

Semen cryopreservation as an oncofertility treatment in 122 Japanese men with cancer: A decade-long study

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Abstract

Purpose: Oncofertility is a subspecialty that is concerned with helping patients with cancer preserve their ability to have children in the future. For men, sperm banking is an established way to preserve fertility. The aim was to determine the prefreeze semen characteristics and reproductive outcomes according to cancer type for men who chose semen cryopreservation.

Methods: The records of 122 men with cancer who requested semen cryopreservation at the authors' hospital from 2006 to 2015 were reviewed. The mean patient age when the semen was cryopreserved was 33.6 years.

Results: The 122 men who banked sperm during the study period had the following types of cancer: testicular (44.3%), hematological (31.1%), digestive (8.2%), and other types (16.4%). The mean sperm concentration by cancer type was $30.5 \times 10^6/\text{mL}$ for testicular, $45.0 \times 10^6/\text{mL}$ for hematological, $40.5 \times 10^6/\text{mL}$ for digestive, and $68.4 \times 10^6/\text{mL}$ for the other types. The mean sperm motility by cancer type was 59.6% for testicular, 50.1% for hematological, 43.0% for digestive, and 44.8% for the other types. For 12 (9.8%) men who used the banked semen, there were five (41.7%) clinical pregnancies.

Conclusion: Semen cryopreservation is a simple procedure that can be accomplished quickly and can preserve fertility.

KEYWORDS

assisted reproductive technology, cancer, cryopreservation, oncofertility, sperm

1 | INTRODUCTION

The subfield of "oncofertility," which was given its name in 2006 by Teresa K. Woodruff (now Director of the Oncofertility Consortium), connects oncology and reproductive research to explore and expand the options for the reproductive future of cancer survivors. Established fertility preservation options for men include sperm banking, in which a semen sample is produced, frozen, and stored for future use.

Men choose to bank sperm for a variety of reasons. Cancers, such as leukemia, lymphoma, digestive cancer, and testicular cancer, often

strike adolescents and young adults during their reproductive years. Testicular cancer is the most common malignancy in men of reproductive age.¹ The level of cancer morbidity in Japan is one per 2500 persons aged 25-29 years and one per 900 persons aged 35-39 years (see http://ganjoho.jp/reg_stat/index.html). The 10 year survival rate for cancer is relatively high for adolescents and young adults. The survival rates for men and women are 66.0% and 75.3%, respectively (see http://ganjoho.jp/reg_stat/index.html#0).

Treatments for malignancy may include chemotherapy, surgery, and irradiation of the abdomen and pelvis, any of which can negatively

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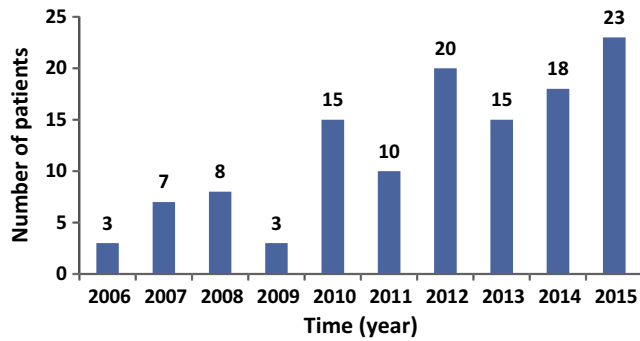


FIGURE 1 Number of patients with cancer each year who cryopreserved semen from 2006 to 2015

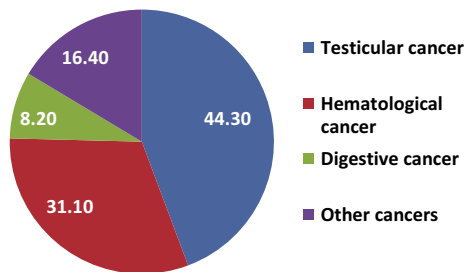


FIGURE 2 Types of cancer (%) in oncological patients who chose to cryopreserve semen. The “other cancers” category included bone sarcoma, thoracic cancer, and cancers of the prostate, mediastinum, mouth, brain, throat, lung, skin, and penis

impact male fertility by directly damaging spermatogenesis or by interrupting the neural pathways that regulate erection and ejaculation. With chemotherapy, the probability of permanent infertility increases with the cumulative dosage.² Thus, sperm cryopreservation prior to chemotherapy or radiation is one of the most valuable and frequently used methods to preserve the reproductive prospects for men with cancer. A single sperm of good quality is sufficient to achieve pregnancy through in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI).

Semen cryopreservation is a simple procedure that holds great importance for men who have cancer and who wish to preserve their reproductive options. The semen should be collected and frozen before the patient begins treatment for cancer, especially if the treatment involves chemotherapy or pelvic radiation.

In this retrospective study, the data from men who had cancer and who were referred to the authors' hospital for sperm cryopreservation during a 10 year period were analyzed. The goal was to determine the

prefreeze semen characteristics among the various types of cancer and the reproductive outcomes of the banked semen samples that were used in assisted reproductive treatment (ART).

2 | MATERIALS AND METHODS

2.1 | Patients and methods

The records of 122 men with cancer who were referred to the Toho University School of Medicine, Omori Hospital Reproduction Center, Japan, for semen cryopreservation from January, 2006 to December, 2015 were analyzed. In some cases, the patients had already started treatment for cancer. The semen was obtained by masturbation and was analyzed manually according to World Health Organization recommendations³ by three independent embryologists. The renewal period for cryopreserved semen at the authors' hospital is every other year.

2.2 | Semen cryopreservation and thawing

The semen was mixed at a 1:1 ratio with Quinn's Advantage™ Sperm Freezing Medium (SAGE, Yokohama, Japan). The semen and medium mixture was dispensed into 2 mL cryogenic tubes that were left to stand at room temperature for 10 minutes, placed in vapor-phase nitrogen for 15 minutes, and then stored in liquid nitrogen. In order to thaw the semen, the tubes were dipped in water at 37.0°C. The cryoprotectant was removed by centrifugation at 1500g/min for 10 min in Quinn's™ Sperm Washing Medium (SAGE). The thawed spermatozoa were used for ART by ICSI.

2.3 | Data collection

The following data were collected from patient records at the Toho University School of Medicine, Omori Hospital Reproduction Center, for each person who banked his sperm: the date of birth, marital status, type of cancer, date of semen cryopreservation, sperm characteristics (concentration and motility), date of semen use, and status of clinical pregnancies.

2.4 | Statistical analysis

The data were analyzed by using IBM SPSS Statistics for Windows (v. 23.0; IBM Corporation, Armonk, NY, USA). A *P*-value of <.05 was considered to be significant.

TABLE 1 Cancer types and sperm characteristics in the oncology patients who requested semen cryopreservation

Characteristic	Testicular cancer	Hematological cancer	Digestive cancer	Other cancers	Total
N	49.0	33.0	10.0	18.0	110
Age (years)	31.8	29.6	41.5	42.3	34
Sperm concentration (×10 ⁶)	30.5	45.0	40.5	68.4	42
Sperm motility (%)	59.6	50.1	43.0	44.8	53

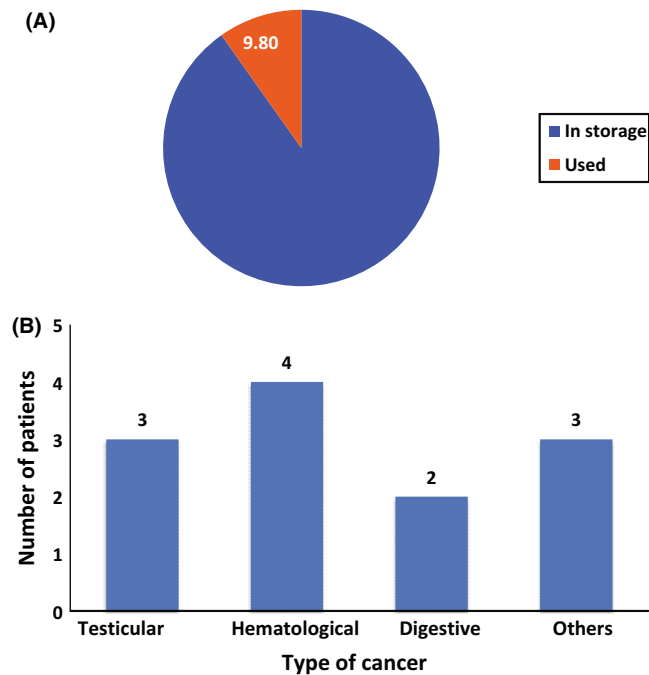


FIGURE 3 A, Rate of usage (%) of cryopreserved semen for assisted reproductive treatment (ART). B, Types of cancer in oncology patients who used their cryopreserved semen for ART

2.5. | ETHICAL APPROVAL

Approval from the institution's medical ethics committee was not necessary because the study was classified as an uninvolved, anonymous, retrospective database study.

3 | RESULTS

3.1 | Cryopreservation

In total, 122 men requested sperm cryopreservation before or during cancer treatment during the 10 year study period: three in 2006, seven in 2007, eight in 2008, three in 2009, 15 in 2010, 10 in 2011, 20 in 2012, 15 in 2013, 18 in 2014, and 23 in 2015 (Figure 1).

3.2 | Patient characteristics

The mean patient age at the time of semen cryopreservation was 33.6 years (range: 17-67). As to their marital status, 64.8% of the patients were unmarried, 33.6% were married, and the status of 1.6% was unknown.

3.3 | Cancer type and semen characteristics

Of the 122 men who chose to bank their semen, 54 (44.3%) had testicular cancer, 38 (31.1%) had hematological cancer, 10 (8.2%) had digestive cancer, and 20 (16.4%) had other types of cancer (Figure 2). The other-types group included eight patients with prostate cancer, two with mediastinal tumors, two with mouth cancer, two with bone

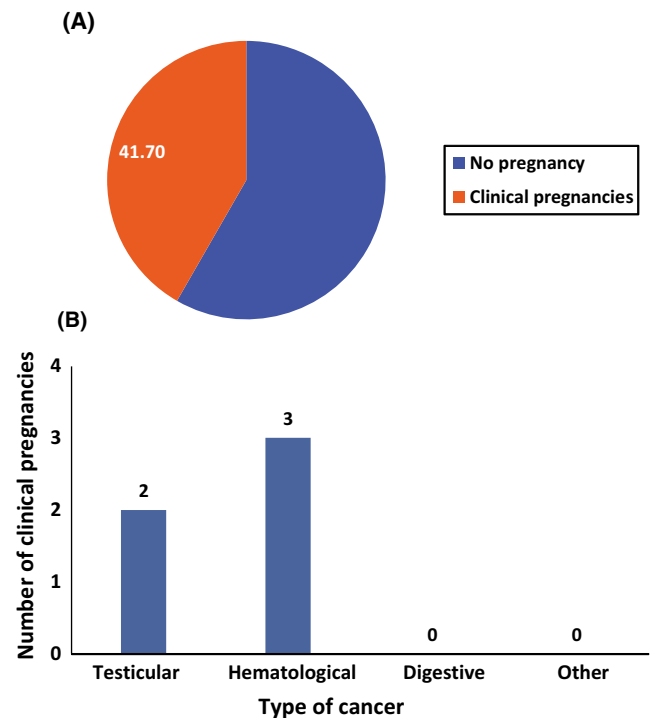


FIGURE 4 A, Rate of clinical pregnancy (%) by assisted reproductive treatment using cryopreserved semen. B, Types of cancer in those patients whose cryopreserved sperm resulted in a clinical pregnancy

sarcoma, and one each with brain, thoracic, throat, lung, skin, and penile cancer. Table 1 shows the patients' and semen characteristics, excluding 12 patients who were not included in this analysis of sperm concentration and motility. Of these, nine were excluded because they had cryptozoospermia and another three men were excluded because they had ejaculate dysfunction and could not provide semen for cryopreservation; two of these chose to undergo testicular sperm extraction and to cryopreserve their testis tissue. Among the 12 patients who were excluded from the analysis of sperm concentration and motility, five had testicular cancer, five had hematological cancer, and two had other types of cancer.

The mean sperm concentration, according to cancer type, was as follows: testicular cancer, $30.5 \times 10^6/\text{mL}$; hematological cancer, $45.0 \times 10^6/\text{mL}$; digestive cancer, $40.5 \times 10^6/\text{mL}$; and the other types, $68.4 \times 10^6/\text{mL}$. The mean sperm motility of the various cancers was as follows: testicular cancer, 59.6%; hematological cancer, 50.1%; digestive cancer, 43.0%; and the other types, 44.8%. An ANOVA of the mean sperm concentration and motility between the four groups showed that the patients with testicular cancer had a significantly lower mean sperm concentration than the patients in the other-types group ($P < .05$). There was no significant difference in the mean sperm motility among the four groups ($P < .05$) (data not shown).

3.4 | Semen usage and clinical pregnancy rates

Of the 122 patients, 12 (9.8%) used their banked semen for ART (Figure 3A). By cancer type, these 12 included four cases of

hematological cancer, three of testicular cancer, two of digestive cancer, and three cases of other types of cancer (Figure 3B). By using ART with cryopreserved semen, five (41.7%) cases of clinical pregnancy occurred (Figure 4A), of which three resulted from semen from patients with hematological cancer and two from patients with testicular cancer (Figure 4B). Thus, of the 122 patients, only five (4.1%) patients both sought and achieved a clinical pregnancy by using the cryopreserved semen.

4 | DISCUSSION

Oncofertility aims to explore and expand the future reproductive options for cancer survivors. Cancer treatments can impair or destroy a person's ability to have children later in life. For men, the cancer or the treatment can damage the testes and interfere with the production of sperm and testosterone. As cancer treatments improve and survival rates increase, the options that are available for preserving fertility in men are increasingly important. Fortunately, there are ways to preserve future fertility options. Men of reproductive age should consult with a reproductive endocrinologist as early as possible after a diagnosis of cancer, optimally prior to starting chemotherapy or pelvic radiation.⁴

Semen cryopreservation, which was introduced in the 1950s by Bunge and Sherman, has become particularly important for preserving fertility in men who will undergo treatment for cancer.^{5,6} The use of semen cryopreservation prior to cancer therapy has increased over the past decade.

This study investigated the type of cancer that is involved when men choose to cryopreserve their semen prior to cancer treatment. It was found that the most common diagnosis was testicular cancer (44.3%), followed by hematological cancer (31.1%). Similarly, a study in the Netherlands reported that, among oncology patients who banked semen, the most common cancers were testicular (n=393, 43.8%) and hematological (n=308, 34.3%).⁷ A report from Italy found that, of 721 patients with cancer who cryopreserved their sperm, the most frequent types of cancer were testicular (42.2%) and hematological (36.2%).⁸ Thus, the types of cancer were quite similar in both the European and Japanese men who chose to bank semen prior to cancer treatment.

A second aim of this study was to determine how often semen that had been banked by patients with cancer is used for ART and a usage rate of only 9.8% was found. Similarly, another study reported a 10.7% usage rate.⁷ Other groups have reported usage rates of <5% or somewhere between 5% and 10%.⁸⁻¹⁶ These low usage rates might be related to the low rates of patient survival, recovery of fertility, and desire for paternity.^{11,17,18}

The low rate of usage of cryopreserved semen raises the question of whether it is important to preserve the option of sperm cryopreservation for patients with cancer. One study found azoospermia in 34% and 26% of oncology patients 6 months after chemotherapy or radiotherapy, respectively, but in only 3% and 6% of oncology patients, respectively, after 2 years.¹⁹ However, semen cryopreservation is the only way for a man who is diagnosed with cancer during his reproductive years to preserve the possibility of having children who are

genetically his own. In addition, little is known about the mutation load in the semen of patients with cancer after chemotherapy and radiotherapy. If semen that is produced after cancer therapy is found to be less likely to produce a healthy child, the use of spermatozoa that have been preserved prior to treatment is likely to increase.²⁰

A third aim of this study was to investigate the pregnancy rate that was obtained with cryopreserved semen. In the authors' hospital, the clinical pregnancy rate was 41.7%, demonstrating that although the usage rate of cryopreserved semen was low, the pregnancy rate when using the cryopreserved semen in ART was quite high. One study reported a pregnancy rate of 31.75%.⁸ Other reports show that semen cryopreservation does not increase the probability of congenital malformation after IVF cycles.¹⁰ In addition, this study found that the patients with hematological cancer had the highest rates for both using the cryopreserved semen and achieving pregnancy. Clinical pregnancies also were obtained with cryopreserved sperm from patients with testicular cancer, but not with sperm from patients in the digestive or other-type cancer groups. However, there were too few cases to demonstrate a statistically significant difference (data not shown). Another study also reported that no pregnancy was obtained by using the sperm from patients with cancers other than lymphoma or testicular tumors.⁷

Semen cryopreservation is a simple procedure that can be accomplished quickly and can preserve fertility, even in emergency situations in which the patient needs to start cancer treatment immediately. Efficient counseling for fertility preservation requires a responsive network in which the oncologist, surgical oncologist, and reproductive specialist can collaborate closely to ensure that sperm cryopreservation is available to all men of reproductive age who have cancer.

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human and Animal Rights:* This article does not contain any study with human or animal participants that has been performed by any of the authors.

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