


Fertility preservation and pregnancy outcomes in adolescent and young adult male patients with cancer

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Abstract

Purpose: Sperm cryopreservation is the gold standard for maintaining fertility in male survivors of cancer. In order to help increase the future success of fertility preservation in these patients, the present state of sperm cryopreservation was examined at the current institution and its challenges were discussed.

Methods: Between January, 2004 and February, 2017, 31 male patients with cancer were introduced to the center for fertility preservation. The ages and semen characteristics of these patients were examined and compared between those whose sperm were cryopreserved before (the pretreatment group) and after (the post-treatment group) cancer treatment.

Results: The mean sperm concentration of the pretreatment group was significantly higher than that of the post-treatment group. Normozoospermia was found in eight and three patients in the pretreatment and the post-treatment groups, respectively, albeit this difference was not significant. In contrast, the prevalence of azoospermia was higher in the post-treatment group (five patients) than in the pretreatment group (one patient).

Conclusion: As many patients possibly suffer from infertility following chemotherapy, it is necessary to provide fertility preservation opportunities to young male patients with cancer prior to the commencement of cancer treatment.

KEYWORDS

male fertility, oncology, sperm cryopreservation

1 | INTRODUCTION

Human sperm cryopreservation first was achieved in 1953, when cryopreserved human sperm was stabilized successfully and artificial insemination with this sperm led to pregnancy.¹

Subsequently, the first cases of delivery following in vitro fertilization and intracytoplasmic sperm injection (ICSI) were reported in

1983 and 1994, respectively.^{2,3} Traditionally, the cryopreservation of sperm for use in methods such as these has been performed in order to increase the fertility of existing couples that wish to conceive. Testicular sperm extraction (TESE) also has been performed to collect sperm from patients with azoospermia.

Due to rapid developments in medicine, many patients with cancer are now able to survive over longer periods. However, the

negative effects of various cancer treatments, such as chemotherapy, radiation therapy, and surgery, on future pregnancies often have been reported, especially when the patient is an adolescent or young adult (AYA) man. Chemotherapy first disrupts spermatocyte type B and then disrupts sperm cell type A. If type A is impaired, it becomes an irreversible insemination dysfunction.⁴ After cytotoxic therapies, germ cells frequently appear to be absent as a result of the killing of spermatogenic stem cells, loss of the support of somatic cells, or a combination of both.⁵ In addition, there is sexual dysfunction as a fertility disorder by surgery. In other words, it is due to anatomical changes in the male reproductive organs and pathways, innervation to the reproductive organs, and changes in the endocrine environment. In order to maintain the possibility of fertility in these patients, sperm cryopreservation (the creation of a sperm bank) is the current gold standard.

The authors recently reported on the status of fertility preservation in AYA women with cancer, which involves the cryopreservation of the oocytes, embryos, or ovarian tissue.⁶ Although the performance of fertility preservation in male AYA patients with cancer also has been occurring here by means of sperm cryopreservation since 2004, there has been no report on this. Therefore, the aim was to examine the present state of sperm cryopreservation at the current center in terms of patient age and semen characteristics and provide herein some discussion of its challenges. It was planned to study the changes in the semen samples before and after the cancer treatment, as the authors believe that this will help to enable more successful fertility preservation in male AYA survivors of cancer, which will be attempted increasingly in the future.

2 | MATERIALS AND METHODS

This study was approved by the University Ethics Committee, Hyogo College of Medicine, Nishinomiya, Japan, prior to its commencement.

2.1 | Semen sample collection

The semen samples were collected before the cancer treatment in 18 patients (the pretreatment group) and after the cancer treatment in 13 patients (the post-treatment group). After the cancer treatment, four patients visited us within 6 months, nine patients over 3 years. The amount of semen that was collected was confirmed first, and after it was confirmed that it was in a liquefied state, the semen concentration and the exercise rate were evaluated with a Makler calculation board. The semen test was evaluated at least twice. These samples were cryopreserved for future use with the liquid nitrogen vapor method. Briefly, the semen was dispensed into a serum tube with a cryopreservation solution (KITAZATO Bio Pharma, Shizuoka, Japan) and stored in liquid nitrogen.

2.2 | Data analysis

The patient's age and the semen's characteristics at cryopreservation were compared between the pre- and post-treatment groups. The

semen's characteristics also were compared within the pretreatment group between those with testicular tumors and those with other cancer types. These statistical analyses were retrospective, with the Student's *t* test and the chi-square test being used, with $P < .05$ being regarded as a significant difference. The course of pregnancy and delivery after the cancer treatment also was reviewed as extensively as possible in the relevant cases.

3 | RESULTS

3.1 | Patient characteristics

Between January, 2004 and February, 2017, 31 male patients with cancer were introduced to the current center for fertility preservation. Their ages at the first visit ranged from 14 to 49 years. In terms of the age distribution within this range, two (3.4%) patients were aged under 20 years, 11 (37.4%) were aged from 20 to 29, 11 (37.4%) from 30 to 39, and seven (20.9%) from 40 to 49 years. The types of cancer among these patients were as follows: testicular cancer in 15 patients (48.6%), with eight patients with testicular cancer in the pretreatment group and six in the post-treatment group; malignant lymphoma in five (16.1%); leukemia in three (9.7%); myelodysplastic syndrome in one (3.2%); germ cell tumor in one (3.2%); pancreatic cancer in one (3.2%); rectal cancer in one (3.2%); colon cancer in one (3.2%); hepatoma in one (3.2%); and maxillary rhabdomyosarcoma in one (3.2%). Three patients died of their original disease after sperm cryopreservation.

3.2 | Comparisons of age and semen characteristics

The average age did not differ significantly between the pretreatment group (33.1 ± 6.2 y) and the post-treatment group (31.5 ± 7.8 y) ($P = .482$). The semen volume also did not differ significantly between groups (pretreatment group, $2.8 \pm .7$ mL; post-treatment group, $2.8 \pm .8$ mL) ($P = .896$), nor did the sperm motility between groups (pretreatment group, $39.0 \pm 17.1\%$; post-treatment group, $33.2 \pm 29.0\%$) ($P = .551$). However, the sperm concentration was significantly higher in the pre- than in the post-treatment group (pretreatment group, $60.2 \pm 50.6 \times 10^6$ mL; post-treatment group, $5.3 \pm 6.3 \times 10^6$ mL) ($P = .031$). These results are summarized in Table 1.

Other semen characteristics at cryopreservation also were compared between the pre- and post-treatment groups. Normozoospermia was found in eight and three pre- and post-treatment group patients, respectively, which did not represent a significant between-group difference ($P = .275$). The prevalence of oligozoospermia and/or asthenozoospermia also did not differ significantly between groups (pretreatment group, nine patients; post-treatment group, five patients) ($P = .717$). However, the prevalence of azoospermia was lower in the pretreatment group (one patient) than in the post-treatment group (five patients) ($P = .059$). All the patients with azoospermia after cancer treatment had cancers other than testicular tumors. These results are summarized in Table 1.

TABLE 1 Comparison of the semen characteristics at cryopreservation before and after the cancer treatment of 31 patients

Characteristic	Before cancer treatment (n = 18)	After cancer treatment (n = 13)	P-value
Age (y)	33.1 ± 6.2	31.5 ± 7.8	.482
Semen volume (mL)	2.8 ± 0.7	2.8 ± 0.8	.896
Sperm motility (%)	39.0 ± 17.1	33.2 ± 29.0	.551
Sperm concentration (10 ⁶ /mL)	60.2 ± 50.6	5.3 ± 6.3	.031*
Normozoospermia (%)	8 (44.4)	3 (23.0)	.275
Oligozoospermia and/or asthenozoospermia (%)	9 (50.0)	5 (38.4)	.717
Azoospermia (%)	1** (5.5)	5 (38.4)	.059

*P < .05.

**The sperm could be cryopreserved by onco-testicular sperm extraction.

Lastly, no significant difference was found between the patients with a testicular tumor or other cancer within the pretreatment group with regard to any of the characteristics examined (normozoospermia: two patients with a testicular tumor and six other patients with cancer, $P = .170$; oligozoospermia and/or asthenozoospermia: five patients with a testicular tumor and four other patients with cancer, $P = .637$; and azoospermia: one patient with a testicular tumor and five other patients with cancer, $P = .444$). These results are summarized in Table 2.

3.3 | Pregnancy and delivery outcomes after the cancer treatment

Among the 31 patients that were included in this study, there were three cases where infertility treatment resulted in a successful pregnancy and delivery. The first case was a 28 year old man who had a germ cell tumor. His wife delivered a female baby weighing 2698 g following ICSI by using fresh sperm 4 years after chemotherapy. The second case was a 37 year old man who had testicular cancer. His wife conceived twice after ICSI by using frozen-thawed sperm. Although the first pregnancy ended in an abortion at 9 weeks' gestation, the second pregnancy resulted in the delivery of a female baby weighing 2948 g. The third case was a 46 year old man with a hepatoma. His wife delivered a male baby weighing 2948 g following ICSI by using frozen-thawed sperm. These results are summarized in Table 3.

4 | DISCUSSION

In recent years, cancer treatment outcomes for young persons have improved significantly. As a result, their quality of life after cancer treatment has been attracting attention. For both sexes, fertility preservation greatly influences the post-treatment quality of life, especially for young persons of reproductive age. This highlights the importance of using fertility preservation measures prior to cancer treatments, such as chemotherapy or radiotherapy. As previously mentioned, sperm cryopreservation is a well-established method

TABLE 2 Comparison of the semen diagnosis at cryopreservation in the testicular tumor to the other cancer before the cancer treatment of 18 patients

Characteristic	Testicular (n = 8)	The others (n = 10)	P-value
Age (y)	32.0 ± 2.7	32.4 ± 8.1	.700
Semen volume (mL)	2.8 ± .9	2.7 ± 0.6	.813
Sperm motility (%)	34.5 ± 20.8	42.5 ± 11.9	.422
Sperm concentration (10 ⁶ /mL)	26.1 ± 23.1	87.4 ± 73.2	.166
Normozoospermia (%)	2 (25.0)	6 (60.0)	.170
Oligozoospermia and/or asthenozoospermia (%)	5 (62.5)	4 (40.0)	.637
Azoospermia (%)	1 (12.5)	0 (.0)	.444

TABLE 3 Pregnancy and delivery outcomes after cancer treatment

Case	Age (y)	Type	ICSI	Outcome
1	28	GCT	Fresh sperm	Delivery (♀, 2698 g)
2	37	Testis	Frozen sperm	Miscarriage (9 wk)
			Frozen sperm	Delivery (♀, 2948 g)
3	46	Hepatoma	Frozen sperm	Delivery (♂, 2948 g)

♀, female; ♂, male; GCT, germ cell tumor; ICSI, intracytoplasmic sperm injection.

and is the current gold standard for fertility preservation, with reports of a successful delivery in 50% of patients with cancer following ICSI with cryopreserved sperm.⁷ As such, it should be the first fertility preservation choice for men of reproductive age. Indeed, the American Society of Clinical Oncology (ASCO) strongly recommends the cryopreservation of sperm prior to cancer treatment for men of reproductive age.⁸

In order to facilitate improvements in fertility preservation for young male patients with cancer, this study aimed to examine the

present state of sperm cryopreservation at the current institution. It was found that although there was no significant difference in the semen volume or sperm motility between the pre- and post-treatment groups, the sperm concentration was significantly higher in the former. These findings are similar to data from other studies in terms of sperm concentration, but not with respect to sperm motility.⁹ However, it should be noted that as the sperm motility already might be impaired in patients with a testicular tumor prior to the cancer treatment, the inclusion of data from these patients could have affected this study's results. Indeed, it was found that when the patients with a testicular tumor were excluded, the sperm motility tended to be higher in the pre- than in the post-treatment group.

Other semen characteristics that are known to be affected by cancer treatment also were examined, with a key finding being that azoospermia was more prevalent in the post- than in the pretreatment group. This is unsurprising as it is known that both chemotherapy and radiotherapy, which are often used to treat testicular tumors following high-grade radical orchiectomy, can cause irreversible azoospermia.¹⁰ Specifically, chemotherapy often impairs spermatogenic function and causes azoospermia within 50-60 days. If low-testicular toxicity drugs are selected, however, the spermatogenic function can be recovered within 3 months.¹¹ In contrast, recovery can be delayed or, in the worst cases, prevented altogether if high-testicular toxicity drugs are selected.¹² With regard to radiotherapy, it is known that testicular irradiation of <0.8 Gy leads to oligozoospermia, irradiation of 0.8-2.0 Gy leads to azoospermia, and irradiation of >2.0 Gy leads to irreversible azoospermia.¹³ Considering this study's finding that the semen characteristics tend to deteriorate further after cancer treatment, it is suggested that fertility preservation by sperm cryopreservation needs to be carried out prior to treatment. This, in addition to continued medical progress, could enable the harmful impacts of testicular tumor treatment on fertility to be minimized even further. However, oligozoospermia and asthenozoospermia often are found in patients with a testicular tumor even before the cancer treatments are started.^{10,14,15} Indeed, it has been reported that 10%-15% of patients with testicular cancer suffer from azoospermia and that >50% suffer from oligozoospermia prior to any cancer treatment.^{14,15} This study found that 11.2% of the patients had azoospermia and 62.5% had oligozoospermia. In particular, one patient with a testicular tumor was found to have azoospermia prior to his cancer treatment. In such cases where sperm cryopreservation cannot be performed by using ejaculated semen, a radical orchiectomy with simultaneous onco-TESE could be an option for fertility preservation.¹⁶

Sperm cryopreservation, or the creation of a "sperm bank," is the only clinically available method of fertility preservation for men. This potentially could impede sperm collection in some preteen boys who have never masturbated. Although this study included one 14 year old boy, fortunately he could collect sperm by masturbation. Also, of the two patients under 20 years, the same was true for another 18 year old man. If a patient never has experienced masturbation, however, sperm can be collected by vibrator stimulation or by electrical stimulation of the penis.^{10,17} The preservation of fertility in prepubertal boys also presents a major challenge as there is no

mature sperm in their gonads. However, fertility preservation methods for preteen boys whose testes have not begun spermatogenesis have yet to be established. The ASCO expresses at present that the only option for prepubertal boys is testicular freezing, though this method is still at the experimental stage. Specifically, although the key aim of this method is sperm induction by autologous transplantation after the thawing and *in vitro* culture of frozen testicular tissues, this has yet to be achieved.¹⁸ Therefore, further research on improving the techniques for the cryopreservation of testicular tissues or immature spermatozoa is required.

Regarding the viability of frozen sperm, it is thought that fertility remains sufficient even after cryopreservation. There are many reports that ICSI outcomes are the same, regardless of whether fresh or frozen sperm are used.^{3,19-21} In this study, the pregnancies in total were established from three patients who underwent infertility treatment. Although one pregnancy ended in an abortion at 9 weeks' gestation, three reached delivery. Among these three successful delivery cases, one involved a patient with a testicular tumor who was referred to the center for sperm cryopreservation prior to cancer treatment. However, the findings from his semen examination 4 years after the cancer treatment were normal and his wife conceived by ICSI using freshly ejaculated, rather than frozen, sperm.

As aforementioned, this indicates that fertility might be sufficiently maintained and that the seminal findings can return to normal after treatment in some patients with testicular cancer. In other cases, however, such as where alkylating agents are used for the treatment of Hodgkin's disease, testicular toxicity occurs. Therefore, as previously stated, sperm cryopreservation before cancer treatment is important, especially when drugs that are known to result in testicular toxicity are used. In addition, there might be a significantly increased risk of chromosomal abnormalities in the sperm of chemotherapy patients during and immediately after treatment. It is suggested that doctors should provide patients with advance notice that semen examination or counseling could be required after cancer treatment.

With regard to the usage patterns of cryopreserved sperm, frozen sperm was thawed and used three times in this study. The usage rate was 9.7%, which is similar to the rates of 2.7%-11.0% in both domestic and foreign reports.²²⁻²⁴ In these reports, the low usage rate of frozen sperm appears to have been related to patients remaining single throughout and after malignant tumor treatment.²⁵ At the authors' center, only 10 (32.3%) of the patients were married. Thus, the low usage rate here can be assumed to be due to the same reasons as in other reports. In this study, the number of target patients was small and it was impossible to examine the difference by type of cancer. In the future, such a study as this should be done on more target patients. Each patient visited us during the post-treatment period. It was not possible to compare the difference between before and after the cancer treatment in the same patient.

ACKNOWLEDGEMENTS

The authors acknowledge Mami Hitokuwada and Teruhito Kojima for their help with the laboratory work.

DISCLOSURE

Conflict of interest: The authors declare no conflict of interest.
Human rights statement and informed consent: The protocol for the research project was approved by the Hyogo College of Medicine Ethics Committee, Nishinomiya, Japan. All the procedures were followed in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all the patients to be included in the study.
Animal studies: This article does not contain any studies with animal participants that have been performed by any of the authors.

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How to cite this article: Ukita Y, Wakimoto Y, Sugiyama Y, et al. Fertility preservation and pregnancy outcomes in adolescent and young adult male patients with cancer. *Reprod Med Biol*. 2018;17:449–453. <https://doi.org/10.1002/rmb2.12211>