Otorhinolaryngologists/head and neck surgeons' knowledge, attitudes, and practices regarding fertility preservation in young cancer patients treated with chemotherapy: An Anonymous Questionnaire Survey

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Abstract

Background: It is well known that chemotherapy for adolescent and young adult (AYA) patients with cancer can reduce fertility regardless of the regimen. A decline in fertility greatly affects the quality of life of cancer survivors in the AYA age group; however, few patients are thought to be receiving fertility preservation measures.

Methods: A questionnaire survey was conducted to assess the current understanding and consideration of fertility among otorhinolaryngologists/head and neck surgeons who treat AYA patients with cancer, and to inform them of the guidelines for fertility preservation. A total of 275 otorhinolaryngologists/head and neck surgeons working at our hospital in Ehime, Japan, six neighboring universities, and their affiliated facilities were included in this study. The questionnaire was mailed and requested to be returned by fax. Twenty questions were asked about respondents' years of experience as physicians, specialties, experience in medical care and chemotherapy for AYA patients with cancer, and knowledge and experience in fertility reduction measures.

Results: Although 58.7% of the physicians were aware that cryopreservation of eggs and sperm prior to chemotherapy was recommended, only 7 out of 40 physicians (17.5%) had referred AYA patients with cancer to an appropriate medical facility (department) after obtaining informed consent for chemotherapy.

Conclusions: Although fertility preservation has been discussed at professional conferences and seminars, consideration and actions in the field of otorhinolaryngology/head and neck surgery have not been sufficient. We hope that the results of this survey will help raise awareness of fertility preservation.

Keywords: fertility preservation, otorhinolaryngology, head and neck cancer, adolescent and young adult generation, guidelines, japan

Introduction

Adolescent and young adults aged between 15 and 40 years (AYA generation) account for about 4% of all cancer patients [1]. According to a 2020 report from the Japan Society for Head and Neck Cancer, the proportion of patients with nasopharyngeal and tongue cancer who were under the age of 40 years was 10.3% and 8.6%, respectively—higher than reported for other parts of the head and neck region [2].

It is well known that chemotherapy for AYA patients with cancer can reduce fertility regardless of the regimen. Guidelines were developed by the American Society of Clinical Oncology (ASCO) [3, 4], and the Japan Society of Clinical Oncology has published "Clinical Practice Guidelines 2017 for Fertility Preservation in Childhood, Adolescent and Young Adult Cancer Patients" [5] (referred to here as the "JSCO Guidelines"), based on the ASCO guidelines. Both sets of guidelines clearly state that consideration should be given to fertility preservation before chemotherapy for AYA patients with cancer. The JSCO Guidelines include "Inform patients about the likelihood of cancer treatment resulting in infertility within the reproductive age and provide information about it," "If the patient wishes to have a baby, the oncologist will refer the patient to a doctor specializing in reproductive medicine as early as possible," and "Consider whether and when to use fertility preservation therapy in close medical collaboration with a physician specializing in reproductive medicine." In this paper, these three points are referred to as "Recommendations." The JSCO Guidelines provide an overview and review of, and recommendations for, each of the eight areas and departments: female genitalia, mammary glands, urinary organs, pediatric, hematopoietic, osteochondral, brain, and digestive organs. However, there is no specific description for otorhinolaryngology/head and neck surgery.

In a questionnaire survey of 167 AYA generation female cancer survivors, 20.4% were reported to have been diagnosed as infertile [6]; 55% of survivors who reported becoming infertile as a result of cancer treatment said that they were not informed of the possibility of infertility before treatment. Although more than 3 years have passed since the 2017 edition of the JSCO Guidelines was published, the number of otorhinolaryngology/head and neck surgery patients receiving information about fertility decline and loss and measures for fertility preservation is expected to be low because of otorhinolaryngologists/head and neck surgeons' unfamiliarity with the topic. To date, no questionnaire study on fertility preservation has been conducted among otorhinolaryngologists/head and neck surgeons, according to our PubMed search. Therefore, we conducted a questionnaire survey to determine the level of understanding and consideration of fertility among otorhinolaryngologists/head and neck surgeons who treat AYA patients with cancer, and to inform them about the contents of the JSCO Guidelines.

Materials and methods

This survey was conducted from September to the end of October 2019. A total of 275 otorhinolaryngologists/head and neck surgeons working at our hospital in Ehime, six neighboring universities (Okayama University, Kawasaki Medical School, Hiroshima University, Hyogo Medical University, Kagawa University, and Ehime University), and their affiliated institutions (77 institutions) were targeted. The respondents answered 20 items anonymously, including their years of experience as a physician, field of specialty, experience in treating AYA patients with cancer and experience in treating AYA patients with cancer using chemotherapy, whether or not they proposed cryopreservation of eggs and sperm before chemotherapy, whether or not they were aware of the JSCO Guidelines, and whether or not they were aware of the recommendations specified in the JSCO Guidelines. The questionnaires were distributed by mail, and respondents were requested to return them by fax.

A total of 155 (56.4%) valid responses were returned. The AYA generation in this study was defined as patients aged between 15 and 40 years according to the JSCO Guidelines. The questionnaire results were analyzed using Fisher's exact test. All analyses were performed using BellCurve for Excel version 2.14 (Social Survey Research Information Co., Ltd., Tokyo, Japan). Values of P < 0.05 were considered significant, while values of P < 0.1 were considered to indicate a tendency. Because this is a questionnaire for physicians and answers were not personally identifiable, we determined that ethics review board approval was not required.

Results

Questionnaire Section 1: profile of the respondents

In terms of the physicians' number of years of experience, 57 (36.8%) had 10–19 years of experience, followed by 43 (27.7%) who had 3–9 years of experience. The respondents comprised 126 men (81.2%) and 29 women (18.7%), and included 47 department heads (30.3%). There were 126 (81.2%) board-certified otorhinolaryngologists, 30 (19.3%) Japanese Board of Cancer Therapy (JBCT)-certified general clinical oncologists, and 21 (13.5%) board-certified head and neck surgeons.

After four years of training in otorhinolaryngology and passing the certification examination, a physician is board-certified in otorhinolaryngology. After training in head and neck surgery and passing its certification examination, board certification in head and neck surgery can be achieved as early as three years after certification in otorhinolaryngology. JBCT certification in general clinical oncology can be achieved one year, at the earliest, after board certification in otorhinolaryngology. It is necessary to pass the certification examination that tests knowledge of all malignancies. Candidates are required to study from a textbook of educational seminars published by the JBCT that is distributed in advance.

Questionnaire Section 2: knowledge of fertility preservation

Although not well known, the JSCO Guidelines had been read by 21 physicians (13.5%), while 91 (58.7%) were aware of the recommendations (Fig. 1a, 1b).

We analyzed perceptions of the recommendations in the JSCO Guidelines by respondent profiles (Fig. 2). Between men and women, 74 of 126 men (58.7%) and 17 of 29 women (58.6%) were aware of the recommendations (Fig. 2a). When considering the years of experience, 50– 60% of all physicians were aware of the recommendations, except for the seven physicians with more than 40 years of experience each, who were all aware of them (Fig. 2b). We further compared the perception among physicians with and without the three types of certification. When compared by the presence or absence of board-certification in otorhinolaryngology, there was no significant difference (P=0.26) (Fig. 2c). When compared by the presence or absence of JBCT certification in general clinical oncology, 22 of 30 (73.3%) JBCT-certified and 69 of 125 (55.2%) non-JBCT-certified general clinical oncologists recognized the recommendations (Fig. 2d). Although not statistically significant, JBCT-certified general clinical oncologists tended to be more aware of the recommendations than non-JBCT-certified general clinical oncologists (P=0.052). A higher percentage of board-certified than non-board-certified head and neck surgeons were aware (71.4% and 56.7%, respectively), although the difference was not significant (P=0.15) (Fig. 2e). This may be due to the relatively small number of board-certified head and neck surgeons (21 out of 155 valid responses).

Only 41 (26.4%) and 35 (22.6%) respondents were aware of nearby egg and fertilized egg storage facilities and sperm storage facilities, respectively, which is not sufficient to ensure effective referral of all adaptive patients to specialized facilities (Fig. 1c, 1d). In total, 131 respondents (84.5%) indicated that they would like to read the JSCO Guidelines on account of this study (Fig. 1e). Many of the physicians who had never read them (111 out of 134, 82.8%) answered that they would like to read them, showing that the JSCO guidelines for fertility preservation are likely to become well known.

Questionnaire Section 3: considerations and behaviors for AYA patients with cancer

A total of 146 physicians (94.1%) had experience treating cancer patients of any age who had received chemotherapy, and 64 (41.3%) had experience treating AYA patients with cancer who had received chemotherapy. Forty of 155 physicians (25.8%) obtained informed consent for

chemotherapy from AYA patients with cancer. Additional questions were asked of these respondents (Fig. 3). Fourteen of the physicians (35.0%) answered that they always asked prior to chemotherapy whether the patient wanted to have a baby, and 16 (40.0%) that they always explained that the patient's fertility would be reduced. These results showed that the outcomes of reduced fertility were not thoroughly explained by otorhinolaryngology/head and neck surgery practitioners, despite being specified in the JSCO Guidelines. Fifteen of the 40 physicians (37.5%) had actually presented cryopreservation of the patient's eggs and sperm and seven (17.5%) had referred the patients to a specialized storage facility.

Discussion

Necessity of considering fertility preservation in head and neck cancer treatment

Long-term support from a multidisciplinary team is necessary for AYA patients with cancer, not only from their physicians but also from other professionals. In addition to fertility preservation, there are many other issues to be addressed, such as schooling, employment, economic problems, and support for parents and children. It is thus desirable to have a multidisciplinary team of reproductive medical doctors, nurses, clinical psychologists, social workers, employment support groups, and peer support, rather than a single doctor. Particularly in the collaboration between

oncologists and reproductive medicine doctors, a common understanding of the prognosis, the urgency of cancer treatment, and the margin of time for fertility-conserving treatment is essential. In otorhinolaryngology/head and neck surgery, the main patients for whom fertility preservation should be considered are those facing radical chemoradiotherapy for head and neck cancer, chemoradiotherapy for high-risk of postoperative recurrence, or systemic chemotherapy for recurrence or metastasis. In the 2020 National Comprehensive Cancer Network Guidelines [7] and the 2018 edition of the Head and Neck Cancer Practice Guidelines [8], the use of cisplatin is recommended for chemoradiation for both locally advanced patients and those at high-risk of postoperative recurrence of squamous cell carcinoma of the head and neck. According to the ASCO [3, 4] and JSCO Guidelines [5], platinum drugs such as cisplatin are classified as "intermediate risk" because they reduce the number of oocytes and spermatogonia cells and cause a permanent loss of fertility when the total usage is high. On the other hand, there are no consistent results for molecularly targeted drugs such as cetuximab and tyrosine kinase inhibitors, and the risk level is "Unknown risk". Radioisotopes are classified as "Very low or no risk"; however, because hypothyroidism can affect fertility and the course of pregnancy [9], due consideration should be given before their use. Similarly, consideration should also be given to stereotactic radiotherapy and whole-brain irradiation for brain metastases. Irradiation of the hypothalamus or pituitary gland with more than 40 Gy results in impaired hormone production [5]; therefore, close

collaboration with radiation oncologists is important in the treatment of AYA patients with cancer. Osteosarcoma, rhabdomyosarcoma, and Ewing sarcoma should also be mentioned. Chemotherapy is administered in the presence of distant metastases or as a preoperative treatment. In the treatment of sarcomas, high doses of chemotherapy are used and affect fertility. Cyclophosphamide and actinomycin are classified as "High risk", while vincristine, doxorubicin and methotrexate are classified as "Very low or no risk"[5]. In accordance with the JSCO Guidelines, physicians should explain the possibility of infertility with each method of treatment and consider referral to a specialist facility if the patient wishes to have a baby and preserve fertility.

It has been reported that counseling on fertility preservation itself improves the psychological quality of life in adult female cancer patients [10], and there is an advantage of fertility preservation in the sense that it has a positive effect on the subsequent fight against cancer, independent of preserving gametes. However, patients with distant metastases who refrain from systemic chemotherapy often have a prognosis limited to several months, depending on the carcinoma. It is thus controversial whether we should propose fertility preservation therapy implementation in such cases. After the death of the patient, consideration of the patient's family is also essential. Therefore, adequate communication with spouses and relatives prior to preservation therapy is necessary.

Comparison of this study with studies from other departments and countries

Similar questionnaire surveys of physicians have been conducted elsewhere in Japan and abroad. Takeuchi et al. conducted a questionnaire survey of 180 physicians in various departments (31.2% of the respondents were gastroenterologists) [11]; 30.0% of these physicians referred their patients to a specialist facility for fertility preservation. Among the 40 physicians in our study who obtained informed consent for chemotherapy from AYA patients with cancer, only 7 (17.5%) had experience in referring patients to a specialty center, although our analysis was limited to physicians who obtained informed consent. Collins et al. conducted a questionnaire survey of 50 physicians in oncology, hematology, and breast surgery-62% were aware of guidelines on fertility preservation, 82% had explained sperm preservation to their male patients and referred them to a specialist facility, and 84% had explained chemotherapy-induced fertility loss to their female patients [12]. Goldfarb et al. conducted a questionnaire survey of all physicians working in cancer hospitals in the U.S. [13]. The survey included 149 physicians; 32% provided male patients with an explanation of reduced fertility due to chemotherapy and 49% provided female patients with an explanation of reduced fertility. In our study, 16 (40.0%) of the 40 physicians explained the reduction in fertility to their patients.

Compared to results of the surveys by Takeuchi, Collins, and Goldfarb, Japanese otorhinolaryngologists/head and neck surgeons are not sufficiently concerned about fertility preservation.

What to do for adequate consideration and action in the field of otorhinolaryngology/head and neck surgery

A textbook of educational seminars published by the JBCT is distributed for study prior to sitting the general clinical oncologist board certification examinations. Since the 2017 edition, the text states that "Various anticancer drugs can affect reproductive functions regardless of gender. It is essential to provide sufficient information, psychological support, and close cooperation among medical professionals before starting treatment, especially for young patients and patients and partners who wish to have a baby." This may be one of the reasons why JBCT-certified general clinical oncologists are relatively aware of the recommendations (P=0.052). However, 64 physicians (41.3%) in this study had treated AYA patients with cancer who had received chemotherapy, and all otorhinolaryngologists/head and neck surgeons may have to deal with this issue at some point in their career. In order to improve consideration and actions to preserve fertility in all medical institutions, it may be effective to increase questions on fertility preservation in the board certification examinations of otorhinolaryngologists and head and neck surgeons, and the JBCT certification examinations of general clinical oncologists. Because otorhinolaryngologists/head and neck surgeons are not accustomed to talking about fertility and sexuality with their patients, we also recommend that fertility preservation be added to the explanatory documents of chemotherapy at each hospital. If a patient wishes to preserve his or her fertility, referral to a specialist department or facility should be considered in advance. Subsidy systems for fertility preservation therapy and the construction of regional fertility networks are being established gradually by local governments and hospitals, but currently they are still inadequate, and it is necessary to call on the government to improve their adequacy. On the other hand, even if otorhinolaryngologists/head and neck surgeons explain the risk of decreased fertility to their patients, some patients may not go to a specialist department or facility for financial reasons. In such cases, it is necessary to respect the patient's wishes[5],but otorhinolaryngology/head and neck surgeon must provide sufficient explanation about the risk of decreased fertility so that the patient does not regret the decision. It is also necessary to explain the necessity of endocrinological examinations after treatments that lead to decreased fertility, and to continue these examinations.

Our first priority is to treat cancer. However, fertility preservation is one of the most important concomitant issues to be addressed in current cancer treatment. We hope that this study will help to improve awareness among otorhinolaryngologists/head and neck surgeons and understanding of fertility issues among their AYA patients with cancer.

Limitations and challenges of this study

Physicians who were less aware of the JSCO Guidelines and recommendations were more likely not to respond, and the percentage of physicians who were actually aware is thus expected to be even lower. In addition, the fact that the survey is self-reported and was only conducted once is also a source of uncertainty. According to a 2018 report by the Ministry of Health, Labour and Welfare, there were 4,006 otorhinolaryngologists/head and neck surgeons working in hospitals in Japan [14]. This study only included 275 physicians, or 6.9% of the total number of otorhinolaryngologists/head and neck surgeons in Japan, and the hospitals were limited to western Japan. A large-scale study of fertility preservation-related physician behaviors should be conducted in a range of geographic areas and at regular intervals.

Conclusions

Our questionnaire survey on fertility preservation in AYA patients with cancer was conducted

among 275 otorhinolaryngologists/head and neck surgeons. Although 58.7% of physicians were aware that cryopreservation of eggs and sperm prior to chemotherapy was recommended, the percentage of physicians who actually referred AYA patients to an appropriate medical facility (department) was 17.5% (among 40 physicians who obtained informed consent), which is significantly lower than in other developed countries. The recognition of fertility preservation is expected to improve with the addition of the topic to the board certification examinations of otorhinolaryngologists and head and neck surgeons, and the JBCT certification examinations of general clinical oncologists.

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Conflict of interest The authors declare that they have no conflict of interest. An abstract from this study was presented at the 121st Annual Meeting of the Japanese Society of Otolaryngology (October 2020, Okayama, Japan).

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Figure captions. All figures were made using the Illustrator graphics software

Fig. 1 Knowledge of fertility preservation among 155 otorhinolaryngologists/head and neck surgeons who treat adolescent and young adult patients with cancer

Fig. 2 Comparison of awareness of fertility preservation recommendations by profile

Fig. 3 Fertility-related practices of physicians caring for adolescent and young adult patients with cancer