Effects of Head and Neck Cancer Treatments on Gonadal Function in Adolescent and Young Adult Patients

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Abstract

Otorhinolaryngologists often encounter and treat adolescents and young adults (AYA; aged 15–39 years) with cancer. Thus, it is important for them to recognize the impact of cancer treatment on the fertility of patients from this generation. In this retrospective review, we evaluated 60 AYA patients who were diagnosed with head and neck cancer at our department. Regarding the risk of gonadal toxicity due to cancer treatment, according to the classification by The Japan Society of Clinical Oncology Clinical Practice Guidelines 2017 for Fertility Preservation in Childhood, Adolescent, and Young Adult Cancer Patients, one and three patients were found to be at high and intermediate risks, respectively. However, the risk of gonadal toxicity was not adequately explained in the guidelines; hence, they need to be revised. To preserve the fertility of AYA patients with head and neck cancer, patient information should be shared with appropriate obstetrics and gynecology or urology specialists before treatment. Furthermore, it is important to build a reproductive medicine network and ensure prompt collaboration with oncologists before initiating cancer treatment.

Keywords
- AYA
- head and neck cancer
- oncofertility

Introduction

It is known that otorhinolaryngologists often encounter and treat adolescents and young adults (AYA) with cancer. Notably, there are several definitions for AYA, and in the present study, we defined AYA as individuals aged between 15 and 39 years.[1] The Japan Society of Clinical Oncology has published the Clinical Practice Guidelines 2017 for Fertility Preservation in Childhood, Adolescent, and Young Adult Cancer Patients (i.e., fertility preservation guidelines). These guidelines include descriptions of the effects of cancer therapies on reproductive function as well as indications for fertility-preserving treatment.[2] It has been reported that the management of fertility preservation during cancer treatment by otorhinolaryngologists is insufficient compared with that by physicians of other disciplines.[3] As otorhinolaryngologists often treat patients with cancer from the AYA generation, they need to develop a better understanding of the effects of cancer treatment on gonadal function and methods of fertility preservation. Therefore, in

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the present study, we retrospectively reviewed data from AYA patients diagnosed with head and neck cancer at our department to investigate the characteristics of the disease in AYA and the impact of treatment on gonadal function.

Materials and Methods

We investigated 60 patients (aged 15–39 years at the initial consultation) hospitalized between April 2011 and March 2021 for head and neck cancer treatment at the Department of Otolaryngology–Head and Neck Surgery, Kanazawa University. The following data were retrospectively collected: age, sex, primary tumor location, tumor-node-metastasis (TNM) classification, stage, specific type of treatment, and 5-year survival rate. Patients who underwent treatments associated with a risk of gonadal toxicity were identified from medical records and classified according to the degree of risk of gonadal toxicity associated with chemotherapy and radiotherapy, as described in the fertility preservation guidelines.[2] The TNM Classification of Malignant Tumors, 8th edition, by the Union for International Cancer Control Classification of Malignant Tumors was used for this study. Furthermore, the Kaplan–Meier method was used to analyze overall survival rates separately for patients with thyroid cancer and those with nonthyroid head and neck cancer.

Results

Patient Background

The primary tumors were in the thyroid gland, oral cavity, major salivary glands, epipharynx, nasal and paranasal sinuses, oropharynx, larynx, and thyroglossal duct in 35, 8, 5, 5, 3, 2, 1, and 1 cases, respectively. ►**Figs. 1** and **2** compare the number, age, and sex of patients; stage of cancer; and specific type of treatments used between patients with primary tumors in the thyroid gland and those with primary tumors in other sites.

Specific Types of Treatment

All patients with thyroid cancer underwent surgery as the first-line therapy. Among them, radioiodine therapy was administered to 14 patients, whereas none of the patients underwent chemotherapy, molecular targeted therapy, or radiotherapy. Overall, 12 patients with nonthyroid head and neck cancer underwent chemotherapy and/or radiotherapy; of them, some underwent chemotherapy and/or radiotherapy in combination with surgery (►**Table 1**). Furthermore, all patients with nasopharyngeal cancer underwent alternating chemoradiotherapy (three cycles of systemic chemotherapy with 5-FU 800 mg/m^2/day [days 1–5, days 40–44, and days 74–78] and cisplatin 50 mg/m^2/day [days 6–7, days 45–46,

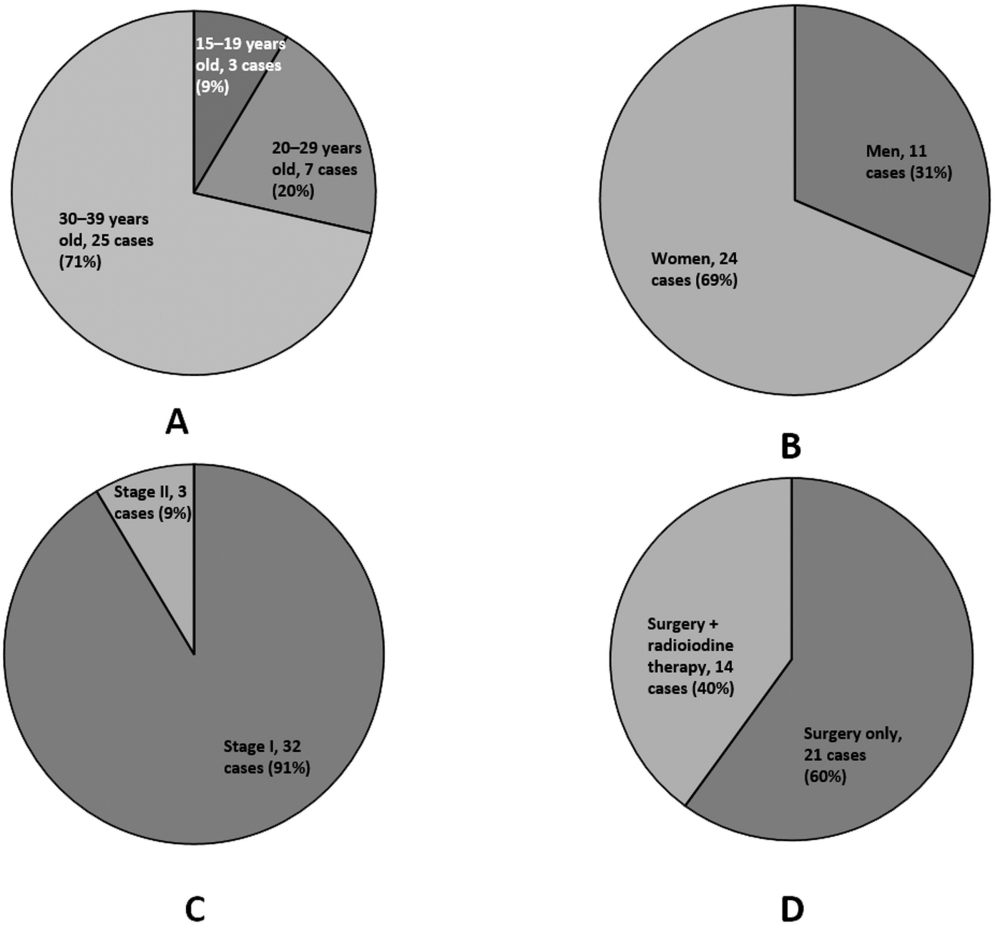

Fig. 1 Characteristics of patients with thyroid cancer: (**A**) age distribution; (**B**) sex; (**C**) stage; (**D**) specific type of treatment.

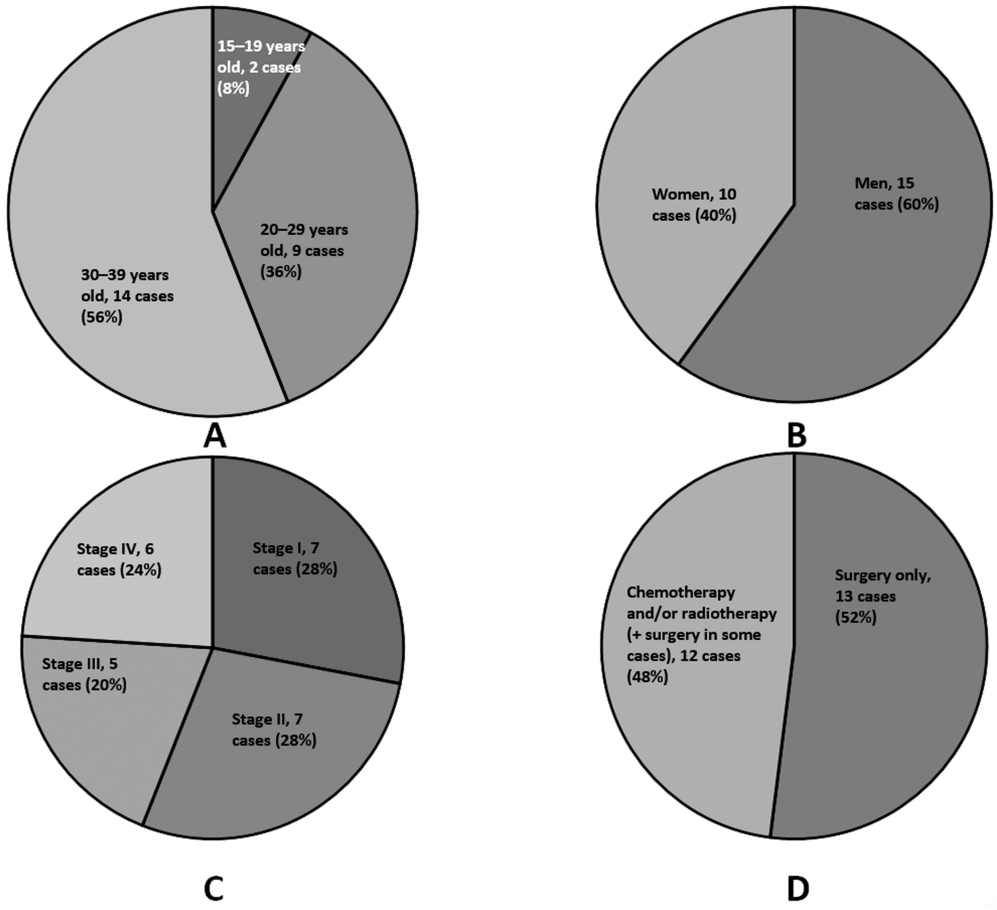

Fig. 2 Characteristics of patients with nonthyroid head and neck cancer: (**A**) age distribution; (**B**) sex; (**C**) stage; (**D**) specific type of treatment.

and days 79–80] along with radiotherapy between the cycles)[4] as the first-line therapy.

Effects on Gonadal Function

The risks of gonadal toxicity associated with chemotherapy and radiotherapy described in the fertility preservation guidelines[2] for men and women are shown in ►**Tables 2** and **3**, respectively. There are five risk categories: high risk (men: treatments generally causing prolonged or permanent azoospermia; women: treatments causing amenorrhea in >70% cases); intermediate risk (men: treatments causing prolonged azoospermia in some cases; women: treatments causing amenorrhea in 30–70% cases); low risk (men: treatments temporarily causing reduced spermatogenesis; women: treatments causing amenorrhea in <20% cases); very low risk (treatments associated with very low or no risk); and unknown risk. In cases of treatments that met any of the abovementioned risk criteria, patients with thyroid cancer underwent radioiodine therapy alone, which was categorized into the very low risk category. ►**Table 4** summarizes the variables related to the risk of gonadal toxicity, including the total cisplatin doses (men), use/nonuse of cisplatin (women), and radiation fields/doses in radiotherapy, for 12 patients with nonthyroid head and neck cancer who underwent chemotherapy and/or radiotherapy. The risk levels of gonadal toxicity associated with treatments in these cases were determined according to the criteria shown in ►**Tables 2** and **3**. Cases 1, 6, and 11 were identified to be at intermediate risk, whereas case 5 was identified to be at high risk. However, these patients were not provided written explanations of potential decrease in fertility before performing treatment. Moreover, treatment methods were not changed for potential effects on fertility in any of the cases, and none of the patients underwent fertility preservation before treatment. Furthermore, no information was available regarding whether the cancer treatments caused childbearing problems in any patient. Given that the present study was retrospective in nature, we could not investigate the details. We categorized case 2 who was treated with intra-arterial cisplatin into unknown risk category because the pharmacokinetics of intra-arterial cisplatin may differ from that of intravenous cisplatin, for which the gonadal toxicity level is described in the fertility preservation guidelines.[2] Furthermore, we categorized case 4 who was treated with proton beam therapy into unknown risk category.

Treatment Outcomes

The 5-year survival rates of patients with thyroid cancer (Stage I/II), early-stage nonthyroid head and neck cancer (Stage I/II), and advanced nonthyroid head and neck cancer (Stage III/IV) were 100, 89, and 80%, respectively (►**Figs. 3** and **4**). Among the 60 patients analyzed in this study, 3

Table 1 Specific types of treatments used for patients with nonthyroid head and neck cancer who underwent chemotherapy and/or radiotherapy

Case	Sex	Age	Primary	Histological type	TNM	Stage	First-line therapy	Postoperative treatment or treatment for recurrent tumors
1	Female	37	Tongue	Squamous cell carcinoma	T2N0M0	II	Surgery	Surgery → CCRT (1) → S-1 → surgery → RT (2) → PTX
2	Female	25	Oral floor	Squamous cell carcinoma	T4aN0M0	IVA	Surgery	CCRT (intra-arterial) → S-1
3	Male	39	Tongue	Squamous cell carcinoma	T3N2cM0	IVA	Surgery	CCRT
4	Male	20	Parotid gland	Mucoepidermoid carcinoma (low grade)	T4aN2bM0	IVA	Surgery	Surgery → proton beam
5	Male	35	Submandibular gland	Mucoepidermoid carcinoma (high grade)	T3N1M0	III	Surgery	CCRT (1) → surgery → RT (2) → RT (3)
6	Male	16	Epipharynx	WHO classification grade II	T4N2M0	IVA	Alternating chemoradiotherapy (1)	Surgery → CCRT (2) → surgery → CCRT (3)
7	Male	21	Epipharynx	WHO classification grade III	T2N2M0	III	Alternating chemoradiotherapy	
8	Male	32	Epipharynx	WHO classification grade II	T2N2M0	III	Alternating chemoradiotherapy	
9	Male	31	Epipharynx	WHO classification grade III	T1N1M0	II	Alternating chemoradiotherapy	
10	Male	39	Epipharynx	WHO classification grade II	T3N2M0	III	Alternating chemoradiotherapy	
11	Female	32	Nasal and paranasal sinuses	Small cell cancer	T4bN0M0	IVB	Surgery	CCRT (CDDP, VP-16 + RT (1)) → RT (2) → CBDCA, CPT-11 → Surgery → RT (3) → PTX → AMR → RT (4)
12	Female	33	Nasal and paranasal sinuses	Poorly differentiated adenocarcinoma	T4bN0M0	IVB	Surgery	S-1

Abbreviations: AMR, amrubicin; CBDCA, carboplatin; CCRT, concurrent chemoradiotherapy; CDDP, cisplatin; CPT-11, irinotecan; PTX, paclitaxel; RT, radiotherapy; VP-16, etoposide.
Note: For cases in which multiple cycles of radiotherapy were performed, numbers in parentheses are used to specify the cycle of radiotherapy.

Table 2 Classification of the degrees of gonadal toxicity risk associated with chemotherapy and radiotherapy (men)

Degree of risk	Treatment protocol	Factors such as patients and doses
High risk	Alkylating agent + total body irradiation	
	Alkylating agent + pelvic or testicular irradiation	
	Total cyclophosphamide dose	7.5 g/m^2
	Regimens including procarbazine	
	Regimens including temozolomide or carmustine + cranial irradiation	
	Testicular irradiation	>2.5 Gy (adult men), >15 Gy (children)
	Total body irradiation	
	Cranial irradiation	>40 Gy
Intermediate risk	Regimens including heavy metals	
	BEP therapy	2–4 cycles
	Total cisplatin dose	>400 mg/m^2
	Total carboplatin dose	>2 g/m^2
	Testicular irradiation with scattered radiation	1–6 Gy
Low risk	Regimens including drugs other than alkylating agents	
	Testicular irradiation	0.2–0.7 Gy
	Anthracyclines + cytarabine	
Very low risk or no risk	Multidrug therapy using vincristine	
	Radioiodine	
	Testicular irradiation with scattered radiation	<0.2 Gy
Unknown	Monoclonal antibodies (cetuximab, trastuzumab)	
	Tyrosine kinase inhibitors (erlotinib, imatinib)	

Abbreviation: BEP therapy, a testicular tumor treatment regimen consisting of bleomycin, etoposide, and cisplatin.
Note: Treatments written in bold are those used in the cases analyzed in this study.
Source: Adapted from Kimura et al[2] with partial modifications.

patients who underwent all treatments with intermediate or high risk of gonadal toxicity died (►**Table 4**). The outcomes of patients undergoing treatments associated with intermediate or high risk of gonadal toxicity were as follows from the date of first-line treatment: case 1 died after 2 years; case 5 died after 1 year; case 6 was alive after 10 years; and case 11 died after 1 year and 2 months.

Case Presentation

Among the patients included in the present study, only one patient was provided information about fertility. That patient was a 34-year-old woman referred to our department with a 7-month history of a mass on the right side of her neck. She was diagnosed with papillary thyroid cancer T3bN1bM0 (Stage I). Notably, the patient was concerned about the impact of thyroid cancer treatment on fertility as she was currently attending a local obstetrics and gynecology clinic for infertility treatment. Based on the consensus developed at a joint conference of our department and the Departments of Endocrinology and Metabolism and Nuclear Medicine, the use of contraception for 6 months after radioiodine therapy was recommended. The gonadal toxicity risk of postoperative radioiodine therapy was classified as very low. Before starting the treatment, the patient was explained about the possible effects of the treatment on fertility. Further, she discontinued the infertility treatment to focus on cancer treatment. The patient underwent total thyroidectomy and D3 dissection followed by radioiodine therapy at 2 and 7 months postoperatively, respectively. Subsequently, the right parapharyngeal space and paratracheal lymph node metastases were noted, which gradually increased in size; however, the patient did not request surgery or molecular targeted therapy and is currently being monitored. Notably, to date, she has not resumed infertility treatment or conceived.

Discussion

Nonthyroid head and neck cancers are rare in young people, but this population accounts for relatively high proportion of patients with nasopharyngeal cancer, carcinoma of the tongue, nasal and paranasal sinus cancer, and salivary gland cancer.[5] In the present study, the most common type of cancer was thyroid cancer, followed by oral carcinoma, salivary gland cancer, nasopharyngeal cancer, and nasal and paranasal sinus cancer. Regarding the treatment outcomes in patients with nonthyroid head and neck cancer, the survival rates of young patients remain unclear. Some studies

Table 3 Classification of the degrees of gonadal toxicity risk associated with chemotherapy and radiotherapy (women)

Degree of risk	Treatment protocol	Factors such as patients and doses
High risk	Alkylating agent + total body irradiation	
	Alkylating agent + pelvic irradiation	
	Total cyclophosphamide dose	5 g/m^2 (>40 y old), 7.5 g/m^2 (<20 y old)
	Regimens including procarbazine	
	Regimens including temozolomide or carmustine + cranial irradiation	
	Whole abdominal or pelvic irradiation	>6 Gy (adult women), >10 Gy (postadolescence), >15 Gy (preadolescence)
	Total body irradiation	
	Cranial irradiation	> 40 Gy
Intermediate risk	Total cyclophosphamide dose	5 g/m^2 (30–40 y old)
	AC therapy for breast cancer	×4 cycles + paclitaxel/docetaxel (<40 y old)
	Monoclonal antibodies (e.g., bevacizumab)	
	FOLFOX4	
	Regimens including cisplatin (dose not stated)	
	Abdominal/**pelvic irradiation**	10–15 Gy (preadolescence), 5–10 Gy (postadolescence)
Low risk	Regimens including drugs other than alkylating agents or low-level alkylating agents	
	Regimens including cyclophosphamide for breast cancer	
	Anthracyclines + cytarabine	
Very low risk or no risk	Multidrug therapy using vincristine	
	Radioiodine	
Unknown	Monoclonal antibodies (cetuximab, trastuzumab)	
	Tyrosine kinase inhibitors (erlotinib, imatinib)	

Abbreviations: AC therapy, a breast cancer treatment regimen consisting of doxorubicin and cyclophosphamide; FOLFOX4, a colorectal cancer treatment regimen consisting of fluorouracil, levofolinate, and oxaliplatin.
Note: Treatments written in bold are those used for the cases analyzed in this study.
Source: Adapted from Kimura et al[2] with partial modifications.

have reported that the survival rates of young patients are higher than those of patients aged ≥40 years,[6] whereas others have reported that the rates are comparable.[5] In the present study, the 5-year survival rates of patients with thyroid cancer (Stage I/II), early-stage nonthyroid head and neck cancer (Stage I/II), and advanced nonthyroid head and neck cancer (Stage III/IV) were 100, 89, and 80%, respectively. The favorable long-term outcomes observed in patients with nonthyroid head and neck cancer in the present study may be attributed to the effectiveness of surgery and the treatment intensity maintained with chemotherapy and radiotherapy in many cases. Therefore, the effects on fertility and late complications, such as secondary malignancies due to radiotherapy and chemotherapy, were considered more important in AYA than in individuals from other age groups.

According to the fertility preservation guidelines,[2] treatments with cisplatin (a key drug for treating head and neck cancers) and cranial and pelvic irradiation in cases of metastasis were classified to be associated with intermediate or high risk of gonadal toxicity. Notably, these treatment modalities are significant in terms of their effects on gonadal function in head and neck cancer therapy. In the present study, the only treatment used for patients with thyroid cancer at risk for gonadal toxicity was radioiodine therapy, which was classified under very low risk category. Conversely, molecular targeted therapy was not administered in any patient. Notably, the risk of gonadal toxicity due to the use of molecular targeted drugs for thyroid cancer is unknown as it has not been described in the fertility preservation guidelines. However, caution must be exercised while using molecular targeted drugs because these drugs can induce hypothyroidism, affecting fertility and the course of pregnancy.[2] Cases 1, 6, and 11 met the criteria for intermediate risk because the male patients received a total cisplatin dose of ≥400 mg/m^2 and the female patients presented with a history of cisplatin use. The effects of cisplatin on male germ cells include reduced spermatogonial cell counts and permanent defects in spermatogenesis occurring early after

Table 4 Gonadal toxicity risk in cases of nonthyroid head and neck cancer

		Cisplatin		Radiotherapy	Gonadal toxicity risk	Outcome
Case	Sex	Total dose (male)	Use/nonuse (female)	Radiation field/dose		
1	Female		**Use**	1. Whole neck 40 Gy, oral; bilateral neck 20 Gy, oral 6 Gy	Intermediate	Death
				2. Supraclavicular metastasis 40 Gy		
2	Female		Use (intra-arterial)	Whole neck 40 Gy, right neck 30 Gy		Living
3	Male	80 mg/m^2		Whole neck 40 Gy, oral 26 Gy		Living
4	Male			54 Gy along the tumor bed and facial nerves		Living
				16 Gy (proton beam) to the tumor bed, avoiding irradiation of the brain		
5	Male	200 mg/m^2		1. Right neck 66 Gy	High	Death
				2. **Left cerebellum resection bed 50 Gy**		
				3. Lumbar spine metastasis 20 Gy, left iliac metastasis 8 Gy, left pubic metastasis 8 Gy		
6	Male	**820 mg/m^2**		1. Whole neck 36 Gy, epipharynx; neck 24 Gy	Intermediate	Living
				2. Right supraclavicular-mediastinal metastasis 60 Gy		
				3. Left main bronchus metastasis 64 Gy		
7	Male	300 mg/m^2		Whole neck 36 Gy, epipharynx; neck 24 Gy		Living
8	Male	250 mg/m^2		Whole neck 36 Gy, epipharynx; neck 24 Gy		Referred to a different hospital
9	Male	300 mg/m^2		Whole neck 36 Gy, epipharynx; neck 24 Gy		Referred to a different hospital
10	Male	300 mg/m^2		Whole neck 36 Gy, epipharynx; neck 24 Gy		Referred to a different hospital
11	Female		**Use**	1. Nasal and paranasal sinuses 66 Gy	Intermediate	Death
				2. Cervical spine (C7) metastasis 20 Gy		
				3. Mediastinal metastasis 40 Gy		
				4. **Lumbar spine (L5) sacral metastasis 20 Gy**		
12	Female		Nonuse			Living

Notes: Treatments written in bold are those with gonadal toxicity risk used for cases analyzed in this study. For cases in which multiple cycles of radiotherapy were performed, numbers in parentheses are used to specify the cycle of radiotherapy.

treatment with cisplatin at a higher total dose, and the effects on female germ cells include reduced oocyte count and premature ovarian insufficiency, which increases with age.[2] Regarding radiotherapy associated with a risk of gonadal toxicity, we used high-risk cranial irradiation in a patient with brain metastases (case 5) and intermediate-risk pelvic irradiation in a patient with sacral metastases (case 11). It has been reported that cranial irradiation can cause testicular and ovarian failure because irradiation of the hypothalamus or pituitary can impair gonadotropin secretion.[2] In particular, in women, pelvic irradiation can cause premature ovarian insufficiency.[2]

In the present study, information regarding the potential effects of cancer treatment on reproductive function was provided to only one patient with thyroid cancer. This patient was undergoing infertility treatment and wanted to have children before undergoing cancer treatment. The information provided regarding the potential effects of cancer treatment on reproductive function partially helped her overcome anxiety related to radioiodine therapy. Furthermore, to focus on her cancer treatment, she discontinued infertility treatment with plans to resume the treatment once the disease was stabilized; however, she did not resume the treatment because new metastatic lymph nodes appeared after treatment. Notably, no other patient receiving treatment associated with risk of gonadal toxicity was previously provided a written explanation about a possible reduction in fertility due to treatment, indicating that a

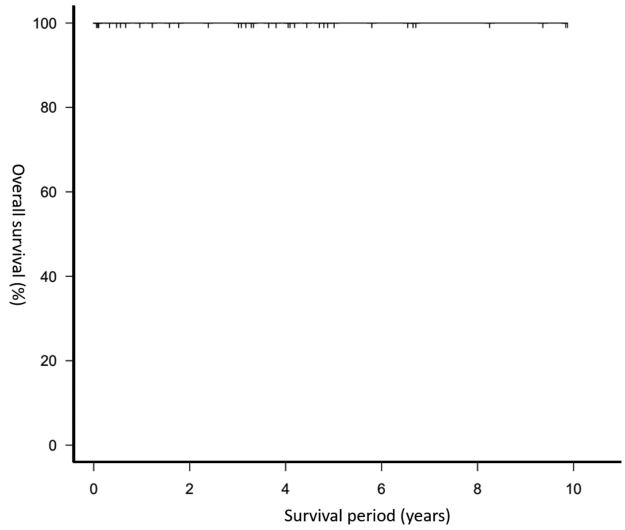

Fig. 3 Overall survival rates of patients with thyroid cancer (Kaplan–Meier method). The 5-year survival rate of patients with thyroid cancer (Stage I/II) was 100%.

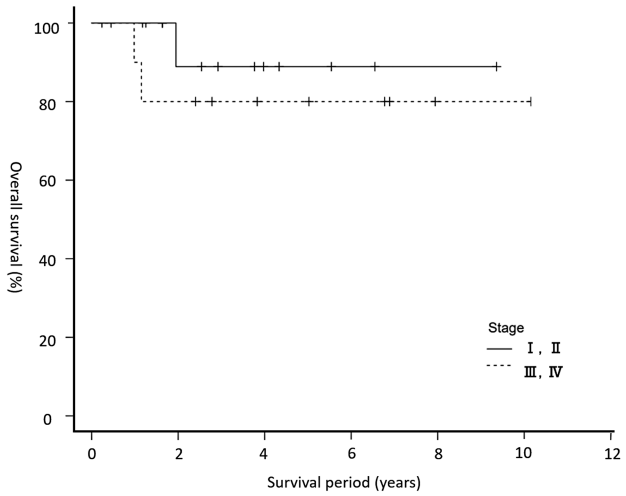

Fig. 4 Overall survival rates of patients with nonthyroid head and neck cancer (Kaplan–Meier method). The 5-year survival rates of patients with early-stage cancer (Stage I/II) and those with advanced cancer (Stage III/IV) were 89 and 80%, respectively.

written explanation of risk needs to be newly added to the informed consent forms. Meanwhile, three out of four patients who underwent treatment with gonadal toxicity (intermediate/high risk) had a poor long-term prognosis and died within 2 years. The provision of fertility-related information to patients with a poor prognosis remains controversial. Careful explanations, taking into account the patient's mental condition, should be given only after it has been confirmed that the patient desires to obtain information about the effects of the treatment on fertility. Furthermore, the feasibility of fertility preservation should be discussed with the patient after they have been provided information about their prognosis.

Common methods of fertility preservation include sperm cryopreservation for men and embryo or oocyte cryopreservation for women; moreover, methods for cryopreservation of testicular and ovarian tissues are under development.[7] Our department has no previous records of performing fertility preservation before cancer treatment in patients with head and neck cancer. Akisada et al[8] reported a case of maxillary antrum cancer (ameloblastic fibrosarcoma) in a 17-year-old woman who underwent egg retrieval and cryopreservation before systemic chemotherapy. This case highlights the need for otorhinolaryngologists to gain insights into the gonadal toxicity of cancer therapies and fertility preservation. However, currently, there is a lack of opportunities for otorhinolaryngologists to learn about fertility preservation. These opportunities could be increased by the addition of questions about fertility preservation to certification and other relevant examinations for otorhinolaryngology specialists. Furthermore, a section on head and neck cancer could be added to the fertility preservation guidelines.[3] In addition, as new drugs are expected to be developed for treating head and neck cancer, otorhinolaryngologists should also update their knowledge about the effects of any new treatments related to fertility. Furthermore, when fertility preservation is performed before cancer treatment, the clinical department responsible for the treatment must immediately share information with the department of obstetrics and gynecology or urology. Some medical institutions have established centers for reproductive medicine to help patients with fertility preservation without delaying their cancer treatment; the examples of such centers are the Reproduction Center (Okayama University) and the Pediatrics, AYA Generation, and Fertility Center (Toyama University).

Several activities related to cancer and fertility preservation in patients with AYA are conducted at Kanazawa University and Ishikawa Prefecture. As projects of Hokushin Ganpro, involving universities from four prefectures in the Hokushin region (Nagano, Toyama, Ishikawa, and Fukui prefectures), Kanazawa University was involved in public lectures and the creation of AYA generation cancer patient groups to increase public awareness about cancer and fertility preservation. These groups provide patients and their families places to gather.[9] In Ishikawa Prefecture, we also collaborated with prefectural designated cancer care hospitals and other medical institutions to create a fertility preservation network and subsidize fertility-preserving treatments (as of November 2022). Finally, in addition to these patient-focused activities, we plan to increase awareness about the importance of forming cancer reproductive medicine networks among medical professionals.

Conclusions

The results of the present study indicate the need to improve the provision of written explanations to patients about the potential effects of cancer therapies on gonadal function before performing treatments that may affect their fertility.[8] Further, it is important to promptly collaborate with

physicians specializing in reproductive medicine when any patient requests fertility preservation.

Conflicts of Interest
None declared.

Acknowledgment
None.

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