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ORIGINAL ARTICLE

Male Fertility

Current status of sperm banking for young cancer patients in Japanese nationwide survey

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This study aimed to ascertain the current status of Japanese sperm banking for young cancer patients. During 2015, we mailed the directors of 695 institutes where sperm cryopreservation might be performed with questionnaires requesting information on the number of patients, age, precryopreservation chemotherapy, semen analyses results and diagnoses, cryopreservation success rate, and causes of unsuccessful cryopreservation. Of these 695 institutes, 92 had cryopreserved sperm before chemotherapy within the study period. In all, 820 cancer patients (237 testicular, 383 hematological, 46 bone and soft tissue, 20 brain, and 134 other malignancy) consulted the responding institutes for sperm cryopreservation. Except for testicular tumor, the number of patients whose sperm was preserved before cancer treatment was low compared to that of young cancer patients. Approximately 20% of patients with malignancies other than testicular tumor underwent chemotherapy before cryopreservation. The success rate of cryopreservation in hematological malignancy was 82.5%, significantly lower than that of both the testicular cancer (93.6%) and other malignancy groups (95.6%) ($P < 0.05$). The primary reasons for preservation failure were azoospermia and poor semen quality. Patients with hematological malignancies had a higher rate of unsuccessful cryopreservation compared to those in other groups, possibly due to the large number of patients requesting sperm cryopreservation after chemotherapy induction. In Japan, information regarding sperm banking prior to cancer treatment appears to be lacking. Information regarding sperm preservation before chemotherapy should be provided to all Japanese oncologists.

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INTRODUCTION

Because of advances in therapy, survival rates among young adult and adolescent patients with cancer have improved substantially.¹ However, many of these therapies are toxic to germ cells and, in male patients, have been known to reduce spermatogenic potential and cause male infertility.^{2,3} Surgery of the abdomen and pelvis obstructs the seminal tracts and may affect sexual function.

Infertility is a considerable problem in Japan, with a declining birthrate in the country. Infertility caused by cancer treatment should be addressed, and fertility preservation is currently the only tool to achieve this. Gamete cryopreservation before chemotherapy for young patients with cancer is recommended by the American Society of Clinical Oncology guidelines, announced in 2006 and updated in 2013.^{4,5}

As with other developed countries, in Japan, treatment results of young cancer patients have notably improved, and cancer survivors are better able to plan for life after treatment. Schover *et al.*⁶ conducted a postal survey about cancer-related infertility; sperm banking was offered to 904 men diagnosed with cancer

within the previous 2 years. Although the return rate was only 27% (201 men) out of the original 904, except for men who died or whose mailing addresses were unknown, responders did not differ significantly from nonresponders regarding institution, age, ethnicity, or cancer site. Overall, 51% of men wanted children in the future, including 77% of men who were childless at the time of cancer diagnosis.

For men, cryopreservation of semen is a fertility preservation therapy that has existed for some time. Recently, in Japan, awareness of enriching fertility preservation treatment for young cancer patients has increased. The number of sperm banking institutes also seems to be increasing. However, unlike egg or embryo cryopreservation systems, the sperm cryopreservation system in Japan is not a registration system. Therefore, the number of institutions and patients involved in sperm cryopreservation is unknown. To clarify the status of sperm banking in Japan, we investigated the number, age, success rate, and presence of chemotherapy prebanking of patients undergoing sperm banking before cancer therapy according to disease over 1 year.

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PATIENTS AND METHODS

The study protocol was approved by the St. Marianna University, Nasu Red Cross Hospital, and Yokohama City University review boards. All respondents provided their informed consents for participation.

Study participants

We conducted a national survey on sperm cryopreservation. Six hundred and ninety-five institutes throughout Japan that met the following inclusion criteria were mailed questionnaires: (1) listed on the homepage of the Japan Society of Reproductive Medicine website as offering sperm cryopreservation, (2) specialized in assisted reproductive technology and accredited by the Japanese Association of Obstetrics and Gynecology, and (3) a university hospital. The institutes' directors were asked to report the number of new patients who participated in sperm banking between April 2015 and March 2016. Directors were also asked to provide information regarding age, chemotherapy before cryopreservation, result of semen analyses and diagnoses, cryopreservation success rate, and causes of unsuccessful sperm preservation.

Statistical analysis

A Chi-squared test was used to confirm bias due to age, result of semen analysis, chemotherapy before banking, and successful cryopreservation according to disease group. Unknown cases were excluded upon verification. Differences were considered statistically significant when $P \leq 0.05$. All calculations were performed with JMP® version 12.0 for Macintosh (SAS Institute Inc., Tokyo, Japan).

RESULTS

Response rate and characteristics of patients

Three hundred and twenty-nine institutes returned completed questionnaires (response rate, 47.3%). Of these, 92 had cryopreserved sperm before chemotherapy within the specified year. These institutes comprised 27 urology, 64 gynecology, and 1 unknown (no entry) departments. Types of institutes were 46 private clinics, 18 university hospitals, and 24 public or private hospitals. Many gynecological institutes that banked sperm were private clinics (40 cases). By contrast, among the urological institutes, sperm banking before cancer treatment was performed most frequently in university hospitals (12 cases; **Figure 1**). According to the number of patients consulting sperm banks, institutes that cryopreserved sperm for 1–5 patients per year represented the majority (55 institutes: 11 urology and

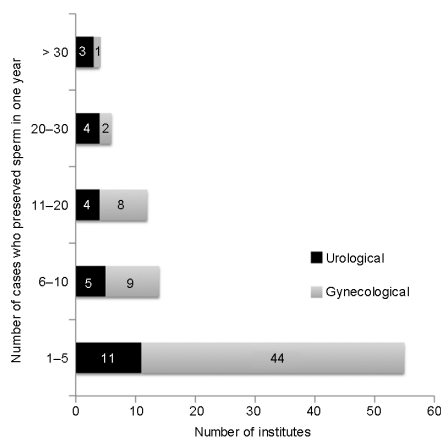


Figure 1: Number of institutes classified according to the number of patients requesting sperm banking for one year.

44 gynecology) of reporting institutes. Four institutes banked for more than 30 patients in a year (3 urology and 1 gynecology; **Figure 2**).

During the designated period, 820 patients consulted these institutes for sperm cryopreservation. Of these, there were 237 patients with testicular tumor, 383 with hematological malignancies including leukemia and lymphoma, 46 with bone and soft tissue tumors, 20 with brain tumors, and 134 with other malignancies. **Table 1** shows the number of patients classified according to disease, age, results of semen analyses on preservation, presence of chemotherapy before cryopreservation, success or failure of preservation, and cause of preservation failure.

Distribution of age and semen analysis according to disease group

In distribution of age, more than half of the patients in the testicular cancer and other malignancy groups were in their 30s–40s and those in the brain tumor, hematological malignancy, and bone and soft tissue tumor groups were in their teens to 20s (adolescent and young adults). In the hematological malignancy and bone and soft tissue tumor groups, the percentage of patients in the adolescent and young adults' generation was significantly higher than that in the testicular tumor and other malignancy groups ($P < 0.05$).

Regarding classification according to the results of semen analyses, based on the World Health Organization 2010 standard,⁷ the proportion of patients with normozoospermia ($>15 \times 10^6 \text{ ml}^{-1}$ sperm concentration and $>40\%$ motility) was more than 50% in the bone and soft tissue tumor group (27 patients, 58.7%), with all other groups having $<50\%$ normozoospermia. In particular, patients with testicular tumors had the lowest incidence of normozoospermia. The proportion of normozoospermia of the testicular tumor and hematological malignancy groups was significantly lower than that of the other groups ($P < 0.05$). The percentage of azoospermic patients was approximately 10% (24/237 [10.1%] with testicular tumor, 43/383 [11.2%] with hematological malignancy, 4/46 [8.7%] with bone and soft tissue tumor), except 1/134 (0.7%) with other malignancy. No patients with a brain tumor had azoospermia.

Proportion of patients who received chemotherapy before sperm banking and successful banking

In all groups except the testicular tumor group, the percentage of patients who underwent chemotherapy before cryopreservation was around 20% (105/383 [27.4%] with hematological malignancy, 11/46 [23.9%] with bone and soft tissue tumor, 4/20 [20.0%] with brain tumor, and 23/134 [17.2%] with other malignancy). The proportion of patients receiving chemotherapy before sperm banking in the testicular

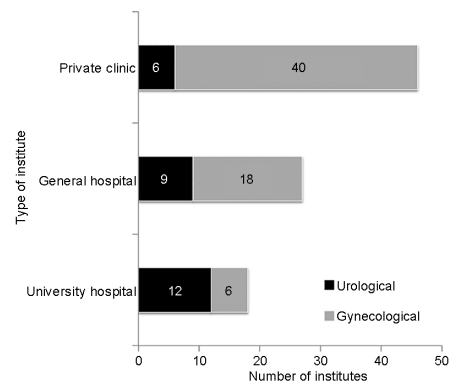


Figure 2: Number of institutes classified according to the type of institute conducting sperm banking.

Table 1: Distribution and background of patients who cryopreserved sperm before cancer treatment

Characteristics	TT (n=237)	HM (n=383)	BSTT (n=46)	BT (n=20)	Others (n=134)
Age (year)					
≤19	23	63	14	5	6
20–29	89	159	22	5	20
30–39	99	104	5	6	39
40–49	26	37	5	3	35
Unknown or no entry	0	20	0	1	34
Groups with significant differences*	HM, BSTT	TT, others	TT, others	NS	HM, BSTT
Semen analysis					
Azoospermia or not ejaculated	24	43	4	0	3
Oligoasthenozoospermia	82	118	8	6	16
Asthenozoospermia	35	50	5	8	31
Oligozoospermia	31	33	1	0	10
Normozoospermia	57	129	27	6	57
Unknown or no entry	8	10	1	0	17
Groups with significant differences*	BSTT, BT, others	BSTT, BT, others	TT, HM	TT, HM	TT, HM
Underwent chemotherapy before preservation					
Yes	15	105	11	4	23
No	222	278	35	16	111
Groups with significant differences*	HM, BSTT, others	TT	TT	NS	TT
Sperm preservation					
Successful	220	316	43	20	108
Unsuccessful	15	51	2	0	5
Unknown or no entry	2	16	1	0	21
Groups with significant differences*	HM	TT, others	NS	NS	HM
Cause of preservation failure					
Total	15	51	2	0	5
Azoospermia	14	33	2	0	2
Unable to ejaculate	0	4	0	0	1
Bad semen quality	0	13	0	0	2
Rejection	1	0	0	0	0
Others	0	1	0	0	0
Group with significant differences*	NS	NS	NS	NS	NS

* $P < 0.05$ in the Chi-square test ($P < 0.05$). BSTT: bone and soft tissue tumor; BT: brain tumor; HM: hematological malignancy; NS: not significant in any group; TT: testicular tumor

tumor group (15/237 [6.3%]) was significantly lower than that in the other groups except for the brain tumor group ($P < 0.05$). Among patients who came to the respondents' institutes, the percentage of patients who had successful cryopreservation, except for the unknown and no entry cases, was over than 90% (93.6% [220/235] patients with testicular tumor, 95.6% [43/45] with bone and soft tissue tumor, 95.6% [108/113] with other malignancy, and 100% [20/20] with brain tumor). The exception was the hematological malignancy group (86.1% [316/367] patients). The rate of sperm cryopreservation failure in the hematological malignancy group was significantly higher than that in both the testicular tumor and other malignancy groups ($P < 0.05$). Azoospermia was the most common reason for banking failure in testicular tumor (14 patients), hematological malignancy (33 patients), bone and soft tissue tumor (2 patients), and other malignancy groups (2 patients). Bad semen quality was the second most common reason in hematological malignancy (13 patients).

DISCUSSION

This is the first nationwide survey on sperm banking in Japan. Although there are many single-center studies on sperm banking,^{8–10} there are very few multicenter, collaborative research,¹¹ and nationwide survey¹² studies. The Japanese sperm banking system does not follow the European method of concentrating patients in one large domestic

specialized institute.¹² There are no laws or regulations currently governing sperm preservation in Japan. Due to the absence of laws and regulations, Japanese doctors must manage sperm banking themselves. The United States, like Japan, has no laws or regulations for sperm banking; however, the Food and Drug Administration (FDA) manages it. Unlike Japan, there are many large sperm banks in the United States. Many articles reporting on the sperm banks in the United States have a large number of patients, even in single-institute studies.^{9,13,14} Our survey revealed that, in Japan, half of the agencies responsible for banking are private clinics and approximately two-thirds are gynecological departments. The number of sperm bank visits in 1 year was revealed to be 5 or less in half or more institutes. Because the sperm banking system in Japan does not have a registration system, these statistics were revealed for the first time in our nationwide survey. Probably because there are many gynecology practitioners running the sperm banks, the institutes capable of enforcing assisted reproductive technology (ART) began to freeze sperm at the request of neighboring cancer therapists. The ART enforcement institute was originally capable of freezing sperm for infertility treatment, and it was easy for oncologists to rely on.

Our findings, regarding the number of patients who consulted responding institutes, are similar to those of other studies, while the numbers of patients with testicular and hematological malignancies

were considerable and those with bone and soft tissue and brain tumors were few.^{8–11} The number of patients with other malignancies, including cancers of the digestive, respiratory, and urology systems, is much lower because the incidence of these malignancies is low among the younger population. We examined the proportion of patients who cryopreserved their sperm with respect to the diseases considered in the present study, except the other malignancy group, from Japanese data (Table 2).

The prognosis of patients with high-stage testicular cancer is good if appropriate treatment is given. However, many patients require chemotherapy based on cisplatin, etoposide, and bleomycin. The American Society of Clinical Oncology classifies this regimen as medium risk,⁵ but because it is administered multiple times, it can cause deterioration and loss of spermatogenesis. In 2014, the Japan Urological Association reported the number of testicular cancer registrations.¹⁵ Registered patients were enrolled in 2005 and 2008. In 2008, 725 patients were enrolled from 274 institutions; 67.9% of all patients in 2005 and 2008 were Stage I, and 32.1% required chemotherapy or radiotherapy. Among the testicular tumors in Stage I, nonseminomatous germ cell tumors (NSGCT) required prophylactic chemotherapy. Just over 63% of patients had pure seminoma and 36.6% had NSGCT and needed prophylactic chemotherapy. Regarding patients enrolled in 2008, 232 (32.0%) patients had disease above Stage II. The number of patients with Stage I NSGCT was unknown. Therefore, the number of patients requiring chemotherapy among those with testicular tumors was estimated to be 200–300. Moreover, this report did not classify patients by age group. Thus, we could not differentiate between patients in their teens and 40s.

Chemotherapy containing alkylating agent and/or total body irradiation, which is a pretreatment for hematopoietic stem cell transplantation for leukemia patients, severely impairs spermatogenesis. Adriamycin, Bleomycin, Vinblastine, and Dacarbazine (ABVD) and Cyclophosphamide, Hydroxydaunorubicin, Oncovin® (Vincristine), and Prednisone (CHOP) therapy administered to patients with malignant lymphoma are classified as low risk in the American Society of Clinical Oncology guideline.⁵ However, these regimens contain cyclophosphamide and there may be a reduction in spermatogenesis due to multiple administrations. The incidence of hematological malignancies (such as leukemia or lymphoma) and brain tumors was registered at the Japanese National Cancer Center until 2012. According to the data, in 2012, 2593 male patients in the 10- to 40-year-old age group had lymphoma or leukemia at the time of our survey. The number of brain and central nervous system malignancies in male patients was 2686. Among them, 681 patients were in the 10- to 40-year-old age group.¹⁶ The number of patients with glioma is high in this age group. High-grade glioma requires radiation therapy and chemotherapy including temozolomide. The American Society of Clinical Oncology guidelines classify this treatment as high risk.⁵ In 2015, the Japanese

Orthopaedic Association (JOA) announced the number of bone and soft tissue tumors registered in Japan. According to their data, the number of male patients with malignant bone and soft tissue tumors was 1221. Among these, 354 were in the 10- to 40-year-old age group at the time of our present survey.^{17,18} Of these tumors, many of the bone tumors required chemotherapy based on ifosfamide.

In our survey, the response rate was <50%, suggesting that not all institutes are cooperative regarding cancer registries. Furthermore, the year of our survey was 2017 and the year of enforcement of the registry of testicular tumor, hematological malignancy, brain tumor, and bone and soft tissue tumor was 2008, 2012, 2012, and 2015, respectively. Because the year of each survey was different, the exact proportion of patients who cryopreserved their sperm with each malignancy cannot be calculated. Although it is difficult to determine the number of patients who need sperm cryopreservation based on these conditions alone, we speculate that approximately 230 of 300 (76.7%) patients with testicular tumors, 380 of 2600 (14.6%) with hematological malignancies, 20 of 680 (2.9%) with brain tumors, and 50 of 350 (14.3%) with bone and soft tissue tumors may need this procedure.

Patients with hematological malignancies, brain tumors, and bone and soft tissue tumors seem to require sperm banking to a lesser extent than patients with testicular tumors. Tiantiana *et al.*¹⁹ reported that among the various cancers, testicular tumor has the shortest period from diagnosis to sperm banking. In addition, there is a report that the sperm banking rate on morbidity in young testicular tumor patients is higher than that in patients with hematological malignancy.¹² Urologists who treat testicular tumors may have more knowledge on the testicular damage caused by anticancer drugs than oncologists in other specialists. This seems to be the reason for the high rate of sperm banking in testicular tumor patients.

Schover *et al.*⁶ reported that the lower sperm banking rate relative to the morbidity rate is due to inadequate information. In our sample, the sperm banking rate for all disease groups, except the testicular tumor group, was lower than the morbidity rate. According to a questionnaire survey conducted by Kobayashi *et al.*²⁰ in 2016 in institutes for hematological malignancy, 21 out of 22 responded that sperm banks are necessary; however, only 15 patients (68.2%) reported that referral to sperm banks is a routine procedure. Hematologists may understand but be unable to explain the importance of sperm banks due to the lack of information and the complexity of the work.

Hoshi *et al.*²¹ reported on sperm banking in patients with bone and soft tissue tumors and explained that there are few orthopedic surgeons considering fertility preservation; therefore, it is important to provide information to increase awareness among these practitioners.

Because the number of patients in the brain tumor and other malignancy groups, including lung and digestive system cancers, is

Table 2: The latest registration or incidence data on the number of cancer patients in Japan (testicular tumor, hematological malignancy, bone and soft tissue tumor, and brain tumor)

Cancer	Year of report	Survey year	Group that conducted the survey	Total male patients (n per year of investigation)	Male patients in the 10s–40s age group (n)	Patients investigated in this study (n)
TT	2014	2008	JUA ¹³	724	Unknown but 32.1% of patients greater than Stage II and Stage I patients with NSGCT are considered to require chemotherapy or radiotherapy	237
HM	2012	2012	National Cancer Center ¹⁴	22,629	2593	383
BSTT	2017	2015	JOA ^{15,16}	1221	354	46
BT	2012	2012	National Cancer Center ¹⁴	2686	681	20

JUA: Japan Urological Association; JOA: Japanese Orthopaedic Association; NSGCT: nonseminomatous germ cell tumor; BSTT: bone and soft tissue tumor; BT: brain tumor; HM: hematological malignancy; TT: testicular tumor



low, the knowledge of sperm banking among doctors treating these malignancies appears to be poor. Thus, teaching the concept of fertility preservation among these professionals may be necessary.

Achille *et al.*²² listed several factors that influence sperm banking from the perspective of survivors, that is, a health-care professional's role in discussing infertility, importance of fatherhood, fatherhood status, influence of a parent or partner, attitudes toward survival at the time of diagnosis, cost, and perception about the complexity and efficacy of sperm banking. Older patients have more partners and sperm banking is promoted, but if they already have children at the time of diagnosis or their family is complete, sperm banking is suppressed. This tendency seems to be supported by medical staff.²³ By contrast, young patients and their families often refuse to cryopreserve sperm because they do not appear to be concerned about marriage and fathering children in the future. In patients with bone and soft tissue tumors and hematological malignancies, the proportion of young patients was high. In the younger generation, especially in minors, the opinion of parents and guardians is sought in addition to the individual's opinion about sperm banking. Patients' parents and guardians also tend to believe that sperm cryopreservation is secondary to the preservation of life. Such a trend exists not only in Japan but also in Europe and the United States.²⁴ The proportion of adolescent and young adults-generation patients referring to sperm banking was less than half (47.3%) in the testicular tumor group. Conversely, it was more than half in the hematological malignancy (58.0%) and bone and soft tissue tumor groups (78.3%). The group of our survey is considered same age as that of patients who did not preserve sperm. It is important to avoid restricting the possibilities of young patients for the reasons stated above.

It is possible that spermatogenesis recovers after chemotherapy.^{25,26} However, there is no guarantee that fertility will be restored at the time of marriage, and it is unknown which patients will recover spermatogenesis after chemotherapy. Furthermore, it has been reported that 16–18 months of contraception is necessary, because the sperm of patients after chemotherapy have mutations.²⁷ There is also a report that the rate of birth defects is high.²⁸ An improved survival rate of young cancer patients has been reported by oncologists and gynecologists.^{1,29} In the future, sperm banking will become a very important supportive tool for young patients who receive treatment for cancer. We believe that it is necessary to ascertain the patient's desire for cryopreservation of sperm prior to disease treatment and to incorporate it into the treatment plan.

Compared to other disease groups, the proportion of patients with normozoospermia was lower in the testicular tumor and blood disease groups, and the proportion of patients with azoospermia was higher (testicular tumor, 10.1%; hematological malignancy, 11.2%). Patients with testicular tumors are said to have poor seminal findings.

The anticancer drug usage rate before banking by the testicular tumor group was 6.3%, which is significantly lower than that in the hematological malignancy, bone and soft tissue tumor, and other malignancy groups. We believe that testicular tumor patients have few chemotherapy treatments before banking because urologists have a better knowledge of the gonadotoxic effects of chemotherapy than oncologists in other specialties. These oncologists may have insufficient perceptions regarding the gonadotoxic effects of chemotherapy and may not understand the timing of referral for sperm banking. The semen quality in patients with hematological malignancies is poor. They also had the highest proportion of banking failure of all disease groups. The poor quality is likely due to receiving chemotherapy before banking. According to Kobayashi's survey, 12 responders (57.1%)

among the 21 hematologists replied that sperm banking was performed before chemotherapy and 3 of 21 hematologists (14.3%) replied that enforcement after chemotherapy was introduced. Close to 28.6% (6/21) of those who said "not sure" may not know the proper timing of banking.²⁰ Azoospermia was the most common reason for that patients in the testicular tumor, hematological malignancy, and bone and soft tissue tumor groups could not preserve their sperm. In the hematological malignancy group, poor semen quality was the second most common reason for failure of sperm preservation. We speculate that the reason for the patient's azoospermia is different depending on the disease. Many patients with testicular tumors have poor semen quality, so there is a high likelihood of patients having azoospermia. Conversely, patients with hematological malignancies and bone and soft tissue tumors are less likely to develop azoospermia because many of these patients are younger and the diseases themselves are less likely to damage the testes. Of course, some patients with hematological malignancy have a poor overall condition, so it is possible that this will cause deterioration of semen quality. We speculate that it is highly probable that chemotherapy before sperm banking is affecting the cause of their azoospermia in many cases. Especially in patients with hematological malignancy, we speculate that there are many patients with azoospermia and bad semen quality because they receive high-risk or multiple courses of intermediate-risk chemotherapy prior to banking. Even though it is reasonable for oncologists to consider immediate treatment, sperm cryopreservation is a procedure that is only possible for a very short time. We must encourage oncologists to recommend sperm banking before chemotherapy to their patients. The reasons for the low banking rate and the high usage rate of anticancer drugs before banking seem to be lack of information, awareness, and knowledge. Finally, an additional reason may be that sperm banking in Japan is not systemized.²⁰ Systemization within medical care would help increase patient knowledge and awareness of the importance of sperm banking, so it should be completed as soon as possible.

Regarding this study's limitations, first, we were only able to investigate the number of patients in a single year due to the risk of a low response rate if a multiyear survey was conducted. Second, the number of users with preserved sperm and the number of pregnancies, among other factors, were not enforced as they were for the single-year survey. According to Agarwal *et al.*,¹³ although the number of patients registering with the sperm bank has increased from year to year, the rate of sperm preservation remains relatively unchanged. Based on reports in the literature, we estimate that the usage rate in Japan is approximately 10%.^{14,30} Third, we could have further subgrouped the diseases. For example, even though they are all blood diseases, chronic myeloid leukemia, acute myeloid leukemia, and lymphoma have different chemotherapy regimens and prognoses. We did not subdivide the diseases due to the risk of a reduced response rate.

CONCLUSIONS

In conclusion, 820 young patients consulted for sperm cryopreservation before cancer treatment in 2015. However, this number is small considering the number of people diagnosed with cancer each year. The number of patients with unsuccessful cryopreservation was higher in the hematological malignancy group than in the other groups, possibly due to the large number of patients requesting sperm cryopreservation after induction of chemotherapy. In Japan, the possibility of precancer treatment sperm banking is not yet common knowledge among patients and oncologists due to the lack of systematization. We believe that information dissemination regarding fertility preservation will benefit young cancer patients in the future.

AUTHOR CONTRIBUTIONS

YY designed the study and questionnaire and drafted the article. NS conceived the study, participated in its design and coordination, and helped draft the manuscript. AT, HO, and TI corrected the questionnaire. ST took delivery procedures nationwide and collected data. TS, TK, and MK summarized and analyzed the data. KO participated in the design of the study and performed the statistical analysis. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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