

# POST-RADIATION HYPOTHYROIDISM IN PATIENTS WITH HEAD AND NECK TUMORS

## Postradiačná hypotyreóza u pacientov s nádormi hlavy a krku

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### Abstract

Head and neck tumors are common in Slovakia. Although the number of tumors associated with smoking and alcohol is decreasing, the incidence of tumors associated with human papillomavirus is rising. Radiotherapy plays an important role in their treatment. Due to its anatomical location, the thyroid gland is predisposed to developing post-radiation dysfunction. Currently, there are already methods to reduce this risk, along with new options for treatment and dispensary care for such patients (*lit. 12*). Text in PDF [www.lekarskyobzor.sk](http://www.lekarskyobzor.sk).

**KEY WORDS:** thyroid gland, radiotherapy, hypothyroidism, prevention, treatment.

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### Abstrakt

Nádory hlavy a krku sú na Slovensku bežné. Hoci počet nádorov spojených s fajčením a alkoholom klesá, počet nádorov spojených s ľudským papilomavírusom sa zvyšuje. Pri ich liečbe má dôležitú úlohu rádioterapia. Štítna žľaza je pre svoju polohu predisponovaná k rozvoju postradiačnej dysfunkcie. V súčasnosti už existujú metódy na zníženie tohto rizika a pribúdajú aj nové možnosti liečby a dispenzárnej starostlivosti o takýchto pacientov (*Ref. 12*). Text in PDF [www.lekarskyobzor.sk](http://www.lekarskyobzor.sk).

**KLÚČOVÉ SLOVÁ:** štítna žľaza, rádioterapia, hypotyreóza, prevencia, liečba.

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### Introduction

Head and neck tumors are not rare diseases in Slovakia and represent a serious public health problem. They include tumors of the upper respiratory tract, swallowing tract, salivary glands, thyroid gland, and tumors arising from the skin, nerves, blood vessels, and other tissues. More than 90% of all head and neck malignancies are squamous cell carcinomas of the oral cavity, pharynx, and larynx, which are among the most common. Most other malignancies are adenocarcinomas, melanomas, or soft tissue tumors. In recent years, an increase in the incidence of oropharyngeal cancer has been observed, while the incidence of oral cavity cancer is decreasing. The incidence of head and neck cancer in Slovakia is 43.6 per 100,000 inhabitants in men and 6.8 per 100,000 inhabitants in women. Head and neck cancers are usually associated with smoking and alcohol, but in recent years the incidence associated with human papillomavirus (HPV) has been increasing. The typical profile of a patient with oropharyngeal cancer is changing - these are now mostly younger, educated individuals in good physical condition and social status, often without other risk factors. HPV-positive head and neck cancers respond better to chemotherapy and radiotherapy than HPV-negative cancers - they have a better prognosis but are more frequently diagnosed at a more advanced stage, as they are characterized by a relatively small primary tumor with large lymph nodes (1).

### Post-traditional hypothyroidism

Radiotherapy, alone or in combination with systemic treatment, is widely used in the treatment of head and neck tumors. Attention is focused not only on the achieved treatment results but also on treatment-related toxicity, possibilities for its mitigation and its potential prediction. During radiation therapy, the development of changes in healthy tissues cannot be completely avoided. In practice, radiotherapy toxicity is classified according to timing into acute (occurring during treatment and within three months after completion) and chronic (developing 3 to 18 months or even several years after treatment). Acute toxicity is most significant in tissues with rapidly proliferating cells. These tissues are characterized by frequent stem-cell division, from which differentiated functional cells arise (a hierarchical arrangement) - loss of these functional differentiated cells leads to the development of acute reactions. Chronic changes occur in tissues with low and slow cell turnover. The cytokine system also plays a significant role in the development of all post-radiation reactions. The changes are diverse and may include atrophy, necrosis, fibrosis or damage to the microvasculature (2).

The thyroid gland is a lobed endocrine organ located at the cranial end of the trachea. It is functionally involved in the regulation of metabolism by producing thyroid hormones - triiodothyronine and thyroxine. These hormones affect oxygen consumption, metabolic rate, growth, and

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development. Hypothyroidism is defined as a state of thyroid hormone deficiency. In clinical practice, the diagnosis of hypothyroidism is based on measuring thyroid-stimulating hormone (TSH) produced by the adenohypophysis, with a significant decrease below 0.2 milli-international units per litre (mIU/l) in blood serum (3).

Rooney (2023) conducted a systematic literature review and found that radiotherapy-induced hypothyroidism is common, occurring in 40–50% of patients, thereby requiring long-term follow-up. Risk factors for post-radiation hypothyroidism include female sex and reduced thyroid volume (<15 milliliters). The review also summarized evidence supporting dosimetry-based toxicity prediction and recommended that clinicians consider using thyroid volume-sparing dosimetric strategies to optimize radiation plans. Ongoing research aims to clarify the potential role of advanced techniques, such as particle therapy or magnetic resonance imaging-guided radiotherapy, in reducing the risk of thyroid toxicity and thereby further reducing the risk of hypothyroidism in patients with head and neck cancer, ultimately minimizing both the symptoms and financial burden associated with lifelong post-treatment hypothyroidism (4).

Post-radiation hypothyroidism usually develops relatively early, with most cases detected within 1–3 years after completion of radiotherapy. Determination of TSH levels and free thyroxine (fT4) should routinely be performed once a year in order to identify hypothyroidism in its subclinical phase. Rarely, hypothyroidism can also develop later, which is why TSH and fT4 assessment should remain a standard component of annual follow-up in long-term patients who have undergone radiotherapy to the neck or upper mediastinum. Timely detection of subclinical hypothyroidism is especially important in young women planning pregnancy. In patients treated for malignancy during childhood and in those who received cranial radiotherapy, hypothyroidism should also be considered within the spectrum of central endocrinopathies, resulting from hypothalamic (secondary hypothyroidism) or pituitary (tertiary hypothyroidism) dysfunctions (5).

### Prevention

The location of the thyroid gland renders radiation-induced damage somewhat inevitable, particularly in the context of laryngeal neoplasms. Consequently, one potential method of prevention would be to completely avoid radiation therapy. This represents a viable option in many cases of early-stage laryngeal carcinomas, where a variety of endoscopic and open partial laryngectomy procedures may be employed in lieu of definitive radiation. However, in circumstances where radiation cannot be avoided, techniques such as hyperfractionation, intensity-modulated radiation therapy, or the use of midline shielding blocks have been implemented in efforts to minimize radiation exposure to the thyroid gland (6).

As a preventive measure, medications have also been proposed. For example, the daily administration of amifostine at a dose of 910 milligrams per square meter

of body surface area, delivered as a single 15-minute infusion administered 30 minutes prior to the procedure, may exert protective effects during radiation therapy (7). Exogenous fT4 and iodine have been hypothesized to suppress TSH and decrease angiogenesis and thyroid metabolism in a rat model, potentially rendering the gland less susceptible to radiation-induced damage. Nonetheless, these interventions have not been proven to provide protection during radiation exposure (8).

Recently, the U.S. Food and Drug Administration expanded the indications for the Gardasil-9® vaccine to include the prevention of head and neck cancer. Two prospective and four retrospective studies have evaluated the vaccine for this purpose, all of which demonstrated a lower prevalence of oral infection within four years of vaccination. The vaccine efficacy was estimated to range between 88 and 93.3%. Oral fluid antibody concentrations were found to correlate with serum levels, although the protective threshold remains unknown. Similarly, the duration of protection has not yet been established. However, HPV vaccination may provide protection against reinfection at various mucosal sites in previously exposed individuals. Further studies should aim to confirm a causal relationship between vaccination and the prevention of persistent oral infection, as well as to clarify the duration of vaccine efficacy (9).

### Current treatment options

The basis of hypothyroidism treatment is hormone replacement with levothyroxine (LT4). The approximate daily dose is 1.5 microgram (µg) of LT4 per 1 kg of body weight, although this depends on several factors. In young and otherwise healthy individuals, almost the full dose can be administered, whereas in elderly and polymorbid individuals, treatment should begin with the minimum dose (12.5 µg per day), followed by gradual increases (by 50% after 4–6 weeks). The target TSH values during treatment are 1–2 mIU/l. LT4 should be taken on an empty stomach, at least 20 minutes before food and other medications, as absorption is significantly reduced otherwise. Absorption is most impaired by iron preparations, drugs that reduce gastric acidity (proton pump inhibitors, antacids), and ion exchangers (resins used in hypolipidemic treatment). Resorption is also reduced in certain diseases of the gastrointestinal tract – especially celiac disease and atrophic gastritis (10).

Before the condition stabilizes and the dose is optimized, TSH should be checked 4–6 weeks after the last dose adjustment; in a stabilized patient, annual monitoring of TSH levels and clinical status is sufficient. Higher doses are required in individuals with a high BMI (body mass index) and especially in pregnant women (for most women, the LT4 dose needs to be increased by 25–50%, depending on the TSH and fT4 values in the 4<sup>th</sup>–6<sup>th</sup> week of pregnancy). At the same time, sufficient iodine intake must be ensured throughout pregnancy and during breastfeeding, through any form of supplementation (dietary modification, pregnancy supplements, or iodine tablets), so that the total

daily intake reaches at least 250 µg of elemental iodine (11).

Unjustifiably high doses of LT4 associated with a decrease in TSH below 0.1 mIU/l demonstrably lead to health complications (osteoporosis, cardiac dysrhythmia, left ventricular dysfunction) and are associated with increased morbidity and mortality. An exception applies to suppression treatment after removal of the thyroid gland for a tumor and, in some cases, subsequent radiiodine treatment. The aim of this approach is to prevent the growth of any residual tissue or metastases by suppressing TSH production. However, such suppressive therapy is now commonly discontinued after 5–10 years, depending on the histological type and stage of the tumor, due to increasing awareness of its potential negative effects (12).

### Conclusions

The frequency of head and neck cancer in Slovakia stands at 43.6 per 100,000 individuals for men and 6.8 per 100,000 individuals for women. HPV-positive head and neck cancers are increasing in prevalence and generally demonstrate a better response to chemotherapy and radiotherapy. A comprehensive review of existing literature indicated that radiotherapy-induced hypothyroidism is prevalent, affecting 40–50% of patients. Traditional hypothyroidism typically develops relatively early, being identified in the majority of patients within 1–3 years following radiotherapy. Measurement of TSH and fT4 levels should be conducted at least once a year to identify hypothyroidism in its subclinical phase. Early identification of subclinical hypothyroidism is particularly important in young women planning pregnancy. In individuals treated for childhood cancers and in those who have received brain radiotherapy, hypothyroidism should also be regarded as a potential central endocrinopathy.

Innovative approaches such as particle therapy or magnetic resonance-guided radiotherapy lower the risk of thyroid damage. Methods such as hyperfractionation, intensity-modulated radiation therapy, or midline shielding blocks have also been utilized to protect the thyroid gland. The daily use of amifostine has been medically validated. Conversely, the use of external fT4 and iodine has not demonstrated protective effects against radiation exposure. The efficacy of the vaccine in averting head and neck cancer is estimated to range between 88 and 93.3%.

The cornerstone of hypothyroidism treatment involves LT4 hormone replacement (which should be taken on an empty stomach for at least 20 minutes before food). The typical daily dosage is generally 1.5 micrograms of LT4 per kilogram of body weight. In older and multimorbid patients, treatment begins with a minimal dose (12.5 µg per day) and is gradually increased (by 50% after a span of 4–6 weeks). Individuals with a high BMI and pregnant women generally require higher doses (for most women, the required increase is 25–50% based on TSH and fT4 levels during the 4<sup>th</sup>–6<sup>th</sup>

week of pregnancy). It is equally essential to ensure adequate iodine intake throughout pregnancy and while breastfeeding, with a total intake of at least 250 µg of elemental iodine per day. Target TSH levels during treatment should be maintained between 1–2 mIU/l. TSH levels should be assessed 4–6 weeks after the last dose adjustment; in a stabilized patient, TSH and clinical evaluations should occur annually.\*

**\*Compliance with Ethics Requirements:** Authors declare no conflict of interest regarding this article. The authors declare, that all the procedures and experiments of this research respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008 (5), as well as the national law.

**Conflict of interest:** The authors declare no conflict of interest.

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