Original Article

Gonadal function, fertility, and reproductive medicine in childhood and adolescent cancer patients: a national survey of Japanese pediatric endocrinologists

Yoko Miyoshi1, 2, Tohru Yorifuji2, 3, Reiko Horikawa2, 4, Ikuko Takahashi2, 5, Keisuke Nagasaki2, 6, Hiroyuki Ishiguro2, 7, Ikuma Fujiwara2, 8, Junko Ito2, 9, Mari Oba10, Hiroshi Kawamoto11, Hiroyuki Fujisaki12, Masashi Kato13, Chikako Shimizu14, Tomoyasu Kato15, Kimikazu Matsumoto16, Haruhiko Sago17, Tetsuya Takimoto18, Hiroshi Okada19, Nao Suzuki20, Susumu Yokoya21, Tsutomu Ogata22, and Keiichi Ozono1

1 Department of Pediatrics, Osaka University Graduate School of Medicine, Osaka, Japan
2 Childhood Cancer Survivor Committee of the Japanese Society for Pediatric Endocrinology
3 Department of Pediatric Endocrinology and Metabolism, Osaka City General Hospital, Osaka, Japan
4 Division of Endocrinology and Metabolism, National Center for Child Health and Development, Tokyo, Japan
5 Department of Pediatrics, Akita University Graduate School of Medicine, Akita, Japan
6 Division of Pediatrics, Department of Homeostatic Regulation and Development, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
7 Department of Pediatrics, Isehara Kyodo Hospital, Kanagawa, Japan
8 Department of Pediatrics, Tohoku University Hospital, Sendai, Japan
9 Department of Pediatrics, Toranomon Hospital, Tokyo, Japan
10 Department of Medical Statistics, Faculty of Medicine, Toho University, Tokyo, Japan
11 Department of Pediatric Oncology, National Cancer Center Hospital, Tokyo, Japan
12 Department of Pediatric Hematology/Oncology, Osaka City General Hospital, Osaka, Japan
13 Consultation, Counseling and Support Service Center, National Cancer Center Hospital, Tokyo, Japan
14 Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan
15 Department of Gynecology, National Cancer Center Hospital, Tokyo, Japan
16 Department of Pediatric Hematology and Oncology Research, National Center for Child Health and Development, Tokyo, Japan
17 Center of Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan
18 Center for Clinical Research and Development, National Center for Child Health and Development, Tokyo, Japan
19 Department of Urology, Dokkyo Medical University Koshigaya Hospital, Saitama, Japan
20 Department of Obstetrics and Gynecology, St. Marianna University School of Medicine, Kanagawa, Japan
21 Department of Medical Subspecialities, National Center for Child Health and Development, Tokyo, Japan
22 Department of Pediatrics, Hamamatsu University School of Medicine, Hamamatsu, Japan

Received: January 15, 2016
Accepted: February 17, 2016
Corresponding author: Yoko Miyoshi, Department of Pediatrics, Osaka University Graduate School of Medicine, Yamadaoka 2-2, Suita, Osaka 565-0871, Japan
E-mail: miyoshi@ped.med.osaka-u.ac.jp

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives (by-nc-nd) License <http://creativecommons.org/licenses/by-nc-nd/4.0/>.
Abstract. An increasing number of pediatric cancer patients survive, and treatment-related infertility represents one of the most important issues for these patients. While official guidelines in Japan recommend long-term follow-up of childhood cancer survivors (CCSs), their gonadal function and fertility have not been clarified. To address this issue, we organized a working panel to compile evidence from long-term survivors who received treatments for cancer during childhood or adolescence. In collaboration with members of the CCS Committee of the Japanese Society for Pediatric Endocrinology (JSPE), we conducted a questionnaire survey regarding reproductive function in pediatric cancer patients. A cross-sectional survey was sent to 178 JSPE-certified councilors who were asked to self-evaluate the medical examinations they had performed. A total of 151 responses were obtained, revealing that 143 endocrinologists were involved in the care of CCSs. A quarter of the respondents reported having experienced issues during gonadal or reproductive examinations. Several survivors did not remember or fully understand the explanation regarding gonadal damage, and faced physical and psychological distress when discussing the risk of becoming infertile. Pediatric endocrinologists had anxieties regarding their patients’ infertility and the risk of miscarriage, premature birth, and delivery problems. Only a limited number of endocrinologists had experience with managing childbirth and fertility preservation. Many councilors mentioned the necessity for inter-disciplinary communication among healthcare providers. Both endocrinologists and oncologists should set and follow a uniform clinical guideline that includes management of fertility of CCSs.

Key words: childhood cancer survivor, adolescent, pediatric endocrinologist, questionnaire survey, fertility

Introduction

Due to improvements in the treatment and prognosis of cancer, the number of childhood and adolescent cancer survivors has increased. Consequently, physicians tend to pay more attention to late complications (late effects) (1–4). Childhood cancer survivors (CCSs) are under risk of various complications, e.g., endocrinological, cardiovascular, pulmonary, neurologic, or gastrointestinal problems. The Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, issued by the Children’s Oncology Group, are recognized resources for healthcare professionals who provide ongoing care to survivors of pediatric malignancies (5). In 2011, the Japanese Society for Pediatric Endocrinology (JSPE) issued a follow-up guide regarding CCS care with the aim of enabling all physicians involved in clinical practice to continue medical examinations for endocrine disorders (6). Chemotherapy, radiation therapy, and surgery may damage the gonadal function in patients with malignant and non-malignant diseases. The issue of gonadal function is important for childhood and adolescent cancer patients because it is directly linked to their social life. Therefore, future fertility is an important consideration. In 2013, The American Society of Clinical Oncology revised its guideline for healthcare providers regarding fertility preservation in adults and children with cancer (7). Even though gonadal dysfunction and subfertility have been recognized as issues affecting long-term survivors of childhood and adolescent cancer (8–11), few surveys on this topic have been conducted in Japan (12, 13). Therefore, appropriate evaluation and treatment are still unavailable.

The aim of the present study was to gather
the opinions of pediatric endocrinologists and reveal current clinical practice, in order to investigate issues associated with gonadal function or fertility in childhood and adolescent cancer survivors.

**Subjects and Methods**

The questionnaire on reproductive medicine in childhood and adolescent patients with cancer was sent to 178 directors or councilors who are members of the JSPE. The questionnaire consisted of 36 closed-ended questions regarding the professional background of the respondents, their experiences with the follow-up of pediatric cancer patients, their opinions regarding gonadal function or fertility in these patients, and the current status of their clinical practice, and a free-entry field to describe what measures they believe should be taken in the future in order to maintain gonadal function or preserve fertility in pediatric cancer patients (Table 1). The non-anonymous, self-reported questionnaire form was sent by mail and the responses were collected in a return envelope. The survey period was from September 2014 to December 2014.

This study was approved by the Ethical Review Board of Osaka University Hospital (approval No. 15203). The work was conducted as a joint study by the “Working Panel Tasked with Compiling Evidence Regarding the Fertility of Long-Term Survivors of Cancer during Childhood or Adolescence and with Developing a Reproductive Medicine Network” (organizer: Yoko Miyoshi) and the CCS Committee of the JSPE. This project was supported by a Health and Labour Sciences Research Grant (Research for Promotion of Cancer Control Program: H26-Ippan-016).

**Results**

**Status of questionnaire responses**

The questionnaire was sent to 178 (139 male and 39 female) directors or councilors who are members of the JSPE. A total of 151 valid responses were obtained, giving a response rate of 84.8%. The male and female response rates were 82.7% (115 out of 139) and 92.3% (36 out of 39), respectively.
Table 1  Questionnaire

|   |                                                                                           |
|---|-------------------------------------------------------------------------------------------|
| 1 | Sex.                                                                                      |
| 2 | Years since graduating from medical school.                                               |
| 3 | Years of experience with clinical practice in endocrinology.                              |
| 4 | Type of the institution in your practice setting.                                         |
| 5 | Scale of the institution in your practice setting.                                        |
| 6 | Existence of pediatric oncologists in your practice setting.                               |
| 7 | Existence of reproductive specialists in your practice setting.                           |
| 8 | Experience with clinical practice of endocrinology in pediatric cancer patients.           |
| 9 | Experience with long-term follow-up of pediatric cancer patients.                          |
| 10| Recognition of the term “childhood cancer survivor (CCS)”.                                 |
| 11| Number of CCSs treated at present.                                                        |
| 12| Knowledge of the late complications (late effects) in CCSs.                               |
| 13| Knowledge of the physician’s follow-up guide for CCS on the JSPE website.                  |
| 14| Importance of gonadal function and fertility as issues in childhood cancer patients.      |
| 15| Gonadal dysfunction or subfertility caused by cancer treatment is acceptable in relation to the risk of cancer death in pediatric patients with cancer. |
| 16| Concerns of guardians regarding the side effect of cancer treatment on their children’s gonadal function or fertility. |
| 17| Concerns of pediatric patients regarding the side effect of cancer treatment on their gonadal function or fertility. |
| 18| Duration of involvement of pediatric endocrinologists in clinical practice with pediatric cancer patients in your institution. |
| 19| Explanations regarding treatment-related gonadal dysfunction before cancer treatment.      |
| 20| Individual mainly providing the explanation regarding treatment-related gonadal dysfunction. |
| 21| Individual receiving the explanation regarding treatment-related gonadal dysfunction.      |
| 22| Explanations regarding treatment-related subfertility before cancer treatment.            |
| 23| Individual mainly providing the explanation regarding treatment-related subfertility.      |
| 24| Individual receiving the explanation on treatment-related subfertility.                    |
| 25| The method for evaluating testicular function in male CCSs: Tanner staging (penile and scrotal growth), testicular volume, FSH, LH, testosterone, semen analysis. |
| 26| The method for evaluating ovarian function in female CCSs: Tanner staging (breast growth), menstruation, FSH, LH, estradiol, anti-Müllerian hormone. |
| 27| Referral (including timing) of male CCSs with testicular dysfunction to reproductive professionals. |
| 28| Referral (including timing) of female CCSs with ovarian dysfunction to reproductive professionals. |
| 29| Experience with childbirth in CCSs during follow-up.                                      |
| 30| Increased incidence of miscarriages, premature births, or delivery problems if female CCSs become pregnant. |
| 31| Increased incidence of fetal malformation if CCSs or their partners become pregnant.       |
| 32| Experience with fertility preservation before cancer treatment.                            |
| 33| Actual experience with fertility preservation.                                             |
|   | Male: sperm cryopreservation, testicular tissue cryopreservation, gonadal shielding before radiotherapy, other. |
|   | Female: ovarian cryopreservation, ovarian tissue cryopreservation, gonadal shielding before radiotherapy, ovarian transposition before radiotherapy, GnRH analogs, other. |
| 34| Experience with any difficult situations in clinical practice due to subfertility (infertility) or maternal health problems in CCSs. |
| 35| Awareness of the problems about fertility preservation before cancer treatment.           |
| 36| Issues you consider in relation to fertility preservation: physical burden on patients, psychological burden on patients, delayed start of cancer treatment, patients uninformed of cancer diagnosis, physical immaturity due to young age (before secondary sexual characteristics), financial issues, ethical issues, technical issues (clinical application), legal issues, other. |
| 37| Free-entry field wherein respondents were asked to suggest potential measures to be taken in the future to maintain gonadal function or preserve fertility in pediatric cancer patients. |
Table 2  Attributes of respondents and their clinical practice status (n = 151)

| Time since graduation from medical school | No. (%) |
|------------------------------------------|---------|
| < 10 yr                                  | 0       |
| 10–20 yr                                 | 48 (31.8) |
| > 20 yr                                  | 103 (68.2) |

| Time in clinical practice in endocrinology | No. (%) |
|-------------------------------------------|---------|
| < 10 yr                                   | 18 (11.9) |
| 10–20 yr                                  | 57 (37.7) |
| > 20 yr                                   | 76 (50.4) |

| Experience with clinical practice of endocrinology in pediatric cancer patients | No. (%) |
|-------------------------------------------------------------------------------|---------|
| Yes                                                                          | 143 (94.7) |
| No                                                                           | 7 (4.6) |
| No answer                                                                   | 1 (0.7) |

| No. of CCSs currently being treated | No. (%) |
|------------------------------------|---------|
| 0                                  | 37 (24.5) |
| 1–9                                | 59 (39.1) |
| 10–49                              | 42 (27.8) |
| ≥ 50                               | 12 (7.9) |
| No answer                          | 1 (0.7) |

CCSs, childhood cancer survivors.

physicians' opinions and recognition of issues regarding gonadal function or fertility in pediatric cancer patients

Regarding the importance of gonadal function and fertility, 98.7% of respondents reported that they “strongly agree” or “agree”, which shows that almost all respondents are aware of the importance of these aspects (Table 3). On the other hand, with respect to the acceptability of gonadal dysfunction or subfertility as a side effect of cancer treatment in comparison to the risk of cancer-related death, 56.3% of respondents answered that they “strongly agree” or “agree” that such side effects are acceptable, while 42.4% of respondents answered that they “disagree” or “strongly disagree” (Table 3).

Based on responses to the question on whether “Guardians had concern regarding the effect of cancer treatment on their children’s gonadal function or fertility”, 23.9% of respondents answered that they “disagree” or “strongly disagree” (Table 3). For the question on whether “Pediatric patients themselves had concern regarding the effect of cancer treatment on their gonadal function or fertility”, 36.4% of respondents answered that they “disagree” or “strongly disagree”, which was a higher percentage than that of guardians for the same question (Table 3).

Current status of clinical practice and explanations to pediatric cancer patients

More than half of the pediatric endocrinologists (n = 92) performed follow-up examinations on patients after cancer treatment, most often on patients who were experiencing physical issues (n = 69). For the question on “Providing explanations regarding treatment-related gonadal dysfunction before cancer
Regarding the individual who had provided the explanation, 88.8% of the respondents reported that it was mainly the oncologists who had provided the explanation on gonadal dysfunction (Table 4). Regarding the individual receiving the explanation, 18 respondents answered that the explanation was only provided to the guardians and to the majority of patients older than adolescent.

Similarly, for the question on “Providing explanations on treatment-related subfertility before cancer treatment”, 54.3% answered “yes”, while 22.5% answered “not sure” (Table 4). Regarding the individual who provided the explanation, 90.2% of respondents reported that it was mainly the oncologists who provided the explanation on subfertility (Table 4). Regarding the individual receiving the explanation, 20 respondents answered that the explanation was only provided to the guardians and to the majority of patients older than adolescent.

**Medical examinations performed by pediatric endocrinologists**

Regarding the methods for evaluating testicular function in CCSs, over 80% of

| Table 3 | Physicians’ opinions and knowledge regarding issues of gonadal function or fertility in pediatric patients with cancer (n = 151) |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| **Gonadal function and fertility are important issues in childhood patients with cancer** |
| Strongly agree | 143 (94.7) |
| Agree | 6 (4.0) |
| Disagree | 1 (0.7) |
| Strongly disagree | 0 |
| No answer | 1 (0.7) |
| **Gonadal dysfunction or subfertility caused by cancer treatment is acceptable in relation to the risk of cancer death** |
| Strongly agree | 22 (14.6) |
| Agree | 63 (41.7) |
| Disagree | 45 (29.8) |
| Strongly disagree | 19 (12.6) |
| No answer | 2 (1.3) |
| **Guardians are concerned regarding the side effect of cancer treatment on their children’s gonadal function or fertility** |
| Strongly agree | 69 (45.7) |
| Agree | 44 (29.1) |
| Disagree | 35 (23.2) |
| Strongly disagree | 1 (0.7) |
| No answer | 2 (1.3) |
| **Pediatric patients are concerned regarding the side effect of cancer treatment on their gonadal function or fertility** |
| Strongly agree | 38 (25.2) |
| Agree | 55 (36.4) |
| Disagree | 45 (29.8) |
| Strongly disagree | 10 (6.6) |
| No answer | 3 (2.0) |
respondents selected Tanner staging (penile and scrotal growth), testicular volume, FSH levels, LH levels, or testosterone levels, while 17.9% (n = 27) of respondents selected semen analysis. Regarding the methods for evaluating ovarian function in CCSs, over 80% of respondents selected Tanner staging (breast growth), menstruation, FSH levels, LH levels, or estradiol levels, whereas 23.8% (n = 36) of respondents selected anti-Müllerian hormone levels.

Regarding the referral of CCSs with gonadal dysfunction to reproductive professionals, 66.9% (n = 101) of respondents answered that they referred male patients with testicular dysfunction to reproductive professionals, with 32 respondents mentioning that they referred the patients from adolescence to adulthood, and 45 mentioning that they referred the patients after the patients had become adults. On the other hand, 74.8% (n = 113) of the respondents referred female patients with ovarian dysfunction to reproductive professionals, with 60 respondents mentioning that they had referred patients from adolescence to adulthood, and 29 mentioning that they referred the patients after the patients became adults. These results show that female survivors were generally referred to a reproductive professional at an earlier stage than male survivors. Only 16.6% (n = 25) of respondents reported having experience with the birth of the survivors’ children during long-term follow-up.

Opinions about miscarriages, premature births, delivery problems, and fetal malformation in CCSs

Regarding a potential increase in the incidence of miscarriages, premature births, or
delivery problems for female CCSs, two-thirds of respondents (n = 101) answered that they “strongly agree” or “agree” that such problems occur more often in CCSs (Table 5). On the other hand, regarding a potential increase in the incidence of fetal malformation in pregnant CCSs or in their pregnant partners, 27.8% (n = 42) of respondents answered that they “strongly agree” or “agree” that such incidence is higher, while 35.8% (n = 54) answered that they “disagree”, and 29.1% (n = 44) “could not decide”, which shows that a substantial number of respondents answered carefully (Table 5).

**Table 5** Viewpoint regarding the increase of problems in CCSs, and the awareness of issues concerning fertility preservation before cancer treatment (n = 151)

| Increased incidence of miscarriages, premature births, or delivery problems if female CCSs become pregnant | No. (%) |
| --- | --- |
| Strongly agree | 47 (31.1) |
| Agree | 54 (35.8) |
| Disagree | 10 (6.6) |
| Cannot decide | 29 (19.2) |
| No answer | 11 (7.3) |

| Increased incidence of fetal malformation if CCSs or their partners become pregnant | No. (%) |
| --- | --- |
| Strongly agree | 6 (4.0) |
| Agree | 36 (23.8) |
| Disagree | 54 (35.8) |
| Cannot decide | 44 (29.1) |
| No answer | 11 (7.3) |

| Do you think fertility preservation before cancer treatment is problematic? | No. (%) |
| --- | --- |
| Yes | 34 (22.5) |
| No | 45 (29.8) |
| Cannot decide | 69 (45.7) |
| No answer | 3 (2.0) |

CCSs, childhood cancer survivors.

**Actual experience with difficult situations due to subfertility or maternal health problems**

A quarter of the respondents (n = 38) had experienced difficult situations in clinical practice due to treatment-related subfertility (infertility) or maternal health problems in CCSs. Specific examples were “inadequate explanation before treatment”, “the shock of being informed about being infertile by endocrinologists and not by oncologists”, “revelation of abnormalities during adolescence”, “difficulty in the absolute evaluation of female infertility”, “issues related to fertility itself, such as infertility and miscarriage”, “difficulty in selecting treatment for patients with recurrent cancer who desire to have children”, and “disagreement between the opinion of patients and guardians”.

**Issues with fertility preservation before the start of cancer treatment**

Only 15.2% (n = 23) of respondents answered that they had experience with fertility preservation before the cancer treatment. Sixteen respondents had experience with sperm cryopreservation, and 15 respondents had experience with gonadal...
shielding before radiotherapy for male patients, whereas 14 respondents had experience with gonadal shielding before radiotherapy for female patients. A few respondents had experience with ovarian cryopreservation (n = 2), testicular (n = 1) or ovarian tissue cryopreservation (n = 1), ovarian transposition (n = 2), or use of GnRH analogs (n = 5).

Regarding the respondents’ opinion on fertility preservation before cancer treatment, nearly half of the respondents (n = 69) answered that they “cannot decide” whether this is a problematic issue (Table 5). A total of 45 respondents pointed out various issues in relation to fertility preservation (Fig. 1). The most commonly mentioned item was “technical issues (clinical application)”, followed by “physical immaturity due to young age (before secondary sexual characteristics are developed)”, “financial issues”, “physical burden on patients”, “psychological burden on patients”, “ethical issues”, “delayed start of cancer treatment”, “patients uninformed of cancer diagnosis”, and “legal issues”. Issues marked as “other” included lack of control of precision or maintenance of fertility preservation systems, difficulty in obtaining understanding from patients and their families, and various attitudes among treatment providers.

**Fig. 1.** Various issues specified by the 45 pediatric endocrinologists who opined on fertility preservation before cancer treatment.

---

**Measures necessary to maintain gonadal function or preserve fertility in the future**

A total of 71 respondents (47.0%) provided answers regarding potential measures to be taken in the future in order to maintain gonadal function or preserve fertility in pediatric cancer patients. These responses were interpreted in detail to evaluate themes that could explain their content. These themes were summarized *a posteriori* and categorized for tabulation. If the response covered a broad range of themes, the response from a single respondent was classified under more than one category. For this analysis, the largest number of respondents voiced the
need for “collaboration among physicians and other healthcare providers in various disciplines”, followed by “safety of medical technology”, “fertility preservation techniques”, “obtaining understanding and providing information to patients and their families”, “discussion, awareness, and educational activities in the medical community”, and “guidelines and consensus” (Fig. 2).

**Discussion**

We conducted a questionnaire survey regarding reproduction in childhood and adolescent cancer patients. The high response rate for the present survey indicates that pediatric endocrinologists are highly concerned about the issue of gonadal function or fertility in pediatric patients with cancer. A relatively large proportion of respondents recognized CCS, late complications, and long-term follow-up guidelines, which suggests that the survey results obtained from JSPE directors and councilors reflected the country’s situation and opinions, based on the actual experience of senior physicians in Japan. The evaluation methods for testicular and ovarian function in CCSs were common for the respondents.

While most physicians commonly considered fertility as an important issue, their opinions regarding acceptability of gonadal dysfunction or subfertility differed in relation to the risk of cancer death. Many physicians thought that miscarriages, premature births, and delivery problems would increase in CCSs. However, there was no consensus regarding the correlation with fetal malformation.

In the free-entry field, several respondents...
pointed out the lack of studies and discussion on fertility. No consensus was achieved even among experienced pediatric endocrinologists, warranting an immediate nationwide survey on maternal health and childbirth in Japanese CCSs. Although only a limited number of respondents (n = 25) had experience with childbirth of survivors, these experienced respondents are undergoing a second survey by our group.

From the viewpoint of pediatric endocrinologists, some guardians and patients did not appear to be so concerned about the effect of the cancer treatment on gonadal function or fertility. One possible reason for this is that they cannot think of the future because the immediate top priority is the cancer and its treatment. However, there is also the possibility that they did not fully understand the explanation provided before the cancer treatment, or that they might hesitate to talk to physicians about their concerns (14). Moreover, one of the characteristics of pediatric cancer is that patients reach reproductive age long after the treatment. Explanations about the disease are often not provided to the patients themselves (15). Since patients are physically, psychologically, and socially immature, they cannot understand their own situation or make their own decisions, making the issues more complicated. On the other hand, cancer treatment should not be negatively affected by excessive concerns about gonadal damage. However, since this issue is strongly associated with the social quality of life, explanations should also be provided to the patients themselves at an appropriate time, and paying close attention to the mental aspect (16–18).

More than half of the respondents answered that the potential risk of gonadal dysfunction or subfertility was explained before cancer treatment. However, in most cases, the oncologists were the ones who provided the explanation. Since endocrinologists and oncologists are not always available at the same institution, clinical guidelines are needed for both specialties in order to provide the same explanations. A substantial number of respondents reported that endocrinologists followed up the patients without knowing what was initially explained to the patients. Several respondents noted that the patients did not fully recognize or remember explanations made before the treatment, and that the patients were very shocked when they were informed about their infertility by endocrinologists at the follow-up visit.

Although only a limited number of respondents had experience with fertility preservation before cancer treatment, an increasing number of institutions are trying to offer gonadal shielding before radiotherapy or sperm cryopreservation. These experienced respondents (n = 23) are included in our second survey. A long-term follow-up survey on the fertility prognosis of these patients and the health of their children is warranted in the future. It is expected that more patients will receive fertility preservation in the future by the means of adequate selection of indications. In order to perform such practice effectively, an infrastructure should be established that could accurately record how oncologists explained reduced gonadal function or fertility, and record for which cases fertility preservation was considered, thereby facilitating long-term follow-up by endocrinologists.

In the free-entry field wherein respondents were asked to write what they thought would be necessary to maintain gonadal function or preserve fertility, the most commonly suggested answer was having a collaborative infrastructure. A broad understanding within the medical community, and a collaborative infrastructure were also proposed, and included providing feedback information from reproductive specialists to oncologists or endocrinologists, and an inter-disciplinary collaboration among healthcare providers including physicians, nurses, and counselors. The same result was achieved by the national survey for Japanese breast cancer patients (19, 20). While there
is an expectation for the advance of medical technologies, many respondents expressed anxiety and uncertainty regarding such technologies. They called for more information on safety, and needed more accurate information. Accurate knowledge and information are needed in order to obtain understanding and provide information to patients and to their families. In the context of remarkable advances in reproductive medicine, efforts to establish guidelines or consensus should be made taking into consideration the need for safer fertility preservation. Therefore, this issue is probably one of the most significant challenges that today’s pediatric endocrinologists must tackle.

One of the major characteristics of discussions on fertility issues is the time lag: patients are young when they are being treated, but problems are brought to light after they reach adulthood. Performing medical interventions such as fertility preservation and assisted reproductive technology involve a wide range of issues such as financial burden, legal and ethical issues, and mental burden. Psychological counseling should also be offered.

This study had high response rate and reflected the opinions of pediatric endocrinologists with abundant clinical experience. However, there are some limitations in this questionnaire survey. We could not gather information from institutions which did not have a pediatric endocrinologist. Similar studies in larger scale should be performed from the viewpoints of specialized pediatric oncologists, gynecologists and urologists.

**Conclusion**

Japanese pediatric endocrinologists are highly concerned about the issue of gonadal function or fertility in childhood and adolescent cancer survivors. Many councilors mentioned the necessity for inter-disciplinary communication among healthcare providers. A nationwide survey on maternal health and childbirth for Japanese CCSs is needed.

**Acknowledgements**

We would like to thank all of the directors and councilors who are members of the JSPE for their contribution to this questionnaire survey. This project was supported by a Health and Labour Sciences Research Grant (Research for Promotion of Cancer Control Program: H26-Ippan-016). The authors declare no conflict of interests.

**References**

1. Foundation for Promotion of Cancer Research Cancer statistics in Japan – 2014. http://ganjoho.jp/en/professional/statistics/brochure/2014_en.html (accessed January 25, 2016).
2. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Childhood Cancer Survivor Study Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355: 1572–82. [Medline] [CrossRef]
3. Dickerman JD. The late effects of childhood cancer therapy. Pediatrics 2007;119: 554–68. [Medline] [CrossRef]
4. Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 2013;309: 2371–81. [Medline] [CrossRef]
5. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, Version 4.0. http://www.survivorshipguidelines.org (accessed February 12, 2016).
6. Childhood Cancer Survivor Committee of the Japanese Society for Pediatric Endocrinology Physician’s follow-up guide for childhood cancer survivors - 2011. http://jspe.umin.jp/medical/gui.html (accessed January 25, 2016).
7. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. American Society of Clinical Oncology Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013;31: 2500–10. [Medline]
8. Chemaitilly W, Sklar CA. Endocrine complications in long-term survivors of childhood cancers. Endocr Relat Cancer 2010;17: R141–59. [Medline] [CrossRef]
9. Kenney LB, Cohen LE, Shnorhavorian M, Metzger ML, Lockart B, Hijiya N, et al. Male reproductive health after childhood, adolescent, and young adult cancers: a report from the Children’s Oncology Group. J Clin Oncol 2012;30: 3408–16. [Medline] [CrossRef]
10. Green DM, Sklar CA, Boice JD Jr, Mulvihill JJ, Whitton JA, Stovall M, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. J Clin Oncol 2009;27: 2374–81. [Medline] [CrossRef]
11. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 2009;27: 2677–85. [Medline] [CrossRef]
12. Miyoshi Y, Ohta H, Hashii Y, Tokimasa S, Namba N, Mushiake S, et al. Endocrinological analysis of 122 Japanese childhood cancer survivors in a single hospital. Endocr J 2008;55: 1055–63. [Medline] [CrossRef]
13. Miyoshi Y, Ohta H, Namba N, Tachibana M, Miyamura T, Miyashita E, et al. Low serum concentrations of anti-Müllerian hormone are common in 53 female childhood cancer survivors. Horm Res Paediatr 2013;79: 17–21. [Medline] [CrossRef]
14. van den Berg H, Langeveld NE. Parental knowledge of fertility in male childhood cancer survivors. Psychooncology 2008;17: 287–91. [Medline] [CrossRef]
15. Parsons SK, Saiki-Craighill S, Mayer DK, Sullivan AM, Jeruss S, Terrin N, et al. Telling children and adolescents about their cancer diagnosis: Cross-cultural comparisons between pediatric oncologists in the US and Japan. Psychooncology 2007;16: 60–8. [Medline] [CrossRef]
16. Letourneau JM, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer 2012;118: 1710–7. [Medline] [CrossRef]
17. Ishida Y, Takahashi M, Maru M, Mori M, Henderson TO, Daugherty CK, et al. Physician preferences and knowledge regarding the care of childhood cancer survivors in Japan: a mailed survey of the Japanese Society of Pediatric Oncology. Jpn J Clin Oncol 2012;42: 513–21. [Medline] [CrossRef]
18. Wallace WH, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol 2005;6: 209–18. [Medline] [CrossRef]
19. Shimizu C, Bando H, Kato T, Mizota Y, Yamamoto S, Fujiwara Y. Physicians’ knowledge, attitude, and behavior regarding fertility issues for young breast cancer patients: a national survey for breast care specialists. Breast Cancer 2013;20: 230–40. [Medline] [CrossRef]
20. Shimizu C, Kato T, Tamura N, Bando H, Asada Y, Mizota Y, et al. Perception and needs of reproductive specialists with regard to fertility preservation of young breast cancer patients. Int J Clin Oncol 2015;20: 82–9. [Medline] [CrossRef]