

Current status of sperm cryopreservation for fertility preservation prior to cancer treatment at Jichi Medical University Hospital

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Abstract

Objective: The objective of this study was to clarify the current status of sperm cryopreservation for fertility preservation prior to cancer treatment at Jichi Medical University Hospital.

Target population and methods: Retrospective analysis of the medical records of patients who underwent sperm cryopreservation at our Center for Reproductive Medicine prior to cancer treatment was done.

Results: Thirty-two patients who underwent sperm cryopreservation between May 1997 and January 2019 were included. The median age at the time of storage was 32 years old (15–52 years). Twenty patients were married and twelve were not married. The primary underlying diseases were hematologic malignancies in 13, gastrointestinal malignancies in 5, germ cell tumors in 4, respiratory malignancies in 4, brain tumors in 2, rhabdomyosarcoma in 2, and urological malignancies in 2 patients. There were 9 patients (28.1%) whose sperm were utilized in intracytoplasmic sperm injection (ICSI), but all did not result in live birth.

Discussion: During a period of about 22 years, sperm cryopreservation for fertility preservation was performed in 32 patients at our institution. This number is comparatively less than those mentioned in previous reports. The reasons for this were as follows: there was a lack of a consultation system, there was an assisted reproductive technology clinic close to our institution, and there was a lack of consideration for fertility preservation by physicians treating cancer. However, the storage number increased after the establishment of a regular consultation system, and this suggested the importance of establishing a system in medical institutions.

(Keywords: Sperm cryopreservation, Fertility preservation, AYA generation)

Introduction

The development of multidisciplinary treatments for adolescent and young adult (AYA) cancer patients has resulted in an increasing number of cancer survivors¹. Conversely, depending on the treatments administered, these treatments are also known to affect male and female fertility after recovery, and it has been pointed out that it is important to carry out fertility preservation prior to starting cancer treatment².

Our institution is designated as a regional cancer care collaborative hospital, and numerous cancer treatments

are carried out in each department, such as hematology, pediatrics, urology, and surgery; additionally, a certain percentage of treatment for the AYA generation is also carried out.

To date, the actual status of sperm cryopreservation for fertility preservation at our institution had not been clear. Moreover, a regular consultation system for sperm cryopreservation was established in our Department of Urology in 2018. This study was conducted in order to clarify the present status of sperm cryopreservation to date and the changes in trends after the regular consultation system was

improved, as well as to identify the issues associated with the procedure.

Target population and methods

The study included patients who underwent sperm cryopreservation for fertility preservation purposes between May 1997 and January 2019 and who had a record of sperm cryopreservation at the Center for Reproductive Medicine at Jichi Medical University Hospital.

The medical records were retrospectively analyzed for the following items: patient age at the time of storage, primary underlying disease, history of marriage, method of sperm collection, date of storage, date of disposal, number of days of storage, number of samples stored, use of cryopreserved sperm, presence or absence of offspring, and patient prognosis.

This study was approved by the Institutional Review Board of Jichi Medical University Hospital (approval number: A19-053).

Results

There were 32 patients who underwent sperm cryopreservation for fertility preservation at our Center for Reproductive Medicine in the 21-year and 8-month period between May 1997 and January 2019.

The sperm collection methods were ejaculated sperm in 31 patients and onco-testicular sperm extraction (onco-TESE) in 1 patient. One of the 31 patients with stored ejaculated sperm was transferred from another institution.

The median patient age at the time of sperm cryopreservation was 32 (15–52) years old. The breakdown of patients who underwent sperm cryopreservation by age group was as follows: 6 who were 15–19 years old, 3 who were 20–24 years old, 4 who were 25–29 years old, 5 who were 30–34 years old, 6 who were 35–39 years old, 5 who were 40–44 years old, 0 who were 45–49 years old, and 3 who were 50 years old or older (Figure 1). The marriage status revealed that 20 (62.5%) were married and 12 (35.5%) were not married (Figure 2). The primary underlying diseases leading to fertility preservation were hematologic malignancies in 13, gastrointestinal malignancies in 5, germ cell tumors in 4, respiratory malignancies in 4, brain tumors in 2, urological malignancies in 2, and rhabdomyosarcoma in 2 (Figure 3).

The median number of sperm cryopreservation days was 642 (21–5916) days (Figure 4); 9 (28.1%) patients utilized frozen sperm, but none resulted in a child. The number of patients in whom sperm cryopreservation was performed by year are shown in Figure 5. The median number of sperm cryopreservation sample aliquots was 5 (1–10) (Figure 6).

Discussion

Despite the onset of malignancies in the AYA generation,

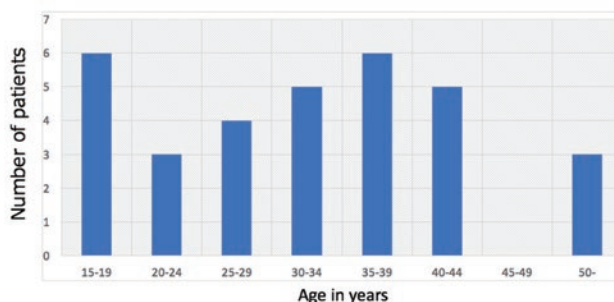


Figure 1. Number of patients undergoing sperm cryopreservation by age

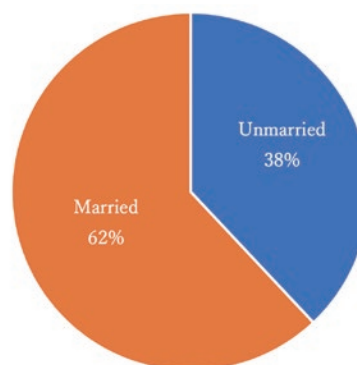


Figure 2. Marriage history

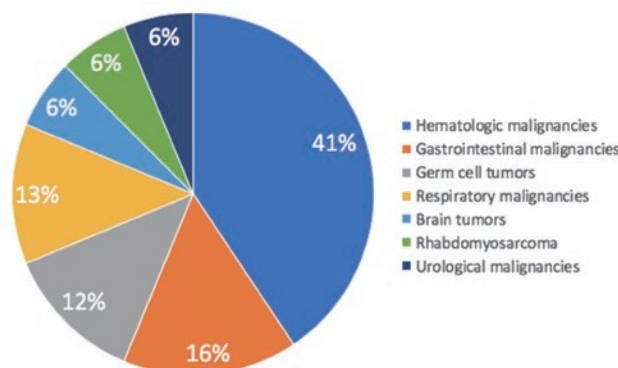


Figure 3. Number of patients by primary underlying disease

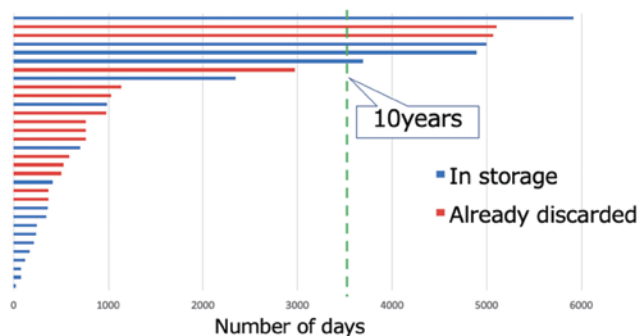


Figure 4. Number of days of sperm cryopreservation by patient

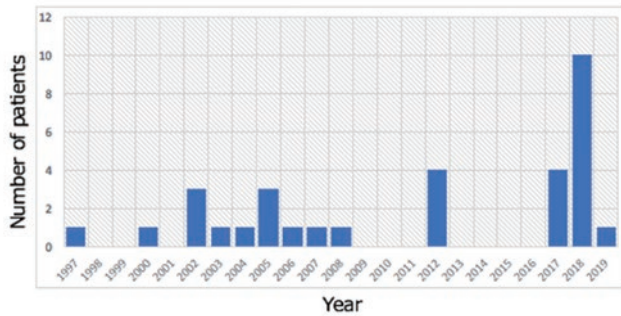


Figure 5. Number of patients undergoing sperm cryopreservation by year

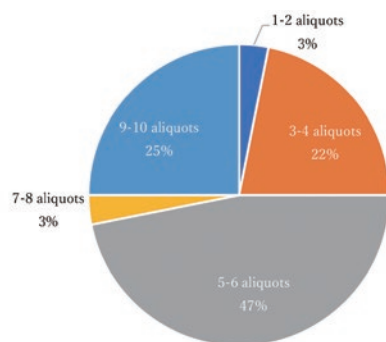


Figure 6. Number of sperm sample aliquots

the development of multimodality treatment has led to promising long-term survival. In the meantime, the effect on fertility is substantial, since temporary or permanent spermatogenic dysfunction is induced by chemotherapy and radiotherapy, and oligozoospermia and azoospermia can occur after chemotherapy³. Semen findings prior to chemotherapy should also be considered; however, for germ cell tumors, 23–25% of patients reportedly present with oligozoospermia and 20–32% present with azoospermia in semen examinations performed 1 or more years after completion of chemotherapy^{4,5}. The treating physician in charge of the primary underlying disease should fully explain the possibility that spermatogenic dysfunction may occur to the patient before the start of treatment and provide information on fertility preservation therapy. In addition, the recommendation is to confirm the patient's wishes regarding sperm preservation². If the patient wishes to preserve their sperm, there is a need to quickly work with the appropriate departments. If this is not feasible within the institution, the patient should be referred as soon as possible to a facility capable of sperm cryopreservation.

In a period of about 22 years, there were 32 patients who had undergone sperm cryopreservation for the purpose of fertility preservation at Jichi Medical University Hospital. There were also years in which sperm cryopreservation had not been performed in a single patient. In a report by Saito et al.⁶, 109 patients underwent sperm cryopreservation in 10 years at Yokohama City University. On average, the

number of patients undergoing sperm cryopreservation at our institution was 14.5 in 10 years, showing there were only a small number of patients. Although there is a population difference between Kanagawa Prefecture and Tochigi Prefecture (9.18 million people in Kanagawa Prefecture and 1.95 million people in Tochigi Prefecture⁷), the difference in cryopreservation numbers is much larger and, therefore, the population difference is not considered to be the reason for this discrepancy. Upon analyzing the reason for this difference, the first thing that comes to mind is that there is no established consultation system for sperm cryopreservation at our institution. The author was transferred to Jichi Medical University in 2016 and a consultation system was established and, since 2017, the number of patients undergoing sperm cryopreservation has dramatically increased. This suggests the importance of establishing a consultation system in medical institutions and consolidating the point of contact. The second possible reason is that there is an infertility treatment clinic adjacent to our institution, so it is possible that patients were referred to the clinic since the contact for consultation at our institution was not known. The third is that oncology physicians may not have actively considered fertility preservation. This suggests the importance of establishing a system that can positively enable the conduct of sperm cryopreservation prior to cancer treatment in collaboration with each department in the medical institution.

In males, sperm cryopreservation of ejaculated sperm is essentially performed. There is a trend toward worse semen findings in cancer patients overall, which is not limited to testicular cancer⁸. However, even in patients with poor findings during sperm cryopreservation, it is still possible to produce offspring with ICSI through developments in assisted reproductive technology (ART). In some patients with azoospermia even prior to treatment, and depending on the institution's system, onco-TESE at the time of orchiectomy is also worthy of consideration⁹⁻¹¹. At our institution, onco-TESE was performed in one patient, allowing the sperm to be cryopreserved. TESE is also option if masturbation is not feasible due to azoospermia or ejaculatory disorders or religious reasons¹². Delayed initiation of treatment with sperm cryopreservation is acceptable in the majority of patients. However, in some patients, treatment initiation cannot be delayed for fertility-sparing therapy. When urgent chemotherapy is required, fertility-sparing therapy is abandoned after adequate explanation and consent is obtained; then chemotherapy is started². Cryopreserved sperm can only be used in ART. The outline of ART should be explained during sperm cryopreservation¹⁰.

The costs associated with sperm cryopreservation and the costs associated with ART are not covered by insurance so these are out-of-pocket expenses. At our institution, the

cost burden on patients is 20,000 yen per year for the first contract and 10,000 yen per year for subsequent renewal (without consumption tax). If insurance coverage is available as part of cancer treatment, patients' cost burden will also be reduced.

It has been reported that 52% of patients who did not undergo sperm cryopreservation prior to chemotherapy and who subsequently received it and became azoospermic underwent microdissection TESE (MD-TESE, micro-TESE), and 29% produced offspring via ICSI¹³. It seems worthwhile to actively evaluate patients who could not undergo sperm cryopreservation.

Although there have been various reports on the use of cryopreserved sperm, Ferrari et al. reported an 8% rate of utilization, a 49% rate of producing offspring using frozen sperm, and a 16% rate of discarding frozen sperm in a mean follow-up of 10 years in their review¹⁴. The utilization rate of frozen sperm at our institution was 28.1%, and none of the patients produced a child. Either way, the utilization rate is not high. Since the number of patients undergoing sperm cryopreservation has increased in recent years, it is likely that some will use these samples to have a baby in the future with long-term follow-up.

Since cryopreservation is associated with a specific contract period at many institutions, there is a need to update the contract before the end of its termination; however, this may be difficult since there are some patients who do not renew the contract and cannot be contacted. Even at our institution, there are patients who do not update the contract for sperm cryopreservation. At our institution, a notice of the contract termination for sperm cryopreservation is mailed once a year. In addition, when renewing the contract, we request a payment for storage fees and the submission of a written consent. When discarding sperms, patients are asked to submit written documents; however, there are patients who cannot be contacted either way. If there is no response or the patient cannot be contacted as to whether or not to renew the contract, the sample is not destroyed immediately, and storage is continued. There is a need to form a consensus on destroying the frozen sperm in the absence of a definitive contract renewal method or contract renewal.

If the number of patients undergoing sperm cryopreservation increases, storage location may become an issue. There are 6 (18.7%) patients for whom samples have been retained for more than 10 years at our institution, and the burden on sites is also high. Traditionally, up to 10 samples were aliquoted and stored; however, this has been decreased to up to 5 samples to accommodate the increase in number of patients in recent years. The amount of sperm required for ART varies among patients, so this cannot be generalized, and it is a challenge requiring future evaluation.

Disclosure of conflicts of interest

There are no relationships causing conflicts of interest that are relevant to this study and should be disclosed.

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自治医科大学附属病院におけるがん治療前の妊孕性温存を目的とした精子凍結保存の現況について

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要 約

【目的】自治医科大学附属病院のがん治療前における妊孕性温存を目的とした精子凍結保存の現況を明らかにする。

【対象と方法】当院でがん治療前に精子凍結保存を施行した患者の診療録を後方視的に分析した。

【結果】1997年5月から2019年1月までの間に精子凍結保存をした32名を対象とした。保存時年齢の中央値は32歳（15-52歳）。未婚者12名，既婚者20名。原疾患は造血器悪性腫瘍13名，消化器悪性腫瘍5名，胚細胞腫瘍4名，呼吸器悪性腫瘍4名，脳腫瘍2名，横紋筋肉腫2名，泌尿器悪性腫瘍2名。精子を顕微授精に供した患者は9名（28.1%）いたが，全例生児獲得に至らなかった。

【考察】約22年で32名の患者で精子凍結保存が行われていた。既報と比較して少ない。その理由として，コンサルト体制がなかった点，当院に近接してARTクリニックがあること，がん治療医の妊孕性温存への配慮不足が考えられた。常時コンサルト体制を構築後は保存件数が増加しており，院内の体制づくりは重要と考えられた。

（キーワード：精子凍結保存，妊孕性温存，AYA世代）