VIA MEDICA

ORIGINAL ARTICLE

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Late side effects in the thyroid gland in association with transforming growth factor β1 (TGF-β1) levels in patients with head and neck cancers treated with radiation therapy

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Oncology in Clinical Practice
DOI: 10.5603/ocp.100103

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. Radiotherapy and radiochemotherapy are, besides surgery, common treatments for head and neck cancers. Despite using advanced modern radiation techniques, the late side effects are a serious problem. From a multitude of cytokines and growth factors shown to contribute to the injury process after cancer therapy, transforming growth factor β1 (TGF-β1) is among the most fundamental ones. The study evaluated if a high level of TGF-β1 before, during, and after treatment can predict thyroid gland fibrosis, which causes hypothyroidism, one of the common late side effects of head and neck cancer irradiation.

Material and methods. Fifty-six patients with head and neck cancer who underwent radiation alone or concomitant chemoradiotherapy were included in the study. Analyzed variables included thyroid stimulating hormone (TSH), volume and echogenicity of the thyroid gland, and the level of TGF-β1.

Results. In comparison to the initial level, statistically significant increased levels of TSH and statistically significant decreased volume of the thyroid gland were observed 6 and 12 months after irradiation. Moreover, statistically significant decreased levels of TGF-β1 were observed one month after irradiation.

High levels of TGF-β1 before treatment or changes in TGF-β1 levels during and after treatment influenced changes neither in TSH levels nor in volume and echogenicity of the thyroid gland one year after radiotherapy.

Conclusions. Early evaluation of TSH after radiation is needed to predict hypothyroidism. High TGF-β1 levels before and changes during and after radiation cannot predict hypothyroidism one year after treatment.

Keywords: cytokin concentration of TGF- β1, radiation-induced hypothyroidism, head and neck cancers

Oncol Clin Pract

Introduction

Radiotherapy and radiochemotherapy, along with surgery, are standard treatments for head and neck cancers. Early side effects of radiation are temporary and disappear after treatment. Late reactions, like hypothyroidism, may occur around 6 months post-radiotherapy. The risk of hypothyroidism after high-dose neck

Received: 10.04.2024 Accepted: 27.05.2024 Early publication: 24.06.2024

irradiation is 20–50% [1]. On average, hypothyroidism appears between 1.4 and 1.8 years after treatment, but changes in thyroid stimulating hormone (TSH) levels are observed earlier, even 3 months after completion of radiotherapy [2] The first symptoms of hypothyroidism may become apparent between 8 months and 2 years after irradiation. The minimum dose likely to cause endocrine dysfunction of the thyroid gland is 10 Gy. Absorption of a mean dose equal to 50 Gy and above results in a significant risk of primary hypothyroidism [3]. Hypothyroidism occurs due to progressive fibrosis of the gland following radiotherapy, and it is visible in the ultrasound examination. As a result of the appearance of connective tissue fibers, there is a gradual increase in echogenicity, which progresses over months and years [4].

The irradiation technique contributes to the risk of late complications in the thyroid gland. It is recommended to use the intensity-modulated radiotherapy (IMRT) technique and to contour the thyroid gland at the planning stage of radiotherapy [5]. Most recommendations suggest not exceeding a mean dose of 45 Gy in the thyroid gland to minimize the risk of hypothyroidism [6].

Ionizing radiation can alter normal levels of many molecules, including cytokines, which induces gradual damage to the healthy tissues under irradiation [7]. Among these, transforming growth factor β1 (TGF-β1) plays a special role. Despite being a regulator of wound healing, it is crucial in the pathogenesis of the reaction to radiation [8, 9]. Transforming growth factor β1 is called multifunctional. Its involvement in the mechanism of fibrosis is the most widely understood, and most data are related to the isoform TGF-β1 [10, 11]. Increased levels of cytokine are observed in diseases with chronic fibrosis [12, 13]. Many data showed massive fibrosis in lung tissue after radiation in association with high levels of TGF-β1 [14]. There are no data indicating the presence of that correlation with fibrosis in the thyroid gland after radiation of the neck area.

Objectives of the study

1. Study TSH level changes before and after head and neck cancer radiotherapy to determine late radiation-related thyroid dysfunction.
2. Examine thyroid gland changes *via* ultrasound before and after head and neck cancer radiotherapy to identify fibrosis progression.
3. Analyze TGF-β1 changes and the impact of radiotherapy on TSH levels post-treatment. Study the effect of TGF-β1 pre-treatment on TSH changes.
4. Investigate how TGF-β1 changes during radiotherapy relate to thyroid volume and echogenicity changes. Explore pre-treatment TGF-β1's effect on these thyroid changes.

Material and methods

Patients and methods

Fifty-six patients with head and neck cancer who underwent radiation alone or concomitant chemoradiotherapy were included in the study. They started primary radiation therapy between July 2014 and March 2016.

The inclusion criteria were:

1) patients with confirmed head and neck carcinoma diagnosed through excisional biopsy and imaging including computer tomography (CT), magnetic resonance imaging (MRI), ultrasonography (USG), and positron emission tomography/computed tomography (PET/CT) if needed;
2) patients eligible for standalone or combined radical irradiation with chemotherapy.

In the chosen group of patients, there were both men (35) and women (21) aged 38–74. The average age was 57 years. They suffered from cancer of the oropharynx (30 patients), larynx (14), nasopharynx (7), or hypopharynx (5). Nineteen patients were found to be World Health Organization (WHO) grade [15] 0 and the remaining 37 patients were found to be WHO grade 1. Thirty-five patients received simultaneous integrated boost in intensity-modulated radiotherapy (SIB-IMRT) and an overall dose of 67.5–66/60/54 Gy in 2.25–2.2/2/1.8 Gy per fraction. Twenty-one patients received conventional fractionation and an overall dose of 70/63/59.5 Gy in 2/1.8/1.7 Gy per fraction. Forty-seven patients received combination therapy. The mean dose for the thyroid gland was 48 Gy (3 Gy to 63 Gy). In 27 patients, the thyroid gland received a mean dose exceeding 45 Gy.

Forty-two patients had all the follow-up examinations during the 12-month follow-up according to the protocol. The reasons for not completing the planned follow-up period included local failure to cure (2 patients), early recurrence or appearance of distant metastases (3 patients), failure to attend follow-up and failure to contact the patient (8 patients), and death of the patient for non-oncological reasons (1 patient).

Data collection

Thyroid stimulating hormone levels were checked before treatment, at 6 and 12 months post-radiation to predict thyroid dysfunction risk. Ultrasound assessed thyroid volume and echogenicity before treatment, at 6 and 12 months post-irradiation for fibrosis features. TGF-β1 plasma levels were examined pre-treatment, during (weeks 2, 3, and 4), immediately after treatment, and one month later (6 total times).

Thyroid dimensions were measured using cursors on outer lobe outlines, and volume was calculated [volume (V) = 0.5 × width (W) × height (H) × length (L)].

Echogenicity was measured using the NUSV660 ROI (Region of Interest Q-App), a dedicated application by Philips. The application utilizes a grayscale and analyzes the intensity of the signal returning to the transducer, expressed in decibels (dB).

Echogenicity measurements were performed in the central part of the thyroid lobes in an area of 1 × 1 cm. The average value was determined collectively for both lobes.

Statistical analysis

T-tests compared normally distributed variables, while U Mann-Whitney or Wilcoxon tests were used for other distributions.

The dynamics of TGF-β1 and its impact on volume, echogenicity, and TSH were analyzed using a Generalized Linear Model (GLM) for repeated measures with IBM SPSS Statistics 23.0. The significance level was set at $\alpha = 0.05$.

Results

Analysis of TGF-β1 levels

Table 1 shows the change in TGF-β1 levels for all patients (56) at the respective time points.

In comparison to the initial measurement, a decreased level of TGF-β1 was observed one month after irradiation, $p < 0.001$.

Analysis of TSH

The median of TSH for all patients (56) before treatment was 0.927 μIU/mL (reference range 0.3–4.2 μIU/mL); 6 months after radiotherapy, it was 1.358 μIU/mL; 12 months after radiotherapy, it was 1.611 μIU/mL.

In comparison to the initial measurement, there was a statistically significant increase in TSH levels at 6 ($p < 0.001$) and 12 ($p < 0.001$) months after radiotherapy.

Nevertheless, changes in TGF-β1 levels during and after treatment did not influence changes in TSH levels one year after radiotherapy, $p = 0.12$. High levels of TGF-β1 before treatment did not influence changes in TSH levels one year after treatment, $p = 0.773$.

Volume and echogenicity of the thyroid gland *vs.* TGF-β1 levels

In comparison to the initial measurement, a decreased volume of the thyroid gland was observed 6 months (19.61 *vs*. 16.77 mL; $p < 0.001$) and 12 months (19.61 *vs*. 15.28 mL; $p < 0.001$) after irradiation In comparison to the initial one, no difference was shown in echogenicity 6 months (31.70 *vs.* 31.28 dB; $p = 0.397$) and 12 months (31.70 *vs*. 31.75 dB; $p = 0.172$). Supplementary Table S1 presents the changes in volume and echogenicity of the thyroid gland after irradiation in all patients (56) at the respective time points.

Changes in TGF-β1 levels during and after treatment did not influence changes in volume and echogenicity of the thyroid gland one year after radiotherapy, $p = 0.169$ and $p = 0.693$, respectively. High levels of TGF-β1 before treatment did not influence changes in volume and echogenicity of the thyroid gland one year after radiotherapy, $p = 0.276$ and $p = 0.5$, respectively.

Discussion

Despite data indicating the manifestation of hypothyroidism on average 1.4–1.8 years after radiotherapy [4, 5], the results of many studies suggest the risk of complications already in the first year after treatment [1, 16, 17]. Some studies found features of subclinical and symptomatic hypothyroidism 3 months after irradiation [4, 5, 18].

In our study, there was a statistically significant reduction in thyroid gland volume six months after treatment and further reduction at one-year follow-up. These changes may be indicative of an incipient fibrosis process due to radiotherapy. Echogenicity measurements are usually based on visual assessment in

Table 1. Transforming growth factor β1 (TGF-β1) levels for all patients (56)

Measurement*	Minimum [pg/mL]	Max [pg/mL]	Mean [pg/mL]	Standard deviation
1	25879	79127	43998	11661
2	7973	84000	32257	14097
3	12454	74124	30167	11419
4	8410	76689	28347	12911
5	5942	84000	33275	17158
6	4579	63870	27633	9397

*1 — before treatment, 2 — after the second week of radiotherapy, 3 — after the third week of radiotherapy, 4 — after the fourth week of radiotherapy, 5 — at the end of radiotherapy, 6 — one month after the end of radiotherapy

which thyroid gland brightness is compared to that of the sternocleidomastoid muscle (reference point) [8, 19]. The assessment of these features is highly subjective, and accuracy largely depends on the ultrasonographer's experience. Some authors suggest the superiority of visual assessment in evaluating echogenicity, claiming that measurements using dedicated software are time-consuming and unintuitive [20].

Other studies have shown the influence of the radiotherapy technique on the risk of complications from the thyroid gland. The introduction of the IMRT technique in irradiating tumors of the head and neck region was initially associated with a higher incidence and shorter time to manifestation of hypothyroidism compared with the older 3D technique [8]. This was related to a higher dose covering the thyroid gland in intensity-modulated beam radiotherapy. Contouring of the thyroid gland using the IMRT technique as a critical organ resulted in a reduction in the mean dose to the gland. Most data suggest that a mean dose of 45 Gy should not be exceeded in the thyroid gland [21].

There are no studies in the literature on the effect of high concentrations of the cytokine on the risk of fibrosis of the thyroid gland tissue after irradiation of the neck region. Most have looked at the effect of TGF-β1 on this process in lung tissues. In a study from 1993, patients with advanced breast cancer were treated with high-dose chemotherapy, autologous bone marrow transplantation, and complementary involved-field radiotherapy (IFRT) [22]. Subsequent work by the author confirmed the association of TGF-β1 levels with a higher risk of severe late pulmonary complications after irradiation [23, 24].

It was found that persistently high cytokine levels after treatment indicated a higher risk of late reaction to radiation in the lung in the form of fibrosis [22, 25–28].

An association between high baseline TGF-β1 and a higher risk of late reaction to radiation in the breast has been shown [29, 30].

In this study, we analyzed the dynamics of the change in cytokine levels before, during, and after radiotherapy. We also examined its effect on changes in the hormonal profile and ultrasound images of the thyroid one year after treatment. A statistically significant decrease in cytokine levels was found after irradiation. There was no correlation between changes in TGF-β1 levels during and after treatment and changes in TSH levels, volume, and echogenicity of the thyroid gland at one-year follow-up after irradiation. High, sustained TGF-β1 levels one month after the end of radiotherapy did not correlate with a higher risk of increased TSH, decreased volume, and increased thyroid echogenicity 12 months after treatment. There was no correlation between baseline TGF-β1 levels and changes in TSH levels, volume, and echogenicity of the thyroid gland one year after the end of irradiation. The reason for this may be that the number of patients in our study was too small. The one-year follow-up period may also have been too short to observe clear changes indicative of emerging thyroid gland dysfunction.

The source of TGF-β1 may be the tumor [31]. In one study, a significant reduction in TGF-β1 levels was found after breast cancer surgery, supporting the thesis that the cytokine is produced by the tumor [32]. It has also been suggested that high cytokine levels before oncological treatment may influence poorer prognosis [33–35]. Among the functions of TGF-β1 are involvement in angiogenesis [36], induction of metastasis [37], suppression of the immune system [38], and triggering resistance to radiochemotherapy [39]. However, baseline TGF-β1 levels did not always correlate with the tumor stage. This relationship was confirmed in breast [40], gastric [41], liver [42], colorectal [43], or renal [44] cancers. Equivocal data were reported for prostate [45–47], head, and neck cancers [48]. It has also been found that cytokine levels in the blood may not reflect important production and concentrations in the tumor microenvironment [49]. The exact mechanism of TGF-β1 action at the cellular level in head and neck cancers is still unclear [50].

In the study that included patients with head and neck tumors, the dynamics of the decrease in TGF-β1 levels did not predict treatment response [50]. However, as we have emphasized, the treatment-induced decrease in TGF-β1 levels may not be measurable by an increase in cytokine levels due to tissue damage after irradiation. This relationship may also depend on other factors, such as the pathomorphological type of the tumor, applied treatment, and personal characteristics related to immune function [50].

In the study, cancer treatment did not raise cytokine levels. TGF-β1 levels dropped significantly post-irradiation. Cytokine changes might have been caused by treatment modes or tumor regression. Further research is needed on TGF-β1 and thyroid tissue fibrosis. Complex actions of TGF-β1 make analysis challenging. Hypothyroidism, a serious outcome after neck irradiation, and TGF-β1's role in fibrosis and cancer require more attention.

Conclusions

Hypothyroidism is a common late side effect of radiotherapy for head and neck cancer. Early evaluation of TSH after radiation is needed to predict the disease. High TGF-β1 levels before and changes during and after radiation cannot predict hypothyroidism one year after treatment.

Article Information and Declarations

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restriction.

Ethics statement

Written informed consent for publication was obtained from all participants. Bioethics Committee approval for the study was obtained.

Author contributions

K.W.-K.: conceptualization (the idea of writing the manuscript, choosing the topic, defining the purpose of the manuscript), methodology (data search strategy), analysis, interpretation of the data, drafting of the manuscript, preparation of the manuscript and execution of editing and revision of the manuscript after receiving reviews, visualization, project management, critical revision for important intellectual content; D.K.: drafting of the manuscript, critical revision for important intellectual content, analysis, interpretation of the data, supervision; M.N., M.F., B.K., P.J., A.J.: interpretation of the data; M.K., M.D.: critical revision for important intellectual content; W.M.: statistical analysis of the study; A.K.: critical revision of the manuscript for important intellectual content, supervision.

Funding

None.

Acknowledgments

None.

Conflict of interest

The authors have no conflicts of interest to disclose.

Supplementary material

Table S1.

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Supplementary material

Table S1. Changes in volume and echogenicity of the thyroid gland after irradiation in all patients (56) at the respective time points

	n	Minimum	Max	Average	SD
Volume 0 [mL]	56	7.79	54.10	19.61	10.32
Volume 6 [mL]	47	3.29	39.80	16.77	8.97
Volume 12 [mL]	42	2.43	46.94	15.28	8.99
Echogenicity 0 [dB]	56	15.34	46.61	31.70	7.13
Echogenicity 6 [dB]	47	15.40	45.98	31.28	7.37
Echogenicity 12 [dB]	42	19.97	43.30	31.75	6.65

0 — measurement before treatment; 12 — measurement 12 months after treatment; 6 — measurement 6 months after treatment; n — number of patients; SD — standard deviation;