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Post-radiation hypothyroidism in patients with head and neck tumors: An overview assessment

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Head and neck tumors are common in Slovakia. Although the number of tumors associated with smoking and alcohol is decreasing, the number of tumors associated with human papillomavirus increases. Radiotherapy plays an important role in their treatment. The thyroid gland, due to its oneself location, is predisposed to the development of post-radiation dysfunction. Nowadays, there are methods able to reduce this risk and also available new options for treatment and dispensary care for these patients. The aim of this work is to analyze the incidence and pathophysiological mechanisms of post-radiation hypothyroidism in patients with head and neck tumors, to highlight the risk factors associated with radiotherapy and evaluation of prevention possibilities and treatments, and an overview of modern therapeutic approaches. Special attention is devoted to the importance of a multidisciplinary approach and the need for a long-term patient monitoring as well as the assessment of thyroid function as an integral part of a comprehensive oncological care.

Keywords: thyroid gland, radiotherapy, hypothyroidism, prevention, treatment

Head and neck tumors are not rare diseases in Slovakia and represent a serious public health problem. The incidence of head and neck cancers in Slovakia is 43.6 per 100,000 inhabitants in men and 6.8 per 100,000 inhabitants in women. 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 the most common. Other malignancies include adenocarcinomas, melanomas or soft tissue tumors (Diba and Hlava 2015). In recent years, we have observed an increase in the incidence of oropharyngeal cancer, while the incidence of oral cavity cancer is decreasing (Chaturvedi et al. 2013). Head and neck cancers are usually associated with smoking and alcohol intake, 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, they are mostly younger educated people 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 ones. They have a better prognosis, but are more often diagnosed at a more advanced stage, as they are characterized by a relatively small primary tumor with large lymph nodes (Dobrovic and Sicak 2017).

Post-traditional hypothyroidism

Today, radiotherapy alone or in combination with systemic treatment represents a substantial tool for the cure of head and neck tumors. Attention is focused not only on the achieved treatment results, but also the toxicity of the treatment, the possibilities

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of influencing it, and its possible prediction. During radiation treatment, the development of changes in healthy tissues cannot be completely avoided (Hynkova and Dolezelova 2008). In practice, the toxicity of radiotherapy is divided into acute (during treatment and within three months after treatment) and chronic (3 to 18 months or even more years after treatment) in terms of the time factor. Acute toxicity is most significant in tissues with rapidly proliferating cells. These tissues are characterized by frequent cell division of stem cells, from which differentiated functional cells arise (hierarchical arrangement). The loss of functional differentiated cells leads to the development of an acute reaction. Chronic changes occur in tissues with low and slow cell turnover (Petera et al. 2007). The cytokine system also plays a significant role in the development of all post-radiation reactions. The changes are diverse – atrophy, necrosis, fibrosis or damage to the microvasculature (Osterreicher et al. 2005).

The thyroid gland is a lobed endocrine gland located at the cranial end of the trachea. It is functionally involved in the regulation of metabolism by producing thyroid hormones, triiodothyronine (T3) and thyroxine (T4). These hormones affect oxygen consumption, metabolic rate, growth, and development (Reiners et al. 2020). Hypothyroidism is defined as a state of thyroid hormone deficiency. To diagnose hypothyroidism in clinical practice, the determination of thyroid-stimulating hormone (TSH) produced by the adenohypophysis with a significant decrease in its level below 0.2 mIU/L in blood serum is used (Rodondi et al. 2010).

Rooney et al. (2023) have conducted a systematic review of the literature from 111 sources and found that radiotherapy-induced hypothyroidism is common occurring in 40–50% of patients requiring long-term follow-up. Risk factors for post-radiation hypothyroidism include female gender and reduced thyroid volume (<15 mL). They also have summarized the evidence for dosimetry-based toxicity prediction and recommended that clinicians may consider using the thyroid volume-sparing dosimetry to optimize radiation plans. Ongoing research could clarify the potential role of advanced techniques such as particle therapy or magnetic resonance imaging-guided radiotherapy to reduce the risk of thyroid toxicity to further reduce the risk of hypothyroidism in patients with head and neck cancers by minimizing the symptoms and financial burden associated with lifelong hypothyroidism after treatment (Rooney et al. 2023).

In 2022, a review of literature summarizing 29 observational studies involving 4,530 patients has been published. It has been found that with a median follow-up duration ranging from 1.0 to 5.3 years, the average crude incidence of post-radiation primary hypothyroidism was 41.4% (range 10%–57%). The parameters considered were primarily radiation dose and thyroid gland volume. In conclusion, to prevent this late complication, it is essential to minimize the unintentional exposure of the thyroid gland to radiation. When planning radiotherapy for head and neck tumors, the total radiation dose should be individually adjusted according to the specific thyroid gland volume (Chow et al. 2022).

The issue of fractionation is considered one of the most intriguing topics in radiation oncology. The matter is influenced by factors such as tumor cell growth kinetics, accelerated repopulation, reoxygenation, and the intrinsic radiosensitivity of the cells. Techniques based on hyperfractionation and acceleration are used (Kubes and Cvek 2008).

Hyperfractionation uses multiple daily fractions [smaller than 2.0 Gy] allowing the administration of a higher total radiation dose, thereby increasing the likelihood of tumor control. In the MARCH meta-analysis, an 8% improvement in overall survival has been demonstrated (Bourhis et al. 2006). Hyperfractionation achieves statistically significant improvement in the regional tumor control with a trend toward longer remission intervals. However, there is a significantly higher risk of acute toxicity, which is reversible and manageable. The incidence of late toxicity, however, is not increased by hyperfractionation (Fu et al. 2000).

Accelerated radiotherapy, by shortening the overall treatment duration, prevents the accelerated repopulation of tumor cells, which occurs between the 21st and 28th day of radiotherapy and is one of the reasons for radiotherapy failure. The benefit of accelerated radiotherapy has been demonstrated by a significant improvement in five-year overall patient survival (75% vs. 33%) (Skladowski et al. 2006). For example, the technique delivering 69.5 Gy over 5 weeks (33 days) shows acceptable treatment tolerance and excellent therapeutic outcomes (Terhaard et al. 2005).

Post-traditional hypothyroidism is usually turned up relatively early, in most patients it is detected within 1–3 years after completed radiotherapy. Determination of TSH levels and free thyroxine (fT4) should normally be performed once a year in order to identify hypothyroidism in the subclinical phase. The hypothyroidism can rarely occur also later, therefore the determination of TSH and fT4 become a standard part of annual inspections of long-term cured patients after radiotherapy to the region of the neck and upper mediastinum (Ballova 2017).

Decreased thyroid function may develop as early as one month after therapy, but it can also have a delayed onset. In some cases, it can appear more than five years after the treatment. Therefore, it is recommended to perform thyroid function tests including TSH and fT4 determination before the therapy initiation. These tests should be repeated one month after the completion of therapy and subsequently at regular intervals every 6–12 months (Miller and Agrawal 2009).

Timeous detection of subclinical hypothyroidism is especially important in young women who are planning pregnancy. In patients treated for malignancy in childhood age and patients after brain radiotherapy, it is also necessary to think about the hypothyroidism as part of central endocrinopathies, as a result of hypothalamic (secondary hypothyroidism) and pituitary (tertiary hypothyroidism) dysfunctions (van Dorp et al. 2012).

Prevention

The location of the thyroid gland renders radiation-induced harm somewhat inevitable, particularly in the context of laryngeal neoplasms. It follows that one method of prevention would be to completely avoid radiation therapy. This certainly represents a viable option among numerous early-stage laryngeal carcinomas, wherein 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 midline shielding blocks have been used in efforts to spare the thyroid (Miller and Agrawal 2009).

As a means of prevention, medications have also been proposed. For example, daily administration of amifostine at a dose of 910 mg per m^2 of body surface in a single 15 min infusion given once daily 30 min before the procedure may have some protective effects during radiation therapy (Dorr and Holmes 1999). Exogenous fT4 and iodine have been hypothesized to suppress TSH and decrease angiogenesis and thyroid metabolism in a rat model. These properties are believed to render the gland less susceptible to radiation-induced damage. Nonetheless, these interventions have not been found to be protective during radiation exposure (van Santen et al. 2006).

Recently, the U.S. Food and Drug Administration (FDA) has 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 the prevention of head and neck cancer, all of which demonstrated a lower prevalence of oral infection within 4 years of vaccination. Vaccine efficacy has been estimated to be 88% to 93.3%. Oral fluid antibody concentrations were found to correlate with serum levels, but the threshold for protection is unknown. The duration of protection has not been established. However, HPV vaccination may provide protection against reinfection at various mucosal sites in previously exposed individuals. Further studies should be aimed to confirm a causal relationship between vaccination and the prevention of persistent oral infection and examining the duration of efficacy (Diana and Corica 2021).

Current treatment options

The basis of the hypothyroidism treatment is hormone replacement with levothyroxine (LT4). The approximate daily dose is 1.5 μg of LT4 per 1 kg of body weight, but it depends on a number of factors. In young and otherwise healthy individuals, we can immediately administer almost the full dose; however, in elderly and polymorbid individuals, we start with the minimum dose (12.5 μg per day) and increase it gradually (after 4–6 weeks by 50%). The target TSH values during treatment are 1–2 mIU/L. LT4 should be taken on an empty stomach at least 20 min before taking food and other medications, because otherwise resorption is reduced. This is reduced most by iron preparations including drugs that reduce the gastric acidity (proton pump inhibitors, antacids) and ion exchangers (resins in hypolipidemic treatment). Resorption is also reduced in some diseases of the gastrointestinal tract, especially celiac disease and atrophic gastritis (Jiskra et al. 2003).

Before the condition stabilizes and the dose is optimized, TSH is checked 4–6 weeks after the last adjustment. In a stabilized patient, TSH and clinical condition inspections once a year are sufficient. Higher doses are needed for people with high BMI (body mass index) and especially pregnant women (for most women, the dose needs to be increased by 25–50% depending on the TSH and fT4 results in the 4th–6th week of pregnancy). At the same time, it is necessary to ensure sufficient iodine intake throughout pregnancy and during breastfeeding by supplementation in it at any form (change of diet, pregnancy food supplements, and iodine tablets).

However, the total intake should reach at least 250 μg of elemental iodine per day (Abalovich et al. 2007).

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. The exception is suppression treatment after removal of the thyroid gland for a tumor and possibly. Subsequent treatment with radioiodine. Its aim is to prevent the growth of any residual tissue or metastases by suppressing TSH production. However, this is also currently being discontinued after 5–10 years depending on the histological type and stage of the tumor due to the awareness of possible negative impacts (Jiskra 2010).

Hormone replacement therapy with LT4 is the cornerstone of hypothyroidism treatment, which needs to be adjusted to the individual needs of the patient, especially in the case of older adults, pregnant women or those with other health problems. Failure to adjust the proper dose of LT4 may lead to serious health complications such as osteoporosis or cardiovascular diseases. Therefore, it is essential not only to identify hypothyroidism early, but also regularly monitor TSH levels and adjust medication doses according to the patient's current condition.

Monitoring patients even years after radiotherapy has ended is equally important, as hypothyroidism can develop with a delayed onset. Special attention should be given to younger female patients planning pregnancy given the potential impact on fertility and pregnancy.

Summary

The prevalence of head and neck cancers in Slovakia is 43.6 per 100,000 men and 6.8 per 100,000 women. The prevalence of HPV-positive head and neck cancers has been increasing in recent years, though they tend to respond better to chemotherapy and radiotherapy. A comprehensive review of the existing literature has shown that radiation-induced hypothyroidism is very common affecting 40–50% of patients. The risk of developing hypothyroidism is significantly influenced by factors such as the patient's gender and the thyroid gland volume before treatment. Early diagnosis and regular monitoring of TSH levels are crucial for effective prevention and treatment of this endocrine disorder.

It has been found that thyroid-sparing radiotherapy techniques, such as intensity-modulated radiation therapy and hyperfractionation, can significantly reduce the risk of post-radiation hypothyroidism. These advanced methods may provide a pathway to optimizing treatment, not only by reducing radiation dose to the thyroid gland, but also by minimizing the long-term occurrence of side effects.

Conclusion

Despite advances in head and neck cancer treatment techniques and improved radiotherapy approaches to protect the thyroid gland, post-radiation hypothyroidism remains a common late complication. Therefore, it is still essential for doctors to consider individual risks and tailor the treatment plan for each patient. A multidisciplinary approach involving the oncologist, endocrinologist, and general practitioner plays a key role in this process. Looking forward, the challenge will be to better identify patients at higher risk of developing hypothyroidism. A comprehensive approach will thus minimize the consequences of this complication and improve the quality of life for long-term cancer survivors.

Future research should focus on radiation techniques optimization and new methods exploring for the prevention and treatment of post-radiation hypothyroidism to reduce its long-term burden on patients and improve the quality of their life.

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