Received: 22 June 2018 | Revised: 6 August 2018 | Accepted: 16 August 2018

DOI: 10.1002/rmb2.12246

ORIGINAL ARTICLE

WILEY Reproductive Medicine and Biology

Sperm cryopreservation: Clinical and fertility outcomes in male oncological patients with germ cell tumors or hematological disorders

Hiromitsu Negoro[1,2] | Yoshiyuki Matsui[1,2] | Takahiro Nakayama[3] | Hiroshi Hatayama[3] | Osamu Ogawa[1] | Kentaro Ichioka[2]

[1]Department of Urology, Kyoto University Graduate School of Medicine, Kyoto, Japan

[2]Ichioka Urological Clinic, Symphonia-Oike 1F, Higashinotoin-Nijo sagaru, Kyoto, Japan

[3]Center For Reproductive Endocrinology and Infertility, Adachi Hospital, Higashinotoin-Nijo sagaru, Kyoto, Japan

Correspondence
Hiromitsu Negoro, Department of Urology, Kyoto University Graduate School of Medicine, Sakyo-ku, Kyoto, Japan.
Email: hnegoro@kuhp.kyoto-u.ac.jp

Abstract

Purpose: There is insufficient understanding of the effects of malignant diseases themselves and chemotherapy on semen quality and final fertility outcomes. Here, the authors focused on the patients with malignant diseases who cryopreserved sperm pre- or post-chemotherapy for future fertility, and revealed how clinical settings can affect semen quality and final outcomes.

Methods: The authors reviewed the records of 257 patients with malignant diseases who cryopreserved sperm. Among 257 cases, 113 men with germ cell tumors (GCTs) and 111 men with hematological disorders (HDs) were included in this study. Twenty-five patients who achieved successful outcomes using cryopreserved sperm were also analyzed.

Results: In the men with GCTs and HDs, respectively, differences were observed in age (28 vs 27 years), sperm concentration (32.6 vs 46.1 million/mL, $P < 0.05$), motility (42.2% vs 41.0%), and the rate of cryopreservation before chemotherapy (90% vs 59%, $P < 0.0001$). For successful pregnancies and deliveries, age at cryopreservation (30.0 vs 35.3 years, $P < 0.05$) and disease type (12/16 vs 3/9, $P < 0.05$) were significant factors.

Conclusions: Compared to patients with GCTs, those with HDs have a lower pregnancy and delivery rate, even though semen quality is higher. Disease type and age at cryopreservation are significant factors for successful outcomes.

KEYWORDS
chemotherapy, cryopreservation, fertility outcomes, infertility, sperm

1 | INTRODUCTION

Increasing numbers of young men with malignant diseases can now achieve long-term cures thanks to progress in multimodal treatments and combined chemotherapy regimens. Thus, preserving the potential of becoming a genetic father is a major issue for cancer survivors. The most reliable method for preserving male fertility is sperm cryopreservation, as recommended by the American Society of Clinical Oncology and the European Society for Medical Oncology.[1–3] However, spermatogenesis can be impaired by malignant diseases themselves, and as a result of chemoradiation therapy.[4–6]

Here, we focused on two major malignant diseases in young men, germ cell tumors (GCTs), and hematological diseases (HDs). We evaluated their background characteristics, quality of semen samples

cryopreserved for future fertility, and the final outcomes of assisted reproductive technology. We also investigated predictive factors for achieving successful pregnancies and deliveries using intracytoplasmic sperm injection (ICSI).

2 | MATERIALS AND METHODS

2.1 | Patients

We reviewed the medical records of 257 patients with cancer who had cryopreserved their sperm with written informed consent at Kyoto University Hospital and Adachi Hospital from October 1994 to December 2013. Cancer diagnoses were classified as HDs (including lymphoma), GCTs (including extragonadal forms), and other malignant diseases. Here, we focused on men with HDs and GCTs; other types of malignant diseases including 9 cases of orthopedics, 8 of neurological, 7 of gastrointestinal, 7 of genitourinary, and 2 of dermatological malignancies were excluded. We evaluated age at the time of sperm cryopreservation, marital status, the use of cryopreservation before/after chemotherapy, sperm concentration, sperm motility, use of cryopreserved sperm, and the duration from cryopreservation to use for ICSI. In addition, factors for achieving pregnancies by ICSI and successful deliveries were analyzed in 25 patients who used their cryopreserved sperm. All of these 25 patients underwent ICSI in our facilities and were followed to the final outcomes.

2.2 | Semen analysis and cryopreservation

Semen samples were collected by masturbation and analyzed before cryopreservation. Semen analysis was performed according to the WHO recommendations.[7] The samples were aliquoted and frozen after dilution with cryoprotectant medium.

All patients were followed by our institutions. We send mail every year, and they are required to fill in the confirmation form and finalize financial procedure to keep their cryopreserved sperm.

2.3 | Statistical analysis

Welch tests and Fisher's exact tests were used for inter-group comparisons. SPSS ver.11.0.1 J software (IBM Corp., Armonk, NY, USA) was used for statistical analyses. P values less than 0.05 were considered significant.

3 | RESULTS

Of the 113 patients with GCTs, 96 (85.0%) had tumors of testicular origin and 17 (15.0%) had extragonadal tumors. Of the 111 patients with HDs, 52 (46.4%), 42 (37.5%), and 19 (17.0%) had leukemia, lymphoma and other forms, respectively. Other background characteristics of the patients are shown in Table 1 and Figure S1. The rate of patients opting to cryopreserve sperm before chemotherapy was significantly higher in the GCT group (102/113, 90.2%) than in those with HDs (67/111, 59.8%, $P < 0.0001$) (Figure S2), while the mean sperm concentration was significantly lower in men with GCTs than in the HD groups (32.6 vs 46.1 × 10^6/mL, $P < 0.05$). There was no statistically significant difference in other semen parameters between the GCT and HD groups, as shown in Table 1.

In 16 of 113 (14.2%) of men with GCTs, cryopreserved sperm samples were used for ICSI and 12 of those 16 (75%) achieved successful pregnancies and deliveries with an average follow-up of 43.2 months. By contrast, 9 of 111 (8.1%) of men with HDs used their cryopreserved sperm samples and 3 of those 9 (33%) achieved success with an average follow-up of 73.4 months. The background characteristics of 25 patients who used cryopreserved sperm associated with successful outcomes or failures are shown in Table 2.

Age at cryopreservation and type of malignancy showed statistically significant differences in term of successful outcomes. The average age at cryopreservation was lower in the successful group than in the failed group.

TABLE 1 Characteristics of patients with germ cell tumors and hematological disorders

	Germ cell tumors	Hematological disorders	*P* value
No. of Pts	113	111	
Average age at cryopreservation (y, range)	28.2 (16-45)	27.2 (13-54)	0.27
No. of married at cryopreservation (%)	25 (22)	19 (17)	0.4
No. of cryopreservation before chemotherapy (%)	102 (90)	66 (59)	<0.0001*
Average sperm concentration (million/mL, range)	32.6 (0-143)	46.1 (0-180)	<0.05*
Average sperm motility (%, range)	42.2 (0-80)	41.0 (0-80)	0.65
No. of Pts who used cryopreserved sperm (%)	16 (14.2)	9 (8.1)	0.2
Average period from cryopreservation to use (mo, range)	42.0 (1-107)	73.4 (6-150)	0.13

Pts, patients
*<0.05.

TABLE 2 Predictive factors for achieving successful delivery

	Achieved	Failed	*P* value
No. of Pts	15	10	
Average age at cryopreservation (y, range)	30.0 (22-39)	35.3 (29-40)	<0.01*
Type of malignancy (%)			
Germ cell tumors	12(75)	4 (25)	<0.05*
Hematological disorders	3 (33)	6 (67)	
Cryopreservation before/after chemotherapy (%)			
Before	12(71)	5 (29)	0.10
After	3 (38)	5 (62)	
Average sperm concentration (million/mL, range)	38.5 (1-101)	46.8 (0.1-140)	0.63
Average sperm motility (%, range)	48.5 (10-79)	45.1 (0-80)	0.75
Average period from cryopreservation to use (mo, range)	55.9 (6-128)	49.4 (1-150)	0.74

Pts, patients.
*<0.05.

4 | DISCUSSION

In this study, we investigated the characteristics of cryopreserved sperm in men with GCTs and HDs, and the outcomes of ICSI using these samples, and attempted to identify predictive factors for successful outcomes. In our facilities, cryopreserved sperm are used only for ICSI, not conventional IVF nor IUI. The reason is that the number of frozen sperm is limited in cancer patients, while other methods require more motile sperm per cycle than ICSI.

In the background analysis, the rate of patients who cryopreserved sperm before chemotherapy was significantly lower in the HD group than in those with GCTs. There are several barriers for patients to cryopreserve their sperm,[8,9] but we suggest three possible reasons for the specific difference in our study. One is that several patients with HDs were in emergency situations and needed immediate cancer treatment before they could opt for sperm cryopreservation. In contrast, there were only a few cases of emergency in GSTs. Second is the lack of awareness of future infertility among hematologists treating these cases. It was discovered that several emergent patients in the HD group had not been offered the option of preserving sperm prior to chemotherapy. However, thanks to recent educational initiatives and awareness campaigns for fertility preservation among cancer survivors, the number of patients who cryopreserved their sperm and the rate of patients using cryopreservation before chemotherapy have been increasing (Figure S2 and Figure S3). Since urologists are major in testis and male fertility, the high rate of cryopreservation before chemotherapy in GSTs may be due to their high concern for residual testicular function and future fertility. The third reason is poor accessibility to a regional cryopreserved sperm bank system in Japan. Most cryobanks in Japan are managed by private in vitro fertilization (IVF) clinics in urban areas, and they are not sufficiently coordinated. Therefore, we advocate creation of a stronger network that oncologists and patients can easily access before initiating chemotherapy.

We showed in this study that the quality of sperm cryopreserved in the GSTs group was lower than that in the HD group. In the GSTs, spermatogenesis can be impaired not only in the affected testis by tumor pressure, but also in the contralateral testis by the effect of cancer and hormonal instability.[10–12] However, it is noteworthy that the successful pregnancy and delivery rates were higher in men with GCTs than in the HD group, though the sperm concentration was lower in men with GCTs than in the HD group. Furthermore, our analysis showed that disease type was a significant predictive factor for successful outcomes. Previous reports also suggested similar results. Ferrari *et al*[13] reviewed the efficacy of assisted reproduction technique treatments carried out with cryopreserved sperm samples and reported that the rate of patients who had at least one baby was 49% (95% CI 44% to 53%). Among patients with testicular cancer in the Indiana University Simon Cancer Center, 9 of 11 (82%) patients achieved successful delivery using cryopreserved sperm,[8] while the success rate of IVF using cryopreserved sperm was observed in 38% of a German study of survivors of treatment for Hodgkin lymphoma.[14] These results strongly indicated that the final outcome of IVF using cryopreserved sperm is strongly influenced by disease types, even though the semen quality measured by conventional parameters is favorable.[15,16] We think this tendency should be more focused on by oncologists, and patients should be better informed.

It is known that increased level of interleukins can be associated with dysfunctional spermatogenesis, and systemic effects by cytokine activity might also act adversely on gonadal function among patients with lymphoma.[17] Smit *et al*[18] reported that the pretreatment sperm DNA fragmentation index was significantly higher in patients with non-Hodgkin's lymphoma than in proven fertile controls, and was also higher than in patients with testicular cancer. Bujan *et al*[19] also

showed that in patients with lymphoma, significantly greater sperm DNA damage was observed compared with fertile controls. Tempest *et al*[20] studied sperm aneuploidy frequencies and reported that patients with Hodgkin's lymphoma were more likely to have aneuploidy for all chromosomes than did patients with testicular cancer or fertile controls. Although it is not clear what has actually happened in our patients, DNA quality and aneuploidy may affect the results in our study.

Our results showed that being young at cryopreservation was a significant factor for better fertility outcomes. However, we should be careful when interpreting these results. Interpreted literally, cryopreserved sperm of younger male patients have better potentials for fertility, but our results may just indicate that younger male patients have been married with younger females, who have better fertility potentials in general. Because we could not evaluate the ages of female partners in this study, further study will be needed.

The limitations of this study include its retrospective nature and the small sample size. However, we think our findings are still important for the clinical management of young men with cancer and their families to preserve their fertility options.

DISCLOSURES

Human rights statements and informed consent: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all patients for being included in the study. *Approval by the Institutional Review Board*: The protocol for this study has been approved by the Institutional Review Board. *Conflict of interest*: Hiromitsu Negoro, Yoshiyuki Matsui, Takahiro Nakayama, Hiroshi Hatayama, Osamu Ogawa, and Kentaro Ichioka declare that they have no conflict of interest.

ORCID

Hiromitsu Negoro http://orcid.org/0000-0003-1144-2755
Kentaro Ichioka http://orcid.org/0000-0002-5395-0240

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Negoro H, Matsui Y, Nakayama T, Hatayama H, Ogawa O, Ichioka K. Sperm cryopreservation: Clinical and fertility outcomes in male oncological patients with germ cell tumors or hematological disorders. *Reprod Med Biol*. 2018;17:500–503. https://doi.org/10.1002/rmb2.12246