

An evaluation of the Gifu Model in a trial for a new regional oncofertility network in Japan, focusing on its necessity and effects

Tatsuro Furui^{1,2} · Motoki Takenaka² · Hiroshi Makino² · Keiko Terazawa² · Akio Yamamoto² · Ken-ichiro Morishige^{1,2}

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Abstract

Purpose We evaluated our 2-year experience of the regional oncofertility network in Gifu Prefecture (GPOFS) in order to establish a more sophisticated regional oncofertility networking model in Japan.

Methods Questionnaires were distributed twice in January 2013 to 57 departments in 35 hospitals that provide cancer treatment in Gifu Prefecture, before the establishment of the regional oncofertility network. The number and type of disease of the referred adolescent and young adult (AYA) cancer patients who visited the oncofertility clinic in Gifu University Hospital via the GPOFS were analyzed.

Results The majority of regional oncologists are aware of the need to provide information about oncofertility to their patients, but they cannot provide sufficient information due to their lack of knowledge about reproductive medicine. Eighty-one AYA patients were referred to our clinic for oncofertility counseling in the first 2 years after the establishment of the GPOFS.

Conclusions The GPOFS as the first regional oncofertility network in Japan has just started and may be working to help both AYA cancer patients and their oncologists. The nationwide establishment of the regional oncofertility network model could help both AYA cancer patients and oncologists.

Keywords AYA (adolescents and young adults) · Gifu Model · Japan Society for Fertility Preservation (JSFP) · Medical network · Oncofertility

Introduction

Total-body irradiation, irradiation of the gonads, and chemotherapy regimens containing high doses of alkylators can place adolescents and young adults (AYA) with cancer at risk of subfertility after the successful completion of cancer treatment. The provision of information on the risk of infertility and possible interventions to maintain reproductive potential are critical for the AYA population at the time of diagnosis. Because patients should be given complicated and detailed information relating to cancer treatment and due to the evolving nature of information related to fertility preservation, and because of the associated ethical issues, it may be preferable to have a specialized team to address these issues with AYA patients rather than the patient's primary oncologist [1]. To achieve the effective and efficient provision of information and support the decisions of patients, a regional medical network system is needed beyond the hospital.

Gifu Prefecture, which is located in central Japan, has a population of approximately 2 million and covers an area of 10,621 km² [2]. Gifu has 7 local cancer centers and about 17 hospitals, which provide multidisciplinary cancer treatment.

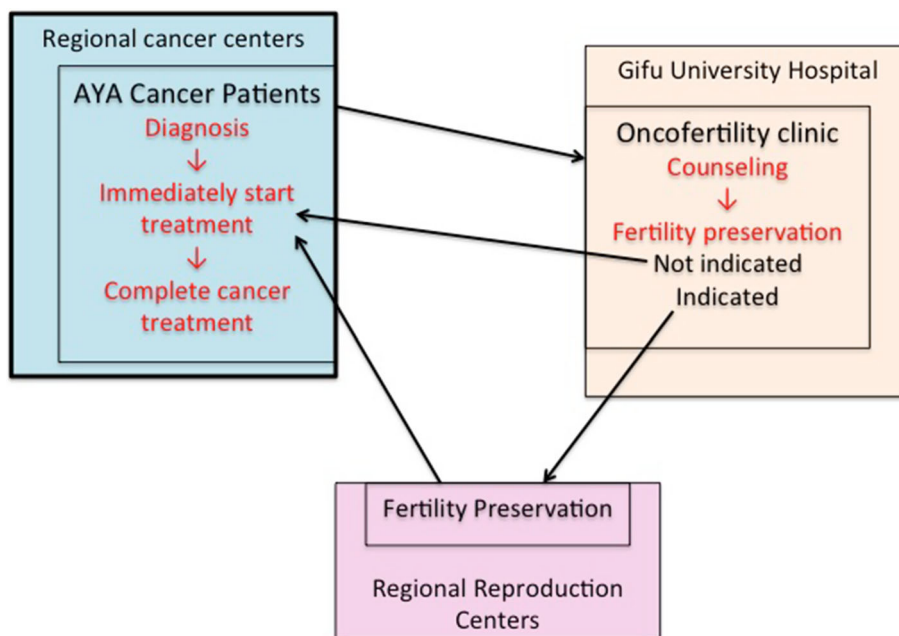
We started a regional oncofertility network of Gifu patients, oncologists, and fertility specialists (GPOFS), which we call the Gifu Model, in February 2013 (Fig. 1). Here we report our 2-year experience with the Gifu Model and attempt to clarify a more sophisticated system.

✉ Tatsuro Furui
furui@gifu-u.ac.jp

¹ Department of Obstetrics and Gynecology, Gifu University Graduate School of Medicine, 1-6-1 Yanagido, Gifu, Gifu 501-1194, Japan

² Department of Obstetrics and Gynecology, Gifu University Hospital, Gifu, Japan

Fig. 1 The Gifu Model as a regional oncofertility network system. AYA cancer patients who wish to obtain more detailed information about the potential impact of cancer therapy on their reproductive function are told to visit the Oncofertility Clinic at Gifu University Hospital as quickly as possible before cancer treatment. The Oncofertility Clinic supports AYA cancer patients in making decisions about the preservation of their fertility



Materials and methods

We sent questionnaires twice in January 2013 to 57 departments in 35 hospitals that provide cancer treatment in Gifu Prefecture, before the establishment of the regional oncofertility network. The questionnaires asked oncologists about the information that they provided to their patients, and their cognisance of oncofertility (therapy-induced infertility and the options for fertility preservation) (Fig. 2). We also asked the oncologists to indicate the number of AYA cancer patients and their disease and obstetric histories among the patients who were treated at their departments from January 2012 to December 2013. We also asked them whether the gynecologists at their hospital provided AYA cancer patients with counseling or

if fertility preservation interventions were performed in their hospitals.

The GPOFS network

The GPOFS network started with 110 oncologists, fertility specialists, nurses and scientists from 43 departments in 23 hospitals, institutes and local government. Regarding oncofertility, the linkage of many types of medical and social specialists is essential. Participation of the local government is very important because local government can access many types of medical and social associations via meetings and their websites and can announce information on the GPOFS system. We started the Oncofertility Clinic in Gifu University Hospital in February 2013. AYA

Fig. 2 The questionnaire for the oncologists. The questionnaire assesses the attitude toward informed consent and the recognition of oncofertility by regional oncologists. The questionnaire was sent to 57 departments in 35 hospitals that provide cancer treatment in Gifu Prefecture

Do you know about the fertility preservation options listed below?

- Semen or oocyte cryopreservation Yes No
- Embryo cryopreservation Yes No
- Ovarian tissue cryopreservation Yes No
- Ovary transposition to the outside of radiation field Yes No

Do you inform your patients of the following points before starting cancer treatment?

- Possibility of gonadal dysfunction Yes No
- Possibility of infertility Yes No
- Options for fertility preservation Yes No
 - Sperm or oocyte cryopreservation Yes No
 - Embryo cryopreservation Yes No
 - Ovarian tissue cryopreservation Yes No
 - Ovarian transposition to the outside of radiation field Yes No

patients who were diagnosed with malignant disease, and whose fertility is potentially threatened by their disease or its treatment, were told to access the Oncofertility Clinic in Gifu University Hospital as soon as possible via the GPOFS network and were given detailed information.

Results

Forty oncologists from 29 clinical departments answered the questionnaire. Their specialties were as follows: breast (*n* = 19), hematology and GI (*n* = 13), urology (*n* = 5), pediatrics (*n* = 2) and orthopedics (*n* = 1). The clinical experience of the oncologists (at the time of the surgery, before the implementation of the GPOFS system) ranged from 7 to 39 years (Table 1). Nineteen oncologists, who were all from major regional cancer centers, completed the questionnaires after the establishment of the GPOFS networking system. Finally, we evaluated the trends of the patients who were counseled at the Oncofertility Clinic at Gifu University Hospital via the GPOFS network.

The provision of information on oncofertility to AYA patients by oncologists in Gifu Prefecture

The status of the information on oncofertility that was provided to AYA cancer patients was surveyed. The percentages of oncologists who provided information about gonadotoxicity, fertility disorder, fertility preservation, cryopreservation (gamete, embryo and ovarian tissue) and ovarian translocation were 90, 90, 62.5, 58.8, 23.8, 8.8 and 8.8 %, respectively (Fig. 3). However, the percentages of patients who were given detailed information about oncofertility, sperm cryopreservation or embryo cryopreservation by gynecologists at their hospital were only 26.7, 20.0 and 13.3 %, respectively (Fig. 4).

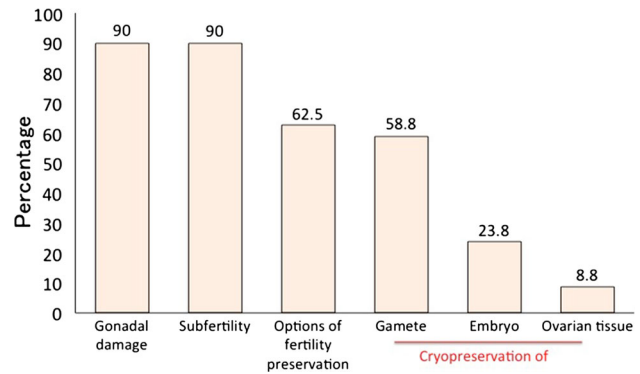


Fig. 3 The present status of information about oncofertility that is provided to AYA cancer patients by regional oncologists. The numbers show the percentages of regional oncologists in Gifu Prefecture who answered “informed” in regard to gonadal damage, subfertility, options of fertility preservation, and cryopreservation of gamete, embryo and ovarian tissue. The questionnaire revealed that 90 % of the oncologists informed their AYA patients about the possibility of reproductive dysfunction after cancer treatment but that fewer oncologists provided more detailed information

The level of understanding on fertility preservation options among oncologists in Gifu Prefecture

We surveyed the level of the understanding of oncologists in Gifu Prefecture on fertility preservation options. The percentages of oncologists who understood the cryopreservation of gamete, embryo, ovarian tissue and ovarian translocation were 60, 30, 5 and 10 %, respectively (Fig. 5).

The number of AYA patients who were treated in the major cancer centers of Gifu Prefecture in 2011

The responses to the questionnaires from 29 clinical departments in 15 facilities were collected with a 50.9 % response rate. The survey showed the responses of 91 young cancer patients (younger than 40 years of age) who were first diagnosed in a major cancer center in 2011. The

Table 1 Responses of the oncologists who answered the survey

Specialties of oncologists	Number of physicians (number of departments)	Clinical experience (years) Mean ± SD
Breast	19 (14)	21.6 ± 6.7
Hematology or GI	13 (3)	14.3 ± 7.3
Urology	5 (5)	29.0 ± 11.3
Pediatrics	2 (2)	14.5
Orthopedics	1 (1)	20
	40 (29)	7–39

February 2013–December 2014; total = 81. The questionnaire was sent to 57 departments in 35 hospitals that provide cancer treatment in Gifu Prefecture. Forty oncologists from 29 clinical departments answered the questionnaires. The number of physicians and their specialties were as follows: breast (*n* = 19), hematology or GI (*n* = 13), urology (*n* = 5), pediatrics (*n* = 2) and orthopedics (*n* = 1). The clinical experience of the physicians ranged from 7 to 39 years. The questionnaire assessed their cognisance of oncofertility (therapy-induced infertility and fertility preservation options)

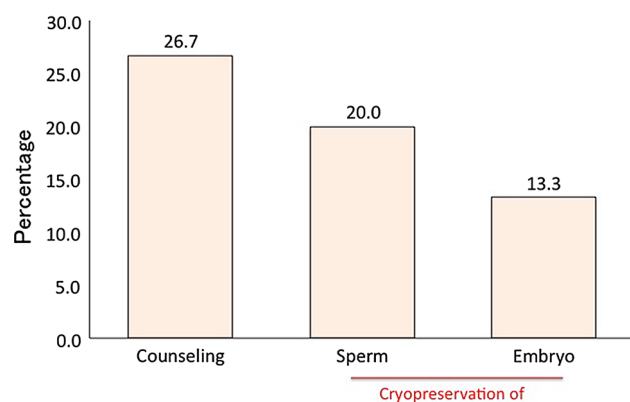


Fig. 4 The presence of gynecologists in regional cancer centers. The *numbers* show the percentages of cancer centers in which there are gynecologists who can provide counseling (26.7 %), sperm preservation (20.0 %) or embryo preservation (13.3 %) to their AYA patients

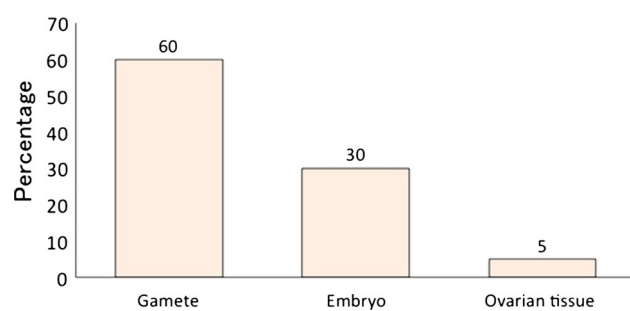


Fig. 5 The level of the understanding of oncologists about each of the fertility preservation treatments. The *numbers* show the percentages of regional oncologists in Gifu Prefecture who indicated that they “understand” each of the fertility preservation treatments. The percentage of oncologists who indicated that they understood the preservation treatments for gamete, embryo and ovarian tissues were 60, 30, and 5 %, respectively

patients included 49 breast cancer patients and 18 hematological cancer patients (Table 2).

A good prognosis was expected in 85 % of the AYA cancer patients in this study for whom a reproductive disorder after cancer treatment could be critical. Fifty-five percent of the good prognosis patients were treated with methods that had the potential to interfere with their fertility.

At least four patients in whom a good prognosis was expected and who indicated that they wished to bear children in the future underwent gonadotoxic treatments (Fig. 6).

AYA cancer patients who visited the Oncofertility Clinic in Gifu University Hospital via the GPOFS network

We started the Oncofertility Clinic at Gifu University Hospital at the same time as the GPOFS network was

created. AYA cancer patients could be given detailed information about oncofertility and were supported in making their own decisions related to the preservation of their fertility preservation as quickly as possible before their cancer treatment. Eighty-one AYA cancer patients (56 female, 25 male, including 3 patients who were over 40 years of age) visited the clinic and were given counseling during the first 2 years of the clinic’s operation (Fig. 7). In total, the clinic was visited by 6–7 visitors each month. The average ages of the female and male visitors were 33.6 ± 7.0 and 28.4 ± 7.5 years, respectively, with most patients indicating that they had no children or only one child. The hospitals that they initially attended were widely distributed in Gifu Prefecture. The clinic was also visited by a small number of patients from outside Gifu Prefecture (Table 3).

The diagnosis of the majority of the female visitors was breast cancer (56 %), followed by hematological cancer (24 %). In contrast, the diagnosis in the majority of male visitors was hematological cancer (60 %), followed by testicular cancer (16 %) (Fig. 8). The rate of female and male visitors who did not selected fertility preservation before cancer treatment remained at 70 and 12 %, respectively, throughout the study period (Fig. 9).

Discussion

According to our study, reproductive failure was widely recognized by the oncologists to be induced by cancer treatment, but they were hesitant to obtain appropriate informed consent and to propose fertility preservation due to the lack of an oncofertility networking system.

In Gifu Prefecture, 90 % of the oncologists informed their young patients that chemotherapy induced reproductive disorders, but less than 30 % of oncologists informed their young patients about the options of egg or ovarian tissue cryopreservation. It was not possible for the AYA cancer patients to receive oncofertility counseling or treatment at the majority of regional cancer centers. All oncologists who answered this questionnaire indicated that they wanted to increase their connections with fertility specialists.

The issue of fertility preservation in AYA cancer patients has become more important because improved survival after cancer treatment has heightened awareness in regard to long-term quality of life, and the development of cryopreservation techniques for gamete, embryo and gonadal tissues [1, 3–7]. The term “fertility preservation” is applied to medical techniques that help cancer survivors preserve their fertility options before undergoing gonadotoxic cancer treatments such as chemotherapy and radiotherapy. Fertility preservation is now considered to be a

Table 2 Number of AYA patients in Gifu Prefecture and their diagnoses

	Number of AYA cancer patients	Number from department
Surgery (mainly breast)	49	13
Hematology	18	3
Urology	3	5
Pediatrics	14	2
Orthopedics	7	1
Number of treated AYA patients	–	5
Total	91	29

A questionnaire for AYA patients who were diagnosed in 2011 was sent to 57 departments in 35 hospitals that provide cancer treatment in Gifu Prefecture and information was collected from 29 clinical departments (50.9 %) in 15 hospitals. Most of the patients were treated by departments of surgery ($n = 49$), hematology ($n = 18$) and pediatrics ($n = 14$)

Fig. 6 The treatment-related fertility risks for the AYA cancer patients. *Left* the percentage of AYA cancer patients in whom a good prognosis was recognized by their oncologists. *Right* the percentage of AYA patients in whom treatment was scheduled that was associated with high-risk to their fertility

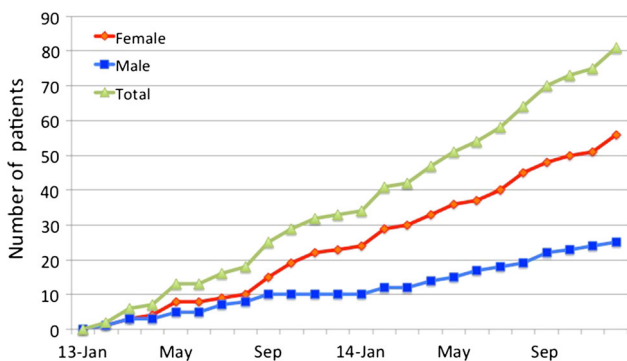
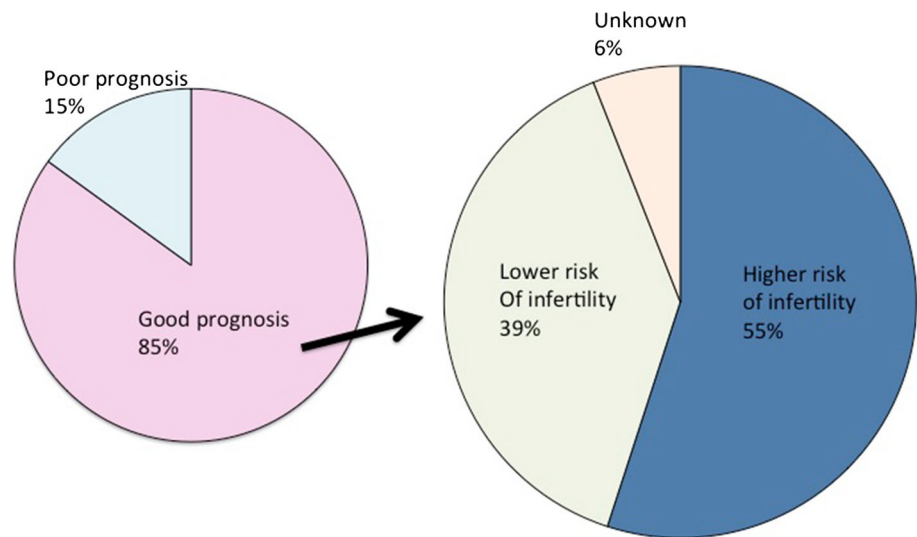


Fig. 7 The cumulative number of patients who visited the Oncofertility Clinic of Gifu University Hospital. *Closed triangles, closed diamonds and closed circles* indicate the total number of patients, the number of female patients and the number of male patients, respectively

major issue in the treatment of young patients with cancer. Previous reports show that a threat to future fertility is a significant concern for cancer survivors [3, 6, 8, 9]. Despite

the heightened awareness of fertility preservation and the increasing number of patients who are referred to fertility preservation specialists, only a small percentage of patients elect to receive treatment [4, 8, 10]. This suggests that making decisions about fertility preservation is a complex process for many young patients with cancer.

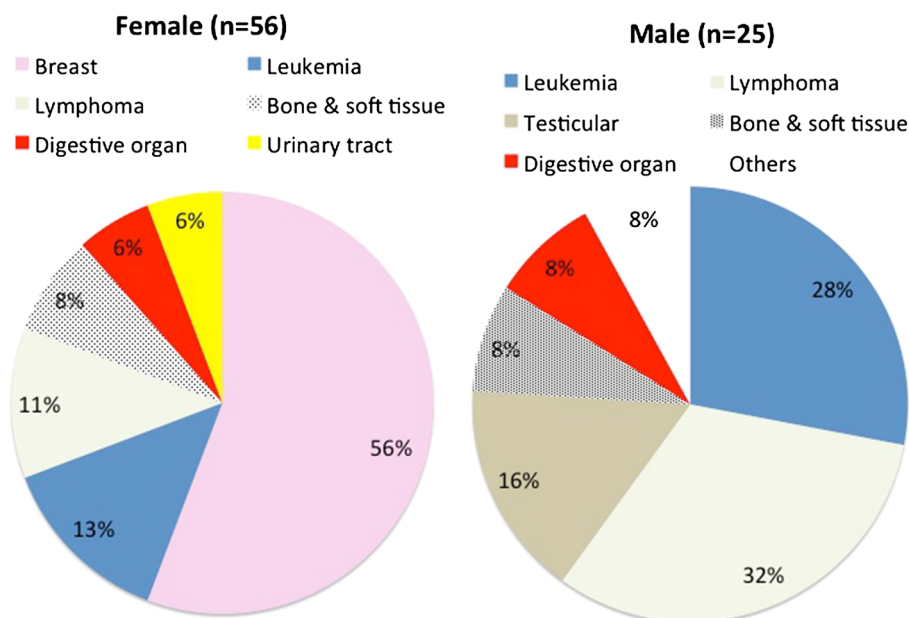
We started the GPOFS network for oncologists and fertility specialists. The network involves the collaboration of regional medical specialists from a range of hospitals and specialties to support AYA cancer patients in making their own decisions on fertility preservation. The Oncofertility Consortium in the United States [11] and the FertiPROTEKT network in German-speaking countries [10, 12] work well and have become good models for the GPOFS network. Their network system is very progressive and mature, not only in their huge scale, but also in enriched content that was comprehensive with regard to research and education.

AYA cancer patients in whom malignant disease is diagnosed and whose fertility may be threatened by their

Table 3 Characteristics of patients who visited the Oncofertility Clinic of Gifu University Hospital

	Female	Male	Total
Number	56	25	81
Age (years), mean \pm SD (range)	33.6 \pm 7.0 (16–46)	28.4 \pm 7.5 (15–40)	32.5 \pm 7.5 (15–46)
Married, <i>n</i> (%)	20 (48.8 %)	4 (21.0 %)	24 (64.9 %)
Original hospital			
Gifu Univ. Hospital	24	16	40
In Gifu City	12	4	16
In Gifu Prefecture	9	1	10
Other	11	4	15
Number of children			
0	42 (75 %)	23 (92 %)	65 (80.0 %)
1	9 (16.1 %)	2 (8.0 %)	11 (13.6 %)
≥ 2	5 (8.9 %)	0 (0.0 %)	5 (6.2 %)

The table describes the age, marital status, original hospital and the number of children born to the patients

Fig. 8 Primary diseases of the visitors to the Oncofertility Clinic of Gifu University Hospital. *Left* female patients; *right* male patients

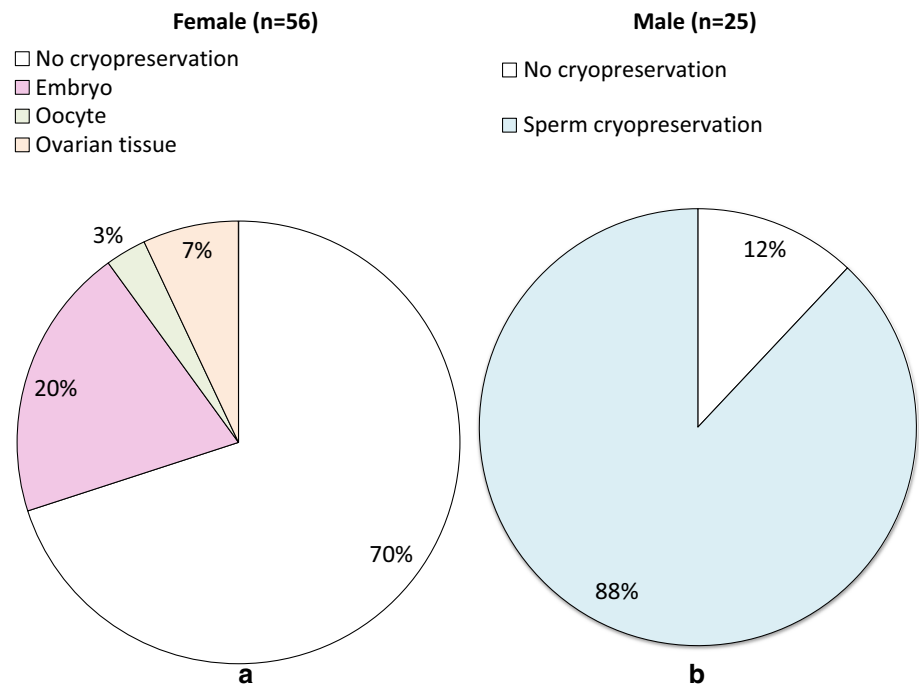
disease or its treatment are told to access the Oncofertility Clinic in Gifu University Hospital as soon as possible via the GPOFS network and are given detailed information about fertility preservation. Our oncofertility clinic supports AYA cancer patients in making their own decisions about receiving fertility preservation with intensively-informed consent in collaboration with fertility specialists and oncologists. However, the cancer treatment should be given top priority as a matter of course in this self-determination.

The GPOFS network, which represents the whole of Gifu Prefecture and the surrounding area, is an interdisciplinary and inter-professional network of medical specialists, scientists and scholars who are exploring the relationships between health, disease, survivorship and

fertility preservation in young cancer patients. The GPOFS network has just started to help both AYA cancer patients and their oncologists.

There are still many problems to solve with regard to the regional oncofertility network: these include determining the appropriate scale of network, creating a systematic means of providing information in relation to oncofertility counseling, and establishing an educational system for medical providers. Furthermore, a greater number of medical providers need to join and discuss the topic of oncofertility in a nationwide study group such as the Japanese Society for Fertility Preservation (JSFP) in Japan. We believe that the nationwide establishment of the regional oncofertility network could help both AYA cancer patients and oncologists.

Fig. 9 Fertility preservation after counselling. *Left* female, *right* male



Compliance with ethical standards

Conflict of interest Tatsuro Furui, Motoki Takenaka, Hiroshi Makino, Keiko Terazawa, Akio Yamamoto and Ken-ichiro Morishige declare that they have no conflict of interest.

Human/animal studies This article does not contain any studies with human or animal subjects performed by any of the authors.

References

- Levine J, Canada A, Stern CJ. Fertility preservation in adolescents and young adults with cancer. *J Clin Oncol.* 2010;28:4831–41.
- Gifu Prefectural Government. Facts about Gifu Prefecture. Available at: <http://www.pref.gifu.lg.jp/English/info/gifu/1.html>. Accessed 23 May 2015.
- Forman EJ, Anders CK, Behera MA. A nationwide survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients. *Fertil Steril.* 2010;94:1652–6.
- Kim J, Oktay K, Gracia C, Lee S, Morse C, Mersereau JE. Which patients pursue fertility preservation treatments? A multicenter analysis of the predictors of fertility preservation in women with breast cancer. *Fertil Steril.* 2012;97:671–6.
- Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer:

American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2013;31:2500–10.

- Suzuki N. Ovarian tissue cryopreservation in young cancer patients for fertility preservation. *Reprod Med Biol.* 2015;14:1–4.
- Suzuki N, Yoshioka N, Takae S, Sugishita Y, Tamura M, Hashimoto S, et al. Successful fertility preservation following ovarian tissue vitrification in patients with primary ovarian insufficiency. *Hum Reprod.* 2015;30:608–15.
- Kim J, Deal AM, Balthazar U, Kondapalli LA, Gracia C, Mersereau JE. Fertility preservation consultation for women with cancer: are we helping patients make high-quality decisions? *Reprod Biomed Online.* 2013;27:96–103.
- Nishijima C, Suzuki N. [Fertility Problems in Oncofertility Treatment—Including ASCO Guidelines]. *Gan To Kagaku Ryoho.* 2015;42:283–8 (**Article in Japanese**).
- Lawrenz B, Jauckus J, Kupka MS, Strowitzki T, von Wolff M. Fertility preservation in >1,000 patients: patient’s characteristics, spectrum, efficacy and risks of applied preservation techniques. *Arch Gynecol Obstet.* 2011;283:651–6.
- Waimey KE, Duncan FE, Su HI, Smith K, Wallach H, Jona K, et al. Future directions in oncofertility and fertility preservation: a report from the 2011 oncofertility consortium conference. *J Adolesc Young Adult Oncol.* 2013;2:25–30.
- von Wolff M, Montag M, Dittrich R, Denschlag D, Nawroth F, Lawrenz B. Fertility preservation in women—a practical guide to preservation techniques and therapeutic strategies in breast cancer, Hodgkin’s lymphoma and borderline ovarian tumours by the fertility preservation network FertiPROTEKT. *Arch Gynecol Obstet.* 2011;284:427–35.