH level and long-term treatment results.

Liel et al. analyzed 13 patients and reported that a TSH concentration >30 mIU/L was achieved in all patients an average of 17 days after LT4 cessation, and an exponential increase in TSH was observed [21].

R. Luna et al. studied TSH levels in 34 patients on days 4, 14, 21, and 28 after LT4 cessation, with an average of 20, 46, 75, and 112 mIU/L, respectively, corresponding to a linear increase in TSH levels. Thus, after 2 weeks, 75% of the patients achieved a TSH level >30 mIU/L, and 100% of the patients achieved this TSH level after 3 weeks of withdrawal [19].

According to A. Piccardo et al., the response to LT in the group with LT4 withdrawal in 2 weeks (n = 85) and 4 weeks (n = 137) did not differ, which was 82% over a 3–4-year follow-up period. However, the TSH level before RIT did not influence the incomplete therapeutic response [22]. Other authors have come to similar conclusions [23, 24].

Alternatively, P.W. Rosario et al. proposed a regimen with a reduction in the LT4 dose to 0.8 mg/(kg × day) 6–8 weeks before RIT, which was associated with the leveling of hypothyroidism that occurs during withdrawal, and this also made it possible to avoid the use of expensive rhTSH. Therefore, in 24 patients on the classic protocol, 71% noted a health deterioration, whereas in 27 patients on the reduced protocol, only 23% had symptoms of hypothyroidism. Laboratory parameters were also better in the second group. An increase in creatinine was noted in 63% of cases with the classic protocol compared with 30% with the reduced regimen, whereas 60% of patients noticed a difference in the various preparation methods, and 100% would prefer the reduced protocol if TSH stimulation was again necessary. The effectiveness rates of RIT were 75% and 79%, in the reduced and classic protocols, respectively [25].

This protocol has not received much attention from clinicians in other countries because the study was limited by a small sample size and previous RIT. However, this method can be considered in the preparation of low- and intermediate-risk groups for diagnostic procedures and RIT, and this issue requires further research.

Optimizing the preparation of patients for RIT is a current area of research. The above papers suggest that the duration of LT4 withdrawal can be reduced to 2–3 weeks without a decrease in the effectiveness of RIT. This may lead to a decrease in the risk of clinically significant hypothyroidism and an improvement in the quality of life of patients because signs of hypothyroidism in most patients start to progress 2 weeks after the cessation of LT4 treatment.

IS TSH CONCENTRATION >30 MIU/L AN OUTDATED DOGMA?

Controversy exists regarding the optimal TSH concentration before RIT in residual thyroid tissue. The efficiency of I-131 uptake by the tumor and residual thyroid tissue was assumed to depend on the level of expression of the sodium-iodine symporter (SIS), which in turn depends on the TSH concentration [26, 27]. D.Yu. Semenova et al. [28] showed that the average expression of SIS on the membrane of thyroid gland cells does not exceed 4.5%, and the maximum reaches 10%, whereas in normal thyroid tissue, the expression level was 30%–50%. More than 60% of patients with relapsed HDTC had an SIS expression level of <1%. Low SIS expression has been theorized to be an independent prognostic factor for the risk of relapse and disease severity; however, further research on this topic is required.

In 1977, C.J. Edmonds et al. first concluded that adequate uptake of I-131 by the tumor was impossible with TSH <30 mIE/L, and since then, this cutoff point has been used as an indicator of adequate patient readiness for RIT, also serving as a standard in most subsequent studies. Notably, in this study, not all patients achieved adequate I-131 uptake at the "target" TSH values, the sample size was small, and patients with distant metastases of thyroid cancer were also included, which could have a greater effect on the radiopharmaceutical uptake than the TSH concentration. Finally, these studies were not subjected to statistical analysis; thus, the conclusions were not considered unambiguous [26].

In 2021, J. Xiao et al. reported that a group of patients with a TSH concentration of 30–70 mIU/L showed better treatment outcomes than a group of patients with a concentration of ≤30 mIU/L at the time of RIT. Moreover, the effectiveness of RIT in the group with a TSH concentration of >70 mIU/L did not differ from that in the group with a TSH concentration of 30–70 mIU/L [29]. However, patients at high risk of disease relapse were excluded from the statistical analysis, and they comprised the majority of patients in the group with TSH <30 mIU/L and could respond worse to therapy because of the stage of thyroid cancer. Therefore, it is impossible to statistically reliably state that RIT is less effective based on TSH levels. Interestingly, 76% of patients achieved a TSH level of ~70 mIU/L by the end of week 4 of LT4 withdrawal, whereas 46% had a TSH concentration of >100 mIU/L. The authors concluded that due to the lack of additional benefit from achieving TSH concentrations >70 mIU/l (probably due to the presence of a certain threshold for rhTSH expression in the tumor cell), the timing of thyroid hormone withdrawal can be reduced.

T. Zhao et al. also reported the need to achieve TSH concentration >30 mIU/L in patients at low and intermediate

risk; however, the study has its limitations: retrospective analysis, variability in I-131 activity (1.1–5.5 GBq), small sample size of patients with TSH <30 mIU/L, and short follow-up period [30].

In contrast to the above studies, an alternative opinion states achieving TSH concentration >30 mIU/L is unnecessary.

Z. Hasbek et al. observed 34 patients with an average median TSH concentration of 19.5 ± 6.0 mIU/L and 227 patients with TSH >30 mIU/L and noted that the lack of RIT effect was observed in one patient from the first group and 11 from the second group, which was not statistically significant. In non-responders, a significant increase in thyroglobulin levels and the presence of locoregional and distant metastases were observed. The authors concluded that TSH concentration is not the only and absolute factor for a successful response to RIT, whereas the patient's age at diagnosis (>45 years), presence of metastases, thyroglobulin concentration, and residual thyroid tissue volume should be considered possible criteria for the low efficiency of RIT [31]. A research group from Germany came to similar conclusions; the TSH level at the time of ablation did not affect the percentage of successful ablation, disease-free survival, or tumor-specific mortality (Figure 1) [32].

In a retrospective analysis of 1873 patients without evidence of distant metastasis who underwent RIT, no statistically significant effect of TSH concentration was found on the effectiveness of RIT, disease-free survival, or HDTC-associated mortality. RIT was effective in 230 of 275 patients with TSH <30 mIU/L and 1359 of 1598 patients with TSH >30 mIU/L. At the time of ablation, incomplete response to RIT depended on the following factors:

- I-131 activity
- Histological characteristics
- Patient's sex
- T-stage
- Presence of metastases in the regional lymph nodes
- Thyroglobulin concentration

The absence of metastases, low thyroglobulin concentration, smaller tumor size, high I-131 activity, and female sex were identified as independent factors for successful RIT. The authors also note that TSH levels are stimulated more slowly in patients:

- With metastatic disease
- At an older age
- Female [32, 33]

In the absence of increased TSH concentrations to generally accepted target values (>30 mIU/L) in this group of patients after 3 weeks, further prolongation of thyroid hormone withdrawal was inappropriate. N. Ju et al. came to similar conclusions (Figure 2) [34].

Slow TSH stimulation is probably associated with the influence of estrogens on the level of mRNA expression of the TSH beta-subunit, leading to its suppression in hyperestrogenism [35]. However, this mechanism of regulation of TSH concentration, as well as the theory about the influence of the estrogen status of the body on the incidence and progression of HDTC, are not fully understood and require further research [36-38].

Therefore, some factors can significantly influence the success of RIT in HDTC. They require attention and an individual approach, and with them, the dominant role of the "target" TSH concentration >30 mIU/L may be exaggerated. The study of RIT in a setting of TSH concentration <30 mIU/L will change views on modern aspects of preparation for RIT toward its greater safety with equivalent effectiveness.

RECOMMENDED HUMAN THYROTROPIN ALPHA

In 1987, rhTSH was obtained from the human TSH cell culture FRTL-5 of Chinese hamster ovaries. In 1998 and 2001, rhTSH was approved in the USA and Europe, respectively, as a preparation for diagnostic examinations with radioactive iodine. rhTSH was later approved as an alternative to thyroid hormone withdrawal when preparing patients for RIT:

- In Europe: since 2005
- In the USA: since 2007
- In Russia: since 2018

Numerous studies have shown rhTSH comparable to thyroid hormone withdrawal as a preparation for

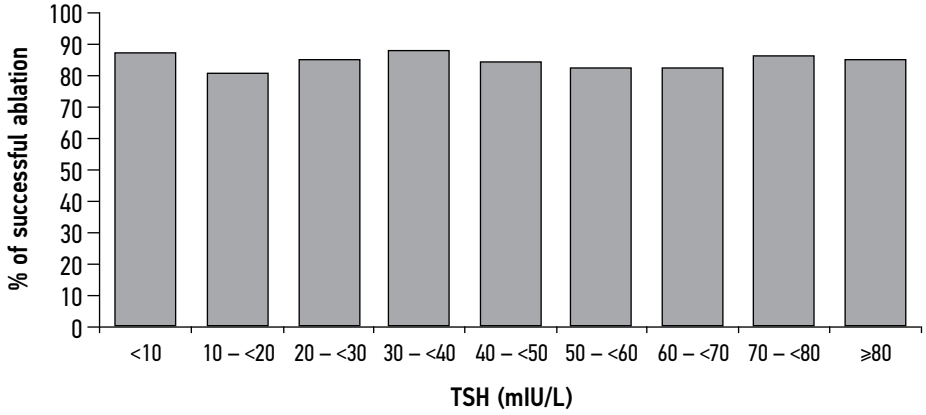

Fig. 1. Percentage of patients with successful ablation relative to thyroid-stimulating hormone levels at the time of therapy I-131

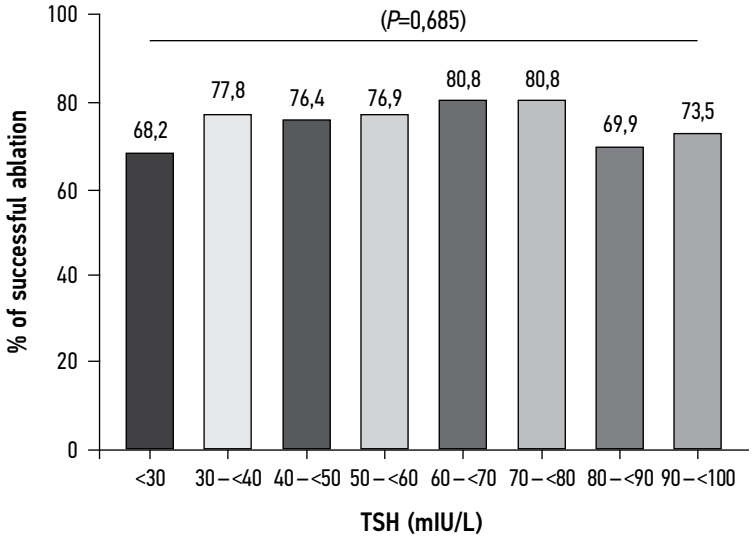

Fig. 2. Percentage of patients with successful ablation of residual thyroid tissue with I-131 relative to thyroid-stimulating hormone levels. In 8 subgroups, no statistical significance was observed.

postoperative RIT [39–43]. However, the issue regarding the possibility of using rhTSH as part of RIT in patients at high risk of recurrent thyroid cancer and in the treatment of distant metastases remains open. Previously, several cases of ineffectiveness of RIT in high-risk patients when prepared with rhTSH have been documented, whereas repeated courses of RIT in a setting of thyroid hormone withdrawal were successful [44–46].

One of the proposed mechanisms is related to the different actions of the recombinant hormone and the endogenous hormone because of the greater sialylation of the molecule, different degrees of glycosylation of the TSH receptor, and polyclonality of tumors, which can develop with increasing number of RIT courses [46].

Currently, the question of whether the dose- and time-dependent effects of TSH (in other words, the area under the curve) on radiopharmaceutical uptake and treatment outcome is more significant than the "cutoff point" of 30 mIU/L. A. Vrachimis et al. suggested that this may be one of the limiting factors in the use of rhTSH [32].

Despite this fact, recent data indicate the same effectiveness of the use of rhTSH in patients not only at low and intermediate risk but also at high risk. In a retrospective study, J. Hugo et al. analyzed 586 patients (321 prepared by stopping LT4 treatment and 265 prepared using rhTSH), including intermediate risk and high-risk groups, and showed that long-term clinical outcomes with a median 9-year follow-up were not different. Moreover, in the short term (median, 2.5 years), the withdrawal group showed a statistically higher likelihood of incomplete response to primary RIT than the rhTSH group (47% vs. 39%, p = 0.03), with a higher rate of requiring repeat therapy, surgical intervention, or an RIT course (37% vs. 29%, p = 0.05). Economically, the use of rhTSH can shorten the period of active follow-up for patients with signs of persistent and/or recurrent disease [41] and reduce the economic budgetary costs [47–51], including a 70% probability of achieving economic benefits with a 30% reduction in the rhTSH cost [52].

Other researchers obtained similar results of at least equal effectiveness of rhTSH in the intermediate risk and high-risk groups [53-59].

In its HDTC guidelines, the American Thyroid Association does not recommend the use of the drug in patients at high risk of relapse [9]. Guidelines of the European Association of Nuclear Medicine allow the use of the drug off-label in patients with distant metastases [8].

The use of rhTSH is associated with fewer side effects. There remains some caution regarding the use of the drug in patients with metastases to the central nervous system because a strong TSH stimulation may lead to their growth/increase and severe clinical symptoms [60].

In a study of 88 patients prepared for RIT through thyroid hormone withdrawal and rhTSH (51 and 37, respectively), the 10-year survival rates were 62% and 73%, respectively. Therefore, the use of rhTSH was not associated with worse treatment outcomes or prognosis [61].

Table 2 summarizes the main advantages and disadvantages of using rhTSH and the target group of patients for its use.

Despite the controversy regarding the use of rhTSH in the high-risk group, a potential benefit may be a greater increase in TSH levels in a shorter period. Patients with metastases have a lower expression of SIS, which may require a higher TSH concentration for I-131 uptake by tumor cells. In addition, long-term preparation by thyroid hormone withdrawal can negatively affect cancer prognosis and lead to progression [62-64].

I.I. Dedov et al. [65] showed that 70% of patients had a TSH concentration >100 mIU/L after the second rhTSH injection; however, no studies are currently conducted on the

Table 2. Advantages and disadvantages of using recombinant human thyrotropin alpha and its preferred indications

Advantages	Disadvantages	Target group
Leveling the hypothyroidism phase is an opportunity to reduce the side effects on some risk organs Better quality of life compared with patients on withdrawal before and after RIT The preparation period for RIT/diagnostic studies is shorter Less risk of salivary gland damage Reducing the radiological load on the body as a whole (because of the absence of changes in GFR) and the risk of bone marrow damage Shorter possible hospitalization periods	Cost Higher incidence of damage to lacrimal gland ducts Lack of sufficient data on use in patients with distant metastases	Older age Chronic diseases of target organs that have a risk of exacerbation in the case of decompensated hypothyroidism (chronic heart failure, coronary heart disease of class II and higher, history of heart attacks/stroke, COPD, hepatitis, rheumatoid arthritis, diabetes mellitus, chronic kidney disease, mental illness, chronic pancreatitis, immunodeficiencies, etc.) Patients with a single/transplanted kidney Patients with carbohydrate metabolism disorders and obesity Patients with infections/diseases of the oral cavity, a history of sialadenitis, and stones in the ducts of the salivary glands Poorly controlled hypertension Non-alcoholic fatty liver disease and liver diseases in the stage of decompensation

optimal TSH level in the high-risk group and its contribution to treatment effectiveness.

Separately, the advantages of rhTSH over LT4 discontinuation must be considered in terms of the effect on organs at risk, which will be discussed further.

SIDE EFFECTS WHEN USING DIFFERENT PREPARATION PROTOCOLS AND WAYS TO SOLVE THEM

When preparing for RIT, patients who are undergoing thyroid hormone withdrawal have severe iatrogenic hypothyroidism, accompanied by a decrease in the quality of life and side effects affecting target organs. Such effects are mediated by the presence of TSH receptors not only in thyroid tissues but also on the membranes of adipocytes, fibroblasts, osteoclasts, leukocytes, monocytes, amyocardiocytes, endothelial cells, and vascular smooth muscle cells, including the afferent glomerular arteriole [66].

In the cardiovascular system, the following are noted:

- Decreased ejection fraction
- Left ventricular diastolic dysfunction at rest
- Increase in total peripheral vascular resistance
- Endothelial dysfunction

All these factors may contribute to a decrease in the control of arterial hypertension in patients with essential hypertension [67]. Because of a decrease in the filtration function of the kidneys, the clearance of adrenaline, norepinephrine, and cortisol slows down [68]. Two studies have reported increased homocysteine levels [69, 70]. Such changes may contribute to the development and progression of the cardiorenal continuum. In patients who underwent thyroidectomy and were taking anticoagulants, an inverse correlation was found between TSH and INR levels during LT4 discontinuation, which may require additional monitoring of blood coagulation parameters to timely correct therapy.

Negative effects on the liver have been repeatedly reported; in patients with thyroid hormone withdrawal, increased activities of alanine aminotransferase and aspartate aminotransferase were reported [71, 72], whereas the use of rhTSH was not accompanied by impaired liver function [71]. Lipid metabolism is disturbed by an imbalance of high-density lipoproteins [67, 73]. This is because the lack of thyroid hormones leads to a decrease in the expression of receptors for high-density lipoproteins [74] and an increase in their concentration and an increase in total plasma cholesterol [73]. A definite connection has been established between thyroid dysfunction and affective disorders [75]. Moreover, disease control worsened as the intensity of hypothyroidism increased, which could be associated with reduced blood circulation in the brain and a diffuse [76] and/or regional [77] decrease in glucose clearance. The potentiation of the symptoms of depression, which most often accompanies hypothyroidism, is possible because of the insufficient ability of brain cells to receive adequate amounts of oxygen and glucose from the blood [78].

The causes of carbohydrate metabolism disorders may be increased evacuation capacity of the stomach and decreased transport of glucose by the liver, which leads to disturbances in both postprandial and fasting glycemia [79].

Evidence shows the influence of thyroid hormones on the modulation of the immune response [80], which in the case of hypothyroidism can lead to an increase in infectious morbidity. Particular attention has been paid to the suppression of renal functions, as proven in many studies [71, 81-87], including those that occur during LT4 discontinuation but not when using rhTSH. A study reported decreased renal perfusion on Doppler ultrasonography with rhTSH use. However, it was performed on a small sample of patients on day 5 after injection of the drug [66].

Cases of hyponatremia have been described following a low-iodine diet [88–91], with the following risk factors:

- Older age
- Treatment with thiazide diuretics
- Long duration of the low-iodine diet
- Long-term hypothyroidism
- Multiple metastases, which can contribute to the development of the syndrome of inappropriate antidiuretic hormone secretion, leading to its excessive increase [93, 94]

A common cause of hyponatremia was self-limitation of table salt by patients because of the low awareness of the principles of a low-iodine diet.

In a study by Horie et al., hyperkalemia developed in 5% of patients, correlating with age (over 60 years) and taking angiotensin-converting enzyme inhibitors, which could potentially also be associated with compromised renal function during long-term discontinuation of LT4 [93].

Interestingly, the choice of preparation method for RIT may also influence the frequency and intensity of side effects after exposure to I-131. Therefore, organs expressing SIS can accumulate I-131, which in some cases can lead to damage.

According to the clinical experience of our center, as well as worldwide publications, 20%–30% of the negative effects are related to the salivary glands [94-97]. Patients may experience taste changes, infections, facial nerve involvement, stomatitis, and candidiasis. The typical first symptom is obstructive swelling of the gland, resulting from the narrowing of the duct lumen associated with the inflammatory process. To prevent sialadenitis, many methods have been used, including the use of cholinomimetics, sialogogs, cytoprotectors (amifostine), and salivary gland massage. However, the efficacy was poor [97-100]. Moreover, the use of sialogogs on the first day after RIT leads to an increase in the radiation dose by approximately 28% in the salivary glands; therefore, the use of lemon/sucking sweets/other sialogogs on the first day after therapy is not recommended [99, 102]. If untreated, only 54% of patients were free of chronic sialadenitis after 6 years of follow-up [100], highlighting the need to find new methods to prevent sialadenitis.

In a study by A. Trukhin et al., rhTSH use was associated with a higher incidence of radiotracer accumulation in the lacrimal ducts than the 4-week discontinuation of LT4 [102]. According to other authors, the use of rhTSH reduced the number of cases of acute sialadenitis after RIT by approximately 20% [103], which may account for only 6.7% over the next year [104].

Secondary leukemia after ablation is one of the side effects of RIT that has not been widely recognized, but which deserves special attention. In a previous study, 148,215 patients were analyzed; the risk of developing acute and chronic myeloid leukemia in the first 3 years was higher and statistically significant in patients who underwent primary RIT for differentiated thyroid cancer compared with those who underwent surgical treatment only. Although the risk of acute myeloid leukemia rapidly declines to baseline levels by 3 years after RIT, the risk of chronic myeloid leukemia remains high for 10 years [105].

Another controversial finding is the increased number of stable chromosomal aberrations in patients after the administration of a low dose of I-131, which persisted longer in patients on LT4 discontinuation than in those on rhTSH [106]. The clinical interpretation of the results requires longer follow-up and a detailed search for cause-and-effect relationships.

Therefore, when preparing for RIT and monitoring patients, a clinician should probably be more cautious about patients with the following:

- Hypertension
- Immunodeficiency
- Moderate/severe dysfunction of the liver and/or kidneys
- Disturbances in electrolyte and/or carbohydrate metabolism
- Affective disorders
- Other previously described conditions

One of the methods to prevent and reduce the severity of side effects in susceptible organs associated with hypothyroidism is the preferential use of rhTSH in patients at risk of hypothyroidism complications and educating them on the basic principles of adhering to a low-iodine diet and regimen during RIT.

LOW-IODINE DIET

Based on the data collected to date, the degree of iodine uptake by tumor and normal thyroid cells is believed to be determined by the following:

- Volume of the residual thyroid tissue
- Adequate TSH stimulation
- SIS expression
- Median iodine concentration at the time of therapy [107]

Early studies have shown that iodine uptake by residual thyroid tissue increases 2–3-fold in patients following a low-iodine diet [108, 109], which may affect the effectiveness of RIT. Most scientific communities adhere to the following criteria when preparing a patient for RIT: optimal level of urine iodine excretion (UIE)<50 μg/L [8-10] and adequate level <100 μg/L [8]. However, no clear criteria have been established for the duration and intensity of adherence to a low-iodine diet.

To answer the question of whether a low-iodine diet is needed, several studies were conducted, including one by J. Tala et al., which caused a certain dissonance in the scientific community. The authors did not find a relationship between the urine iodine level and RIT effectiveness and suggested no differences between groups of patients with urine iodine levels of >100 μg/L and <100 μg/L. However, the study was conducted in a moderately deficient region (Siena, Italy), the sample of patients with high iodine content in the body was

not sufficient, and the I-131 dose varied, which could greatly contribute to the clinical outcomes of RIT than moderate iodine deficiency [110].

The question of the optimal level of iodine in the body, after which the patient's preparation for RIT is considered adequate, remains ambiguous.

M. Lee et al. did not find the difference in the effectiveness of RIT in the moderate and mild iodine deficiency groups [111]. A.E. Tobey et al. showed no significant difference in the RIT effectiveness between groups with iodine levels 50/100/150 mg/day; however, the risk of disease progression was higher in groups with urinary iodine levels >200 mg/day. To our knowledge, this is the first study to evaluate the relationship between pre-RIT iodine status and long-term clinical outcomes with a median follow-up of 3.7 years [112]. Other authors came to similar conclusions [45, 107, 113]. However, in a study by L.F. Morris et al., the success of RIT did not differ between groups with and without a low-iodine diet [114].

The diet duration is the next urgent issue. The most common recommended period is 1–2 weeks; however, approaches and protocols for a low-iodine diet vary from country to country. The timing and intensity of the diet could not be specified because of differences in the iodine supply of regions. A 2-week diet with restriction of iodine-containing foods can affect the quality of life, social functioning, and risk of hyponatremia. However, in regions with excess iodine intake, 2 weeks may be preferable to achieve adequate pre-ablation iodine levels in the body [107, 115-117]. An important point is to properly educate patients about the basic aspects of a low-iodine diet. In studies with minimal patient education by dietitians/nutritionists or dietary nurses, with the distribution of handouts, in some patients provided with a 3–7-day menu, better results were seen in the percentage reduction of iodine levels compared with baseline [112, 117-119].

In studies conducted in regions with moderate iodine deficiency or adequate iodine intake, optimal levels were achieved after a week of a low-iodine diet [118, 120] and after 4 days in studies by M.J. Pluijmen et al. and B.L. Dekker et al. [113, 121]. Some studies conducted in regions with high iodine intake have also shown the effectiveness of a weekly low-iodine diet [111, 112, 118, 119].

A limitation of many studies, other than the study by A.E. Tobey et al. [112], was that they have been conducted in the low- and intermediate-risk groups. This does not allow a full assessment of short- and long-term outcomes in the high-risk group. In studies conducted in countries with moderate iodine deficiency (e.g., Italy), with a median urinary iodine level of 95 μg/L in patients discontinuing LT4, values ranged from 25 to 1890 μg/L, which may affect the effectiveness of treatment in some cases. In this study, patients were not assigned to a low-iodine diet because of regional iodine deficiency status, and the high-risk group was excluded from the analysis.

Studying the patient's iodine status before RIT is one of the methods for personalizing treatment. In each case, including those at high risk of disease relapse/progression, special attention should be paid to achieving an optimal iodine pool before RIT because each factor in the preparation process, including iodine status, can affect treatment success. The main studies on this topic are highlighted in Table 3.

When considering adherence to a nearly stringent low-iodine diet protocol, no clear evidence was found to support a restrictive diet in either the degree of iodine reduction or the effectiveness of RIT. A more stringent protocol may be more associated with iodine reduction, lower quality of life, and psychological discomfort of patients. Therefore, the choice of a specific preparation protocol will depend on the ability of a particular site to inform/educate patients, presence of comorbid pathology, and initial iodine status of the region.

The 2020 Russian Clinical Guidelines recommend a 2-week low-iodine diet. Considering the iodine status of the region and world data, the diet duration can be reduced to 4–7 days.

CONCLUSION

To date, no consensus has been made regarding the indications for adjuvant RIT in patients with low and intermediate risk of recurrence, who represent the majority of patients with HDTC. The use of RIT carries a potential risk of complications; thus, the clinical benefit in each specific case must be assessed. This can only be done with the help of dynamic stratification of the risk of recurrence of thyroid cancer. The studies presented in the literature over the 80-year history of the method show the heterogeneity of options for the preparation and treatment of HDTC, which form the modern view of RIT.

In the low-/intermediate-risk group, performing RIT in an euthyroid state with a TSH level of <30 mIU/L may neutralize the risks associated with hypothyroidism and its complications. To date, limited but methodologically sound studies have demonstrated that achieving a pre-ablation TSH level >30 mIU/L is not necessary, as well as the efficacy of 2 weeks of LT4 discontinuation (compared with 4 weeks) to induce hypothyroid status. More studies are needed to extrapolate the results to a high-risk group. Theoretically, higher TSH levels may be required to stimulate SIS and improve the quality of therapy. The preferred drug for use in this patient population would be rhTSH; however, studies of the influence of its pharmacokinetic characteristics on the efficacy of RIT are required. In addition, its availability is currently limited by its high cost, which justifies the need to reduce the cost of its production technology in the Russian Federation and consider its availability to needy patient groups.

To increase the effectiveness of RIT, one of the steps in a personalized treatment approach may be to measure the iodine concentration in a single urine sample before RIT

Table 3. Comparative characteristics of a low-iodine diet and its effectiveness in countries with different iodine levels

1	2	3	4	5	6	7
Study	**Patient sample (details)**	**Characteristics of the LID**	**Education**	**Method for assessing the iodine concentration/efficacy of RIT**	**Results (effects on RIT outcomes, % reduction in the iodine pool in the body)**	**Study limitations**
Brazil: moderate–high iodine intake						
R.P. Padovani et al. 2015 [122]	n = 125*	LID 15 days, n1 = 79; LID 30 days, n2 = 46	+	24-UIE	n1: M = 99 mg/L (60% reduction) n2: M = 80 mg/L (70% reduction)	*Most patients were excluded because of difficulty in complying with the protocol (initial, n = 306)
Korea: excess iodine intake						
S.U. Sohn et al. 2013 [107]	n = 295 (single activity I-131 – 1100 MBq)	LID 2 weeks	+++	UIE in a single urine sample adjusted for Cr	Successful ablation: 74.9% (221/295); in the group with UIE <66 μg/g (I/Cr ratio), the results were better than those in the group with UIE >66 μg/g: 81% versus 67%, $p = 0.03$; significantly lower results in the group with UIE >250 μg/g ($p < 0.05$)	Retrospective analysis; patients with distant and cervical metastases were excluded, which could affect the statistics of RIT outcomes, without considering antithyroglobulin antibodies
IDKS Yoo et al. 2012 [115]	n = 161: n1(SLID) = 90; n2(MLID) = 71	SLID/MLID 2 weeks	++	UIE was not measured	Successful RIT: SLID, 75.8%; MLID, 80.3% ($p = 0.48$)	Patients with distant metastases were excluded. No information is available regarding patients receiving thyrotropin alpha
H.K. Kim et al. 2011 [118]	n = 19 (on LT4 discontinuation)	SLID 2 weeks	+++	UIE in a single urine sample, adjusted for Cr daily, 14 days	I/Cr ratio 0→7 day: ↓ from 576 to 26 μg/g 0→14 day: ↓ up to 19.6 μg/g By day 3: 95% I/Cr <150 μg/g By day 6: 95% I/Cr <66 μg/g	A single sample of urine was used to assess iodine excretion. The study results are not suitable for interpretation in iodine-deficient regions; the effectiveness of ablation has not been assessed
C.Y. Lim et al. 2015 [117]	n = 101 n1(SLID) = 47; n2(MLID)=54	SLID/MLID 4 weeks	++	24-UIE, adjusted for Cr, weeks 2 and 4	No statistical differences were found between n1 and n2. I/Cr ratio: Week 2: 28.6 μg/g Week 4: 35.0 μg/g. % I-131 uptake at weeks 2 and 4 did not differ between the groups	Short- and long-term outcomes of radioiodine therapy have not been assessed
M. Lee et al. 2014 [111]	n = 195	LID 2 weeks	+++	24-UIE at the end of weeks 1 and 2	Week 1 - M =12.8 μg/L , 87.2% UIE <50 μg/L Week 2 - M=13.4 μg/L, 92.3% UIE <50 μg/L Successful ablation: 82.4%; no differences were found between the moderate and mild iodine deficiency groups	Various therapeutic activities (3700–7400 MBq) Exclusion of the high-risk group

DOI: https://doi.org/10.17816/DD532728

Table 3. Continued

1	2	3	4	5	6	7
Study	**Patient sample (details)**	**Characteristics of the LID**	**Education**	**Method for assessing the iodine concentration/efficacy of RIT**	**Results (effects on RIT outcomes, % reduction in the iodine pool in the body)**	**Study limitations**
Italy: moderately deficient region						
J. Tala et al., 2010 [110]	n = 201 (n1 = 25, discontinuation of LT4 for 4 weeks; n2 = 76 on rhTSH)	Absent	–	UIE in a single urine sample	Successful ablation in 84.6% (UIE M=104 μg/L, from 25 to 1890 μg/L). No statistical differences were found between the groups with complete (M = 104 μg/L) and incomplete (M = 104 μg/L, 25 to 851 μg/L) responses. No difference was found in the response to therapy between the groups with UIE <100 μg/L and >100 μg/L (p = 0.98)	Retrospective analysis, small sample of patients with high iodine concentrations in urine, various levels of I-131 activity at the time of ablation (1100–5550 MBq), and no control group and high relapse group
Netherlands: adequate iodine intake						
M.J. Pluijmen et al., 2003 [113]	n = 120: n(LID) = 59 n (RD) = 61	LID 4 days	+++	24-UIE: n (RD) = in 9 patients n (LID) = in 60 patients	n (LID): UIE avg. = 27 μg/day n (RD) UIE avg. = 159 μg/day I uptake in the thyroid region was higher in the LID group (5.1 ± 3.8 vs. 3.1 ± 2.5%, p < 0.001). Efficacy was higher in the LID than in the. RD group (71% and 45%, respectively)	Retrospective analysis Patients with metastases were excluded
B.L. Dekker et al., 2022 [123]	n = 65	–	+++	24-UIE on days 4 and 7	Day 4: 24-UIE <50 μg in 72.1%, UIE avg. 36.1 g; Day 7: 24-UIE <50 μg in 82.0% (p = 0.18), UIE avg. 36.5 μg	These studies may not be applicable to countries with high iodine intake. Initial urinary iodine levels were not assessed
USA: moderate-to-high iodine intake						
L.F. Morris et al., 2001 [116]	n = 94: n (LID) = 44 n (RD) = 50	LID 10–14 days RD: limit preparations with iodine, iodized salt, and seafood	++	UIE in a single urine sample (in seven patients on LID and in seven on RD)	Successful ablation in 68.2% (LID) versus 62% (RD), p = 0.53. In patients with metastases: 80.0% and 66.7. n (LID): ↓ I by 69.4% (UIE avg. 567.7 μg/L → 173.9 μg/L); n (RD): ↓ by 23.6% (UIE avg. 444.0 μg/L → 498.9 μg/L)	Various therapeutic activities (3700–7400 MBq) Small sample of patients for urine iodine screening The ablation criteria excluded the level of thyroglobulin or antibodies to thyroglobulin
A.E. Tobey et al., 2018 [114]	n = 70 n1(rhTSH) = 16 n2 (discontinuation of LT4) = 54	LID 2 weeks	+++	24-UIE	21% had disease progression, and the risk was higher in patients with UIE >200 μg/day. Between groups with UIE 50, 100, 150 μg/day, no difference was found	Retrospective study and small sample I-131 activity from 1.1 to 11.1 GBq at RIT; Observation period of 3.7 years

DOI: https://doi.org/10.17816/DD532728

DOI: https://doi.org/10.17816/DD532728

Table 3. Ending

1	2	3	4	5	6	7
Study	**Patient sample (details)**	**Characteristics of the LID**	**Education**	**Method for assessing the iodine concentration/efficacy of RIT**	**Results (effects on RIT outcomes, % reduction in the iodine pool in the body)**	**Study limitations**
J.T. Park et al., 2004 [125]	n = 36	n1 = 15: 2 weeks of LT4 + 2 weeks of LID; n2 = 21: 2 weeks LID without LT4	+	UIE in a single urine sample at weeks 1 and 2, adjusted for Cr	I /Cr ratio: n1: M (week 1) = 76.91 μg/ g (21% UI <50; 71% <100 μg/g); n2: M (week 1) = 26.16 μg/g (78% <50 μg/g), p < 0.001 The UI after 2 weeks of LID did not differ between groups 1 and 2 (p < 0.15)	Short- and long-term outcomes of RIT were not assessed
Japan: excess iodine intake						
S. Ito et al. 2018 [118]	n = 45 (single activity I-131 1100 MBq)	LID 2 weeks (SLID n = 12; LID n = 25)	+++	UIE in a single urine sample adjusted for Cr	UIE (I/Cr): M before and after diet: 286 μg/ g (range, 40–7100 μg/g) and 74 μg/g (range, 16–816 μg/g), respectively. Successful ablation in 56% of the entire sample	Small sample; the effectiveness of RIT was assessed based on the results of scintigraphy without considering thyroglobulin and antibodies to thyroglobulin Patients with M1 were excluded. Complex interpretation for regions with moderate or adequate iodine intake
C. Tomoda et al. 2005 [121]	n = 252: n 1(MLID) = 220 n 2(LID) = 15 n 3(SLID) = 17	MLID = 1 week LID = 1 week SLID = 2 weeks	+	UIE in a single urine sample adjusted for Cr	n3(SLID): M I/Cr - 130 μg/ g (range 23–218 μg/g) n1(UYND): M I/Cr 125 μg/g (range 13–986 μg/g), (p <0. 01) I/Cr <100 μg/g - in 26% (n1) and 70% (n3)	Short- and long-term outcomes of radioiodine therapy have not been assessed. Iodine content was assessed in a single urine sample (not the “gold standard”)
Malaysia: moderate iodine deficiency						
W.F. Sohaimi et al. 2019 [122]	N = 104 (LT4 discontinuation)	SLID/MLID = 1 week	+	UIE in a single urine sample	Day 0→7: UIE <100 μg/L in 89.1% (SLID) and 91.8% (MLID) MLID: UIE avg. 89.24 μg/L → 56.85 μg/L (↓ by 36.3%) SLID: UIE avg. — 107.8 μg/L → 63.82 μg/L (↓ by 40.8%)	Short- and long-term outcomes of radioiodine therapy have not been assessed

Note:
“–”: lack of any education
“+”: printed instructions
“++”: printed and oral instructions
“+++”: printed, oral instructions, and training by healthcare personnel
24-UIE: daily urinary iodine excretion;
Cr: creatinine
I: iodine
LID: low-iodine diet
LT4: levothyroxine
M: median
MLID: moderate low-iodine diet
RD: regular diet
RIT: radioiodine therapy (first postoperative radioiodine therapy)
SLID: strict low-iodine diet
UI avg: average iodine levels in urine
UIE: urinary iodine excretion.

to assess the patient's compliance with a low-iodine diet and predict the effectiveness of treatment. The procedure can be simplified by measuring the iodine concentration in saliva, as proposed by B.L. Dekker et al. [126]; although the information value is equivalent to the "gold standard" (iodine in 24-h urine sample), this method still needs to be validated and has certain limitations. An important contribution to the determination of patient management strategy can be made by determining the level of SIS expression as part of a standard pathological examination to predict the response to RIT, which may also influence the therapeutic activity of I-131.

The wide range of therapeutic activities of I-131 is one of the significant limiting factors in RIT preparation studies, affecting the final assessment of complex efficacy, which should be considered when carefully studying the issue addressed in the publication. The development of more precise and personalized approaches to RIT is based on an understanding of the many complex mechanisms, including individual patient characteristics, tumor biology, and other factors that underlie the efficacy and safety of this treatment. Careful selection of patients who will benefit from this intervention is necessary to minimize adverse events. The issue of the validity of prescribing RIT requires special attention and further study.

To summarize modern ideas and trends in the preparation for RIT, the following aspects are promising:

- Educate patients about the disease, RIT preparation, posttreatment regimen, and follow-up to improve quality of life.
- Reduce the period of a low-iodine diet to 4–7 days, eliminate significant dietary restrictions, or expand the dietary regime during the period of a low-iodine diet, depending on the iodine status of the region, and lower the "threshold" of optimal iodine level before ablation to 100–150 μg/L,
- Consider the possibility of performing RIT with a TSH level <30 mIU/L in some groups of patients (low/intermediate risk of relapse) by reducing the RIT withdrawal period from 4 to 2 weeks.
- Expand the indications for the use of rhTSH to include patients at high risk of relapse and those with significant comorbidities.

ADDITIONAL INFORMATION

Funding source. This work was conducted within the fund of the State Assignment "Study of pharmacosafety of theranostic radiopharmaceuticals using hybrid molecular imaging in the diagnosis and treatment of endocrine and oncological diseases in children and adults". Registration number 123021000041-6.

Competing interests. The authors declare that they have no competing interests.

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. M.V. Reinberg — contribution to the concept of the paper, design of the review, collection and processing of materials, analysis of the obtained data and writing the text; K.Yu. Slashchuk — assistance in collection and processing of materials, data analysis, making substantial revisions to the manuscript to improve the scientific value of the article; approval of the final version of the manuscript; A.A. Trukhin — text editing, data analysis, adding valuable comments to improve the scientific value of the article; K.I. Avramova — assistance in collection and processing of materials, text editing; M.S. Sheremeta — adding valuable comments, approval of the final version of the manuscript.

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