



# Clinical Practice Guidelines for Fertility Preservation in Pediatric, Adolescent, and Young Adults with Cancer

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## Abstract

In recent years, more cancer patients are achieving long-term survival owing to advances in treatment. However, cancer treatment can cause gonadal dysfunction that leads to loss of fertility. Thus, it is important for clinical oncologists to consider fertility preservation in children, adolescents, and young adults with cancer who are expected to have a favorable outcome and may wish to have children in the future. Sometimes, fertility preservation has to be abandoned depending on the stage of the cancer and the general condition of the patient, because fertility preservation procedures may unacceptably delay cancer treatment or be too risky for the patient. The Clinical Practice Guidelines for Fertility Preservation in Children, Adolescents, and Young Adults with Cancer were published in 2017 as the first guidelines for this field in Japan. These guidelines cover general principles and recommendations for 8 oncological categories, which is a point of difference from other guidelines. Close coordination between clinical oncologists and reproductive medicine specialists is important over the long term from the pretreatment phase through the post-treatment phase. Therefore, the guidelines were devised to help medical staff consider the available fertility preservation therapies and determine whether performing fertility preservation is appropriate before initiating the treatment for cancer, and to ultimately improve survivorship for children, adolescents, and young adults with cancer. This article reviews the latest information concerning clinical practice guidelines around the world, including the American Society of Clinical Oncology guidelines that were the first to be published in this field.

**Keywords** Fertility preservation · Pediatric, adolescent, and young adults with cancer · Guideline · FertiPROTEKT · Oncofertility Consortium · Japan Society of Clinical Oncology

## Introduction

In recent years, an increasing number of cancer patients have achieved long survival, thanks to various advances in treatment. Accordingly, maintaining gonadal function and preserving fertility after successful treatment of cancer have become critical concerns for young patients. Because cancer treatment can cause gonadal dysfunction and loss of fertility, clinical oncologists should consider fertility preservation for young cancer patients who are expected to respond to treatment and may wish to have children in the future. Of course, it may be necessary to abandon fertility preservation because of the patient's condition since treatment of cancer

itself must be prioritized. The American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients state as follows: “As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists” [1]. The American Society of Clinical Oncology (ASCO) guideline was updated in 2013 [2]. In 2006, Woodruff's group at Northwestern University in Chicago established the Oncofertility Consortium, which is a nationwide network for coordination of oncologic and reproductive healthcare, and they also published clinical pocket guides to oncofertility for health care providers and patients [3].

In 2006, von Wolff at the University of Berne in Switzerland founded FertiPROTEKT as a German language network to supply information about fertility preservation, and this group issued oncofertility guidelines in 2011 [4].

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Furthermore, Donnez and colleagues founded the International Society for Fertility Preservation (ISFP) in 2007. They have hosted biennial academic conferences attended by researchers from around the world and have published recommendations for fertility preservation [5–7].

In Japan, there has been no comprehensive guideline on fertility preservation in patients with specific cancers. Clinical oncologists in Japan should recognize the importance of fertility preservation in children, adolescents, and young adults with cancer to improve survivorship. However, there are not a few cases in which young patients with cancer are obliged to give up fertility because treatment for cancer must have the top priority. In October 2015, the Japan Society of Clinical Oncology (JSCO) started to develop guidelines that focused on cancer treatment while taking fertility preservation into consideration. In July 2017, JSCO completed the “2017 Clinical Practice Guidelines for Fertility Preservation in Pediatric, Adolescent, and Young Adult Cancer Patients”.

This article reviews clinical practice guidelines from around the world for fertility preservation in children, adolescents, and young adults with cancer.

## ASCO guidelines

In 2006, ASCO and the American Society for Reproductive Medicine (ASRM) published the world’s first guidelines on fertility preservation in patients with cancer (The American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients), which was updated in 2013 [1, 2]. The 2006 ASCO guidelines were based on a review of published articles from 1987 through 2005. The authors remarked that it was difficult to devise guidelines supported by robust evidence-based research because it is ethically impossible to conduct randomized controlled studies of fertility preservation therapy in cancer patients. The ASCO guidelines stress the following 3 points: (1) Clinical oncologists should provide timely information to patients about the possibility of infertility associated with cancer therapy and discuss possible options for fertility preservation before initiation of treatment, followed by referral to reproductive specialists if patients express interest in fertility preservation. (2) Cryopreservation of sperm and embryos is a standard fertility preservation therapy, while experimental therapies should only be performed at institutions with sufficient expertise. (3) Resumption of menstruation does not always reflect maintenance of fertility, so regular menstrual cycles after treatment of cancer do not necessarily equal fertility preservation. The ASCO guidelines concluded that cancer patients do not receive sufficient information about fertility preservation options.

In the 2013 update, all of the medical professionals engaged in fertility preservation (doctors, nurses, clinical

psychotherapists, social workers, etc.) are referred to as healthcare providers. The update indicates that healthcare providers should adopt a team approach for the management of cancer patients, and that clinical oncologists should inform patients about the possibility of fertility impairment due to treatment of cancer [2].

In the 2013 ASCO update, cryopreservation of unfertilized oocytes is no longer referred to as experimental therapy. The risk of ovarian failure related to bevacizumab is stated to be “unknown” in the 2013 ASCO update, but the 2014 update classifies bevacizumab as intermediate risk. This change was supported by the NSABP C-08 Study (a Phase III study of add-on bevacizumab with chemotherapy as postoperative adjuvant therapy for colon cancer), which showed that patients receiving mFOLFOX6 and bevacizumab had a higher incidence of ovarian failure (defined as amenorrhea for 3 months with a follicle stimulating hormone level  $\geq 30$  mIU/mL) than patients receiving mFOLFOX6 alone, and the FDA warning issued in 2011: “Female patients with cancer should be informed of the possible development of ovarian failure before starting administration of bevacizumab” [8].

## National Comprehensive Cancer Network guidelines

The National Comprehensive Cancer Network (NCCN) Adolescent and Young Adult (AYA) Oncology 2 Version 2 (one of the clinical practice guidelines in oncology) focuses on adolescents and young adults with cancer who are scheduled for the treatment by alkylating agents or radiation associated with a high risk of loss of fertility [9]. The NCCN guidelines emphasize the following 2 points: (1) When cancer is diagnosed in an adolescent or young adult, the clinical oncologists should discuss the risk to fertility and refer the patient to a center specializing in fertility preservation. (2) The clinical oncologist should also refer the patient to a healthcare provider with expertise in providing psychological support for cancer patients who are making difficult decisions. With reference to the ASCO guidelines, the NCCN guidelines specify fertility preservation methods separately for male and female cancer patients. Cryopreservation of sperm is recommended for male cancer patients, while cryopreservation of embryos, ova, or ovarian tissue is recommended for female cancer patients. The NCCN guidelines also state that cryopreservation of embryos or ova is suitable for patients with a low-to-medium risk of fertility loss, such as patients with Hodgkin’s lymphoma, low-grade sarcoma, or breast cancer, if sufficient time is available before initiation of anticancer therapy. The guidelines mention that there have been conflicting reports with regard to ovarian protection by gonadotropin-releasing hormone (GnRH) analogs,

although such therapy may be beneficial in patients with breast cancer.

The 2018 NCCN guidelines have been updated with regard to the following 4 points: (1) “Discuss risks for infertility due to cancer and its therapy (especially for high-risk therapies such as alkylating agents or gonadal irradiation), fertility preservation, and contraception prior to the start of therapy”. (2) For males, the wording has been changed to: “Discuss the option of sperm banking”. (3) For females, the wording has been changed to: “Discuss the option of embryo or oocyte cryopreservation or ovarian tissue cryopreservation (if available)”. (4) For males and females, the following has been added: “Consider follow-up with fertility specialist post-treatment”. Thus, the guidelines now indicate the importance of follow-up by a fertility specialist after treatment of the patient’s cancer.

### **Oncofertility Consortium guidelines**

In 2007, the Oncofertility Consortium was founded by Woodruff at Northwestern University (Chicago, USA). It is a national, interdisciplinary initiative designed to explore the reproductive future of cancer survivors. The Oncofertility Consortium and the associated Center for Reproductive Health after disease bring together professionals in reproductive medicine, reproductive health research, oncology, biomechanics, materials science, mathematics, social science, bioethics, religion, policy research, and educational sciences to expand current knowledge, research, clinical practice, and training for a broad spectrum of issues including the following: (1) mechanisms by which cancer treatments cause infertility, (2) methods for cryopreservation, storing, and growing ovarian and gonadal tissue, (3) in vitro follicle growth and oocyte maturation using three-dimensional culture, (4) communication barriers between cancer patients and healthcare providers, and (5) ethical and legal concerns regarding use of fertility preservation techniques in cancer patients. The Oncofertility Consortium has published pocket guides for healthcare providers and cancer patients on its website [10]. It also has published detailed information about specific fertility preservation therapies [11].

### **FertiPROTEKT guidelines**

FertiPROTEKT is a network founded by von Wolf in 2006 for the German-speaking sphere, and it has published guidelines on fertility preservation for female cancer patients in relation to specific anticancer treatments [4]. The FertiPROTEKT guidelines also indicate the importance of psychological support. In 2017, this network published practical recommendations in the archives of gynecology and obstetrics.

Part 1 deals with breast cancer, Hodgkin’s lymphoma, borderline ovarian malignant tumors, uterine cervical cancer, endometrial cancer, rheumatic and autoimmune disorders, Ewing sarcoma, osteosarcoma, colorectal carcinoma, non-Hodgkin’s lymphoma, acute lymphoblastic leukemia, and acute myeloid leukemia, detailing the prognosis, risk to fertility, risk of ovarian metastasis, and fertility preservation measures for each disease [12]. Summarized recommendations are also presented, and the effects of irradiation on the gonads and uterus are described. Part 2 describes the background, efficacy, risks, and practical approach to ovarian stimulation and cryopreservation of ova, cryopreservation and transplantation of ovarian tissue, ovarian protection using GnRH agonists, and ovarian transplantation [13]. These guidelines also present information about in vitro maturation and experimental techniques. The FertiPROTEKT guidelines most strongly recommend ovarian stimulation (including double stimulation) and cryopreservation of ova for fertility preservation in female cancer patients under 35 years old. Ovarian tissue cryopreservation is also considered useful, especially for young cancer patients who have limited time before initiation of treatment. The guidelines state that ovarian protection using GnRH agonists prevents premature ovarian failure in 50% of patients, with the duration of efficacy being limited. For patients scheduled to undergo abdominal radiotherapy, the guidelines state that ovarian transplantation is relatively simple and can be performed in combination with ovarian tissue cryopreservation. Thus, ovarian tissue cryopreservation is not considered to be an experimental procedure in the FertiPROTEKT guidelines, while ovarian protection by GnRH agonist therapy is regarded as inadequate.

### **ISFP guidelines**

Donnez founded the International Society for Fertility Preservation (ISFP) in 2007, and the society has since held biennial conferences that bring researchers together from across the world for vigorous discussion. In 2012, the ISFP published fertility preservation guidelines for patients with lymphoma, leukemia, and breast cancer [5–7]. These guidelines also describe the indications for ovarian tissue cryopreservation.

### **Japan Society of Obstetrics and Gynecology perspectives**

The Japan Society of Obstetrics and Gynecology (JSOG) issued “perspectives on harvesting, freezing, and storage of gametes and ovarian tissue based on medical indications”, following approval at the JSOG Special Meeting in 2014. The

JSOG Perspectives states as follows: “If a woman with cancer is anticipated to sustain impairment of ovarian function leading to loss of fertility before having children as a consequence of surgery, chemotherapy, and/or radiation therapy for the treatment of her cancer, it is reasonable to harvest, freeze, and store unfertilized oocytes for fertility preservation based on the patient’s own decision. Fertility preservation should be offered if the patient seeks it, even when the patient does not wish to have a child at the time of receiving treatment for cancer. However, there are various uncertainties regarding this fertility preservation technique, including the impact on the prognosis of cancer, the probability of achieving pregnancy using stored ova in the future, and the safety of pregnancy arising from stored ova. Therefore, it is important to provide the patient with sufficient information to make her own decision”. Thus, the JSOG Perspectives consider this fertility preservation technique to be indicated when treatment of the patient’s cancer is expected to lead to ovarian dysfunction and when employing this technique will not cause any notable disadvantage to the patient’s future fertility and/or anticancer therapy. The JSOG Perspectives were updated in 2016 to include information about cryopreservation of embryos (fertilized ova). For male patients, the JSOG first published “Perspectives on Sperm Cryopreservation” in 2007. The current Perspectives state as follows: “Cryopreservation of human sperm is widely applied clinically for infertility treatments such as artificial insemination and *in vitro* fertilization. There have been various advances in treatment for cancer, including surgical procedures, chemotherapy, and radiotherapy, but it has been found that such interventions can reduce gonadal function. Therefore, it is reasonable to perform cryopreservation of the sperm before starting cancer treatment, based on the patient’s own decision, in order to allow for the possibility of the patient employing such methods to have a child in the future”.

The JSOG Perspectives summarize current practice, while taking into account the medical standards and ethical issues concerned with oncofertility, so Japanese healthcare providers should fully understand and comply with the principles stated in the perspectives. In Japan, only centers authorized by the JSOG are permitted to harvest, freeze, and store gametes, embryos (fertilized oocytes), and ovarian tissue for medical indications. As of January 2018, 54 centers are authorized to perform cryopreservation of unfertilized oocytes and 35 centers are authorized for ovarian tissue cryopreservation.

## Japan Society of Clinical Oncology Guidelines (Fig. 1)

The Japan Society of Clinical Oncology (JSCO) Clinical Practice Guidelines for Fertility Preservation in Pediatric, Adolescent, and Young Adults with Cancer (JSCO

guidelines) are focused on pediatric, adolescent, and young adult cancer patients aged < 40 years when starting treatment, in principle. The term “in principle” was added because male patients aged over 40 years may be included. The guidelines are intended for Japanese medical staff providing chemotherapy and radiotherapy for the treatment of solid or hematopoietic cancers and medical staff engaged in reproductive support (doctors, nurses, pharmacists, psychologists, counselors, oncology counselors, social workers, etc.).

In 2015, the JSCO set up a working group to develop guidelines for medical staff that would improve patient management. The working group consisted of 52 members representing oncologists treating various cancers (female genital tract, breast, urinary tract, hematopoietic, pediatric bone and soft tissue, brain, and gastrointestinal tract), as well as reproductive medicine specialists, nurses, and pharmacologists. The resulting guidelines contain 9 chapters, which include 1 chapter on each category of cancer and a chapter providing an overall summary. The chapter on female genital tract cancer includes a statement about support of pregnancy, while the other chapters only have a statement about fertility preservation. These guidelines are consensus based, not evidence based, and take into consideration ethical matters related to oncofertility. Because there have been few randomized controlled studies on fertility preservation in children, adolescents, and young adults with cancer, the JSCO guidelines were drawn up with reference to the ASCO guidelines (2006 and 2013 versions), which are the only systematic guidelines in this field. Draft versions of each part were reviewed by a core group of specialists and then further reviewed by other groups. The contents and grade of recommendations were determined after discussion by the core specialists until consensus was reached.

The guidelines list 6 key points regarding reproductive management of cancer patients. Healthcare providers should: (1) fully understand and comply with the JSOG principles expressed in “perspectives on harvesting, freezing, and storage of gametes and ovarian tissue based on medical indications” and “Perspectives on Sperm Cryopreservation”, (2) understand the impact of specific cancer treatments on germ cells and fertility, (3) consider the need for fertility preservation by taking into consideration the patient’s malignancy and general physical condition and the impact of cancer treatment on germ cells and fertility, (4) understand methods for preservation of gonadal function, (5) understand fertility issues in patients with hereditary malignancy, and (6) refer cancer patients to reproductive medicine specialists after discussion with each patient and family members, and provide support for patients making decisions about fertility preservation.

The JSCO guidelines include 4 clinical questions to ask about each cancer patient (Table 1), and presenting a total



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JSCO Clinical Practice Guidelines 2017  
 for Fertility Preservation in Childhood,  
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総論  
 女性生殖器  
 乳腺  
 泌尿器  
 小児  
 造血器  
 骨軟部  
 脳  
 消化器

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**Fig. 1** The Japan Society of Clinical Oncology Clinical Practice Guidelines for Fertility Preservation in Pediatric, Adolescent, and Young Adults with Cancer include 4 clinical questions to ask about

each cancer patient (Table 1), and presenting a total of 40 recommendations based on the clinical questions

of 40 recommendations based on the clinical questions. In this regard, the JSCO guidelines differ from other guidelines published to date. To grade the recommendations, the 2007 MINDS guide [14] was used with minor modifications. External opinions on the key recommendations were obtained at a consensus discussion during the 54th annual meeting of the JSCO (Yokohama, 2016). After amendments were made based on the opinions obtained, the working group version was shown to the JSCO members, 23 related academic societies, and 6 patient associations for input before the final version was released. The comprehensive statement about the responsibilities of clinical oncologists regarding fertility preservation in young cancer patients is shown in Table 2. A recommendation grade is not specified because although consensus has been

obtained, it is ethically difficult to perform clinical studies and there is no robust scientific evidence.

## Future tasks

The JSCO guidelines were prepared to reflect the current status of pediatric, adolescent, and young adult patients with cancer. Issues that need to be solved in the future are summarized in Table 3. Currently, the “Oncofertility medical coordination network”, which provides information about reproductive medicine for patients, is not available nationwide in Japan, and coordination between clinical oncologists and reproductive medicine specialists is insufficient or a system for such coordination has not been established in some institutions. Moreover, reproductive

**Table 1** Clinical questions

1.	Which patients with OO cancer do you think can become pregnant after cancer treatment?
2.	Would you recommend delaying the start of anticancer treatment if a patient with OO cancer wants fertility preservation therapy?
3.	When do you think a patient with OO cancer can become pregnant after treatment of her cancer if she undergoes fertility preservation therapy?
4.	What fertility preservation method do you recommend for a patient with OO cancer who wishes to have children in the future?
Other questions can be added as required	

**Table 2** General statements of the JSCO guidelines

What information about fertility should be provided to a patient with cancer who wishes to have children in the future?	
Recommendations	
1.	Clinical oncologists should prioritize treatment of cancer above other considerations
2.	Clinical oncologists should inform patients about the possibility of treatment-related infertility at the reproductive age and provide patients with relevant information
3.	Clinical oncologists should promptly refer patients who wish to have children to specialists in reproductive medicine
4.	Clinical oncologists should consider the availability and timing of fertility preservation therapy through close coordination with reproductive medicine specialists

**Table 3** Future tasks related to the JSCO guidelines

1.	Establish a system for treatment selection and guidance on oncofertility, including an informed assent form (for children and adolescents) and an informed consent form (for adults)
2.	Management of patients who do not want fertility preservation or in whom fertility preservation is contraindicated
3.	Medical intervention to maintain and improve the QOL of cancer survivors who underwent treatment before 2012
4.	Obtaining further knowledge about oncofertility and promotion of information delivery (including peer support groups for cancer survivors)
5.	Consider public financial assistance for fertility preservation therapy
6.	Nurture expert healthcare providers dealing with oncofertility
7.	Promote technical innovations in the oncofertility field

medicine is not covered by the national health insurance scheme in Japan, so cancer patients who choose fertility preservation incur a financial burden that can interfere with the application of recommendations in the guidelines. In the future, the influence of the present JSCO guidelines on the live birth rate should be evaluated. In the United States, the ASCO guidelines were published in 2006 and updated in 2013 [1, 2], with a further update being published on the ASCO website in 2014. However, two reports have suggested that the ASCO recommendations have not been widely adopted by healthcare providers in that country. In 2014, a prospective study on fertility preservation in 620 young patients with breast cancer < 40 years old was published [15]. Multivariate analysis revealed that factors associated with significant anxiety about loss of fertility were (1) young age, (2) non-white ethnicity, (3) no prior pregnancy, and (4) chemotherapy. In particular, it revealed that young unmarried patients with breast cancer were anxious about future loss of fertility, and it was found that clinical oncologists had not informed these patients about hormone therapy possibly compromising fertility preservation depending on the duration of treatment. Accordingly, there may have been insufficient coordination between clinical oncologists and reproductive medicine specialists up to 2014 despite the ASCO guidelines being issued in 2006.

Also, a report was published in 2016 on a survey conducted in Georgia to investigate fertility counseling for female cancer patients before starting treatment [16]. This survey aimed to evaluate the effect of the 2006 ASCO guidelines on decision-making about fertility preservation by patients. A total of 1,116 female cancer patients were surveyed with respect to counseling on fertility preservation at the time of diagnosis and whether their cancer treatment had an impact on pregnancy. It was found that counseling and referral for fertility preservation increased between 2005 and 2006, but there was no dramatic change after publication of the ASCO guidelines in 2006. In fact, < 80% of the patients received counseling. Only patients with breast cancer or lymphoma were commonly referred for reproductive treatment, but the referral rate did not exceed 20%, although not all cancer patients can be referred to institutions specializing in reproductive medicine for practical reasons. Healthcare providers should refer female cancer patients to reproductive medicine specialists to help the patients make decisions, even if they decide not to undergo fertility preservation therapy. Therefore, it seems problematic that around 80% of patients in Georgia were not referred to specialist institutions at 10 years after publication of the ASCO guidelines according to this survey. Therefore, the impact of the ASCO guidelines should be evaluated on a national scale, and education on fertility preservation is urgently required for clinical oncologists and various other healthcare providers. In

Japan, there are plans for public research to periodically evaluate the impact of the JSCO guidelines.

## Conclusions

For many years, cryopreservation of gametes or fertilized ova, or displacement or shielding of the ovaries during radiotherapy, was the standard approach for fertility preservation in young cancer patients. In 2004, Donnez reported the first live birth after ovarian tissue cryopreservation and transplantation [17]. Since then, this technique has been applied as a new approach to fertility preservation for young female cancer patients. The discipline of “oncofertility” has been established in the United States and Europe, and clinical management of fertility preservation in children, adolescents, and young adults with cancer has been re-considered. However, it should be emphasized that treatment of the cancer should be prioritized and it is important to implement such treatment without delay, while supporting patients to make their own decisions about future fertility. After cancer is diagnosed, the patient and family members must simultaneously face various issues and make various decisions within a short period. In children or adolescents, diagnosis of cancer has a significant psychological impact on the parents and other family members as well as the patient, which means that ongoing support by a clinical psychotherapist is necessary. To carry out fertility preservation therapy, good coordination between institutions is required as well as an environment that enables the patient to make decisions rapidly through careful counseling. In the future, we need to overcome the information gap about fertility preservation among clinical oncologists, reproductive medicine specialists, and patients and create a society where safe fertility preservation therapy can be selected accurately. From this perspective, publication of the 2017 Clinical Practice Guidelines on Fertility Preservation in Pediatric, Adolescent, and Young Adult Cancer patients is thought to be beneficial for cancer patients in Japan and elsewhere.

## Compliance with ethical standards

**Conflict of interest** The author declares that he has no conflict of interest.

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