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Thyroid dysfunction after intra-arterial chemotherapy for hypopharyngeal and laryngeal cancer

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ABSTRACT

Objective: Hypothyroidism is a late side effect after curative radiotherapy in the head and neck region. Superselective intra-arterial chemotherapy (SSIAC), when combined with radiation (SSIAC-R), shows higher control potential for locally advanced head and neck cancers, which is attributable to a delivery of higher concentrations of chemotherapeutic agents. However, it could enhance damages in the normal tissues. Hypothyroidism is a late adverse effect after curative radiotherapy in the head and neck region. This study focuses on the toxic effect of treatment modality for thyroid function.
Methods: A retrospective analysis was performed to examine patients' thyroid function after SSIAC-R for laryngeal and hypopharyngeal cancer.
Results: Hypothyroidism was observed in 21 (77.8%) of 27 patients receiving SSIAC-R, 4 (33.3%) of 12 patients treated with radiation alone, and 7 (41.1%) of 17 who underwent systemic chemoradiotherapy. The number of administered vessels significantly correlated with the incidence of developing hypothyroidism among SSIAC-R treated patients ($P = 0.03$).
Conclusion: Concurrent setting of SSIAC with radiation significantly raises the possibility of hypothyroidism. Therefore, monitoring late complications of therapeutic procedures is essential during follow-up visits.

1. Introduction

The management of head and neck squamous cell carcinoma (HNSCC) requires careful consideration for disease control, treatment consequences, and patients' quality of life (QOL). Radiotherapy, utilized alone or in combination with concomitant chemotherapy, is an integral part of conventional HNSCC treatment. However, hypothyroidism is a significant late side effect after definitive radiotherapy in the head and neck region [1–3]. Its clinical symptoms include fatigue, weakness, cold intolerance, weight gain, cognitive dysfunction, constipation, dry skin, hoarseness, edema, hearing loss, myalgia, paresthesia, depression, menorrhagia, and arthralgia [4]. Although such symptoms could severely affect patients' QOL, they are often vague and overlapping with those of other conditions including HNSCC. Additionally, since many head and neck surgeons are not aware of hypothyroidism, thyroid function is not routinely assessed in HNSCC patients after therapy.

For the purpose of morphological and functional organ preservation, superselective intra-arterial chemotherapy (SSIAC) was first introduced by Robbins et al. as radiotherapy and concomitant intra-arterial cisplatin (RADPLAT) to specifically deliver chemotherapeutics to the tumor bed and overcome tumor resistance to chemoradiotherapy (CRT) [5]. In the last decade, RADPLAT and RADPLAT-based protocols have been successfully implemented by an increasing number of institutions. In comparison with systemic chemotherapy, SSIAC offers the potential of delivering higher concentrations of chemotherapeutic agents while reducing systemic adverse effects. Such an approach has resulted in a favorable rate of local control and disease-specific survival [6,7]. Although several studies have assessed health-related QOL after SSIAC, none has evaluated patients' thyroid function after treatment.

In the present study, a retrospective analysis was conducted to compare the thyroid function of laryngeal and hypopharyngeal cancer patients receiving SSIAC combined with radiation

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(SSIAC-R), radiation alone, or systemic concurrent CRT. We also evaluated the influence of tumor site, total radiation dose, age, total amount of cisplatin, and the number of administered vessels in SSIAC on the risk of developing hypothyroidism.

2. Materials and methods

2.1. Patients

Data on 56 patients (51 men and 5 women) histologically diagnosed with squamous cell carcinoma of the larynx or hypopharynx at Kanazawa University Hospital from August 2000 to April 2013 were retrospectively analyzed. Patients with a history of thyroid disease or surgery that could affect response and those who had recurrence diseases were excluded.

2.2. Study design

All patients received a curative radiation dose between 60 and 70 Gy. Conventional radiotherapy was delivered at 2 Gy per fraction. The thyroid glands were within the radiation field. For patients in the CRT group, cisplatin was administered intravenously at 80 mg/m^2 on days 1, 21, and 42. For those in the SSIAC-R group, cisplatin was administered intra-arterially 3 or 4 times at 100 mg/body [6]. After transfemoral carotid arteriography for the assessment of blood supply to the tumor, the contribution of each vessel was determined using real-time angio-computed tomography. If the blood flow to the primary tumor was mostly via a single vessel, 100 mg of cisplatin was administered through that artery. In cases when the tumor was supplied by two or three different blood vessels, the cisplatin dose was distributed to each artery according to its contribution to the tumor perfusion. Additional cisplatin (50 mg/body) was also infused intra-arterially to lymph nodes larger than 3 cm in diameter.

For thyroid function assessment, baseline serum concentrations of thyroid stimulating hormone (TSH, reference range: 0.27–4.20 mU/ml), free triiodothyronine (FT3, reference range: 2.3–4.0 pg/ml), and free thyroxine (FT4, reference range: 1.0–1.8 ng/dl) were measured in all cases after treatment. Subclinical hypothyroidism was defined as high levels of TSH and normal FT4 levels, whereas clinical hypothyroidism involved high TSH and low FT4 levels. Three patients underwent salvage surgery. Those undergoing hemithyroidectomy or total thyroidectomy were excluded from this study. Thyroid function was assessed within 1 month after the completion of the initial treatment for all patients, and every 6 months for the patients who developed either symptomatic or asymptomatic hypothyroidism. The latency period for hypothyroidism was measured from the end of initial treatment until the occurrence of hypothyroiditis. Levothyroxine was provided to clinical hypothyroidism and symptomatic patients with subclinical hypothyroidism [8].

2.3. Risk for hypothyroidism

The risk factors for hypothyroidism, including age, tumor site, total dose of radiation, cumulative dose of cisplatin, and the number of administered vessels in SSIAC were evaluated.

2.4. QOL assessment

After providing written informed consent, all patients responded to a questionnaire survey from April to December 2013. Their hypothyroidism-related QOL after treatment was measured by appetite, depression, cold intolerance, fatigue, and weakness. Symptoms were graded on a scale of 0–4 points (0 = no symptoms, 1 = mild, 2 = moderately severe, 3 = severe, and 4 = very severe symptoms).

2.5. Statistical analysis

Analysis of variance was used to determine differences among groups. The Fisher's exact test was employed to identify potential risk factors for hypothyroidism from relevant clinical information (tumor site, age, total dose of radiation, total amount of cisplatin, and the number of administered vessels in SSIAC). All statistical tests were two-tailed with a P value of <0.05 considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 10.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Patient demographics

Fifty-six patients (51 men and 5 women) were recruited for this study. The main characteristics of all enrolled patients are summarized in Table 1. The age range was 52–87 years, with a mean of 68.9 years and a median of 67.5 years. The primary tumor sites were the larynx ($n = 33$) and hypopharynx ($n = 23$). Tumor-node-metastasis staging according to the 2009 Union for International Cancer Control classification criteria8 (seventh edition) included 18 cases of stage I/II and 38 of stage III/IV. Of all characteristic measured, AJCC stage distribution of patients with RT was statistically early-stage disease among the three groups. All patients were evaluated by an endoscopic examination, computed tomography, and positron emission tomography after completing therapeutic protocols. The median follow-up time was 26.9 months (range, 1–112 months).

Table 1
Demographic data of the patients.

Characteristics	All cases ($N = 56$)	SSIAC-R ($N = 27$)	RT ($N = 12$)	CRT ($N = 17$)	P
Age					
Mean	68.9 years	68.7 years	68.9 years	70.6 years	0.496
Median	67.5 years	68 years	68.5 years	71 years	
Gender					
Male	51	21	11	16	0.702
Female	5	3	1	1	
AJCC stage					
I/II	18	1	11	6	0.001[#]
III/IV	38	26	1	11	
Diagnosis					
Larynx	33	18	9	6	0.056
Hypopharynx	23	9	3	11	

P values are from ANOVA for continuous variables.
[#] P value <0.05.