Original Article

Testicular sperm extraction for fertility preservation in young patients with cancer

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Background: Cancer survivors in the adolescent and young adult generation often experience marriage, pregnancy, and childbirth after treatment; thus, fertility preservation is very important. In male patients, testicular sperm extraction (TESE) is sometimes performed due to azoospermia. Such a procedure is called oncological TESE (onco-TESE). In the present study, we aimed to define onco-TESE as TESE for fertility preservation in cancer patients, including those receiving gonadotoxic treatment.

Methods: Seventeen male patients with cancer who had undergone onco-TESE for fertility preservation at Yokohama City University Medical Center between April 2014 and March 2023 were included in the study.

Results: Motile testicular sperm were acquired by TESE in 9 out of 17 cases. Among patients who had initiated chemotherapy before surgery, Motile sperm could be acquired by onco-TESE in 3 out of 9 cases. In chemotherapy-naive patients, Motile sperm were acquired by onco-TESE in 6 out of 8 cases. In the end, sperm cryopreservation was performed in 10 patients. Cryopreserved sperm were used in 2 of the 10 cases, and live birth was achieved after intracytoplasmic sperm injection in both cases.

Conclusions: Before starting gonadotoxic treatment, it is important to confirm whether the patient desires to bear children. If having a baby is desired, a referral to a reproductive medicine doctor is recommended. Fertility preservation before starting gonadotoxic treatment is preferable, but fertility preservation could be considered even after such a treatment.

Keywords: Adolescent and young adult (AYA); fertility preservation; male infertility; onco-testicular sperm extraction (onco-TESE)

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Introduction

The survival rate of young patients with cancer is increasing owing to the recent advances in medical technology. Their quality of life after treatment is becoming more and more important. Cancers occurring in the adolescent and young adult (AYA) generation include testicular, cervical, uterine, ovarian, and hematologic tumors, but they may develop various cancer types similar to those observed in the elderly. In Japan, the 5-year survival rate of cancer patients in the AYA generation has been increasing as compared to the past, exceeding 80% (1). Fertility preservation is important for cancer survivors in the AYA generation because they often experience major life events, including marriage, pregnancy, and childbirth after treatment. Cancer treatment often includes gonadotoxic treatment, such as cytotoxic drugs, radiation therapy, and surgical treatment. The use of alkylating agents and platinum-containing drugs in the treatment causes azoospermia with high possibility. The American Society of Clinical Oncology (ASCO) has published the risk of gonadotoxicity for each chemotherapy and radiotherapy, reporting that fertility preservation should be offered to all cancer patients (2). Schover *et al.* advocated that fertility preservation treatment should be proposed from the psychological aspect as well because the psychological burden of loss of fertility is quite strong (3). Although the number of facilities where sperm cryopreservation is available and doctors who know about fertility preservation have increased compared to the past due to the awareness of the importance of fertility preservation, the existing relevant data are still insufficient. The first choice for fertility preservation is semen collection through masturbation, which is the simplest method. In patients with ejaculation disorders, the use of electric ejaculation or vibrator devices may be considered; however, their use is less common due to safety issues and their limited availability. In addition, intravesical sperm retrieval may be performed in cases of retrograde ejaculation. If sperm retrieval is difficult with these methods, consider testicular sperm extraction (TESE) to retrieve sperm in the testes. While semen collection by masturbation is easy and uncomplicated, TESE involves the risks of postoperative bleeding, pain, wound infection, low testosterone levels, and anesthesia. Therefore, freezing the ejaculated sperm, if possible, is preferable. In all cases, intracytoplasmic sperm injection (ICSI) using frozen sperm is basically used for fertilization in Japan.

However, azoospermia is observed in 3–18% of cancer patients before surgery or chemotherapy (4,5). Fertility preservation for cancer patients with azoospermia or almost no motile sperm or those with ejaculation disorders in whom the abovementioned methods are not effective before treatment is TESE, which is referred to as oncological TESE (onco-TESE). Although the ASCO guidelines do not explicitly mention onco-TESE, the term onco-TESE was used to refer to TESE before initiating gonadotoxic treatment in cancer patients in a previous study (6). In this study, we define onco-TESE as TESE for fertility preservation in cancer patients, including those receiving gonadotoxic treatment. The present study aimed to investigate onco-TESE and cryopreservation outcomes in our reproduction center. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-21/rc).

Highlight box

Key findings

- Cryopreservation of motile sperm was possible in 10 of the 17 patients who underwent onco-testicular sperm extraction (TESE) at our hospital. Intracytoplasmic injection of cryopreserved sperm resulted in two babies.
- Fertility preservation prior to gonadotoxic treatment initiation is desirable; however, fertility preservation can also be considered after initiating such treatment because there are cases in which motile sperm can be acquired even after initiating gonadotoxic treatment.

What is known and what is new?

- Fertility preservation in young patients with cancer should be considered because cancer treatment often includes gonadotoxic treatment. Only a few studies have reported the use of TESE for fertility preservation; moreover, the definition of oncological TESE (onco-TESE) has not been clearly defined.
- We defined onco-TESE as TESE conducted for fertility preservation in patients with cancer, including those receiving gonadotoxic treatment; and had achieved successful fertilization and subsequent pregnancy with cryopreserved sperm obtained by onco-TESE.

What is the implication and what should change now?

- Fertility preservation is crucial as cancer treatment may lead to permanent loss of reproductive function.
- Before initiating gonadotoxic treatment, patients should be informed about the risks and asked if they wish to have children in the future. If yes, then they should be referred to a reproductive specialist.
- Institutions and the city as a whole should be more supportive of fertility preservation.

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Methods

Study design

Between April 2014 and March 2023, 17 male cancer patients who had undergone TESE for fertility preservation due to azoospermia, severe oligozoospermia or necrozoospermia, or ejaculation difficulties at the Yokohama City University Medical Center were enrolled. Data on patients' age, primary disease, indication for onco-TESE, preoperative chemotherapy, motile sperm retrieval via TESE, marital status, and outcome were collected. All patients underwent surgery under general anesthesia, and the acquired testicular sperm were cryopreserved by the embryologist. The sperm retrieval rate, the number of pregnancies, and live births achieved by using the frozen sperm were examined retrospectively. Endpoints were set for outcomes, such as delivery, cryopreservation, deceased, and discarded. As this was a retrospective study, only patients with electronic medical records were included.

Onco-TESE

TESE was performed to preserve fertility in cancer patients with azoospermia, severe oligozoospermia, or ejaculation disorder. Onco-TESE is broadly classified into the following two types: narrowly defined onco-TESE performed simultaneously with radical inguinal orchiectomy for patients with testicular tumor, while broadly defined onco-TESE performed for non-testicular cancer patients. This study covered both narrow and broad onco-TESE.

Surgical procedures

TESE for the patients with testicular cancer (simultaneous with radical inguinal orchiectomy)

The surgical procedure was performed simultaneously with a radical inguinal orchiectomy. In the case of patients with solitary testis or bilateral testicular tumors, normal testicular tissue was extracted from affected testicle. The extracted specimen was processed on the bench, and the normal seminal tubules were collected visually at a sufficient distance from the tumor. Sperm retrieval was then performed by an embryologist subsequently.

TESE for patients with non-testicular cancer

If there was a difference in testicular volume between the right and left testes, the approach was performed from the side with the larger volume. A 1-cm skin incision was made on the scrotal skin, and the tunica vaginalis was incised to identify the tunica albuginea of the testis. Two stitches were placed on the tunica albuginea of the testis, and the testicular tissue was extracted through the incision between the supporting threads. A sperm search in the testicular tissue extracted by the embryologist was performed in parallel with the surgery. In the present study, most of the patients had poor general conditions after the start of treatment. In addition, because a continuation of chemotherapy and a bone marrow transplant were scheduled immediately after the surgery, a small incision was made, and the surgery was short, considering the invasiveness of the procedure. Therefore, if the sperm could not be acquired by conventional TESE, microdissection TESE was not performed.

Sperm cryopreservation

The collected testicular tissue was cut into small pieces and suspended in a sperm-freezing medium. The suspension was divided into 1–10 straw tubes, which were sealed on both edges of the straw tube using a sealer. The straw tubes were put together in one column, put it in liquid nitrogen, and frozen.

Follow-up after sperm cryopreservation

Once a year, the patient's intention to continue sperm cryopreservation storage is confirmed. If the patient wishes to discard the cryopreserved sperm or dies, the cryopreserved sperm is discarded. If the patients wish to have children, frozen-thawed sperm is usually used with ICSI.

Statistical analysis

Summary statistics were calculated. Age was expressed as mean and sperm recovery as percentage. Fisher's exact test was used to confirm the significant differences. Statistical significance was set at $P<0.05$.

Ethics statement

The protocol for this research was approved by a suitably constituted Ethics Committee of Yokohama City University Medical Center (approval No. F211100008). This study was conducted in accordance with the provisions stipulated in the Declaration of Helsinki (as revised in 2013). Individual

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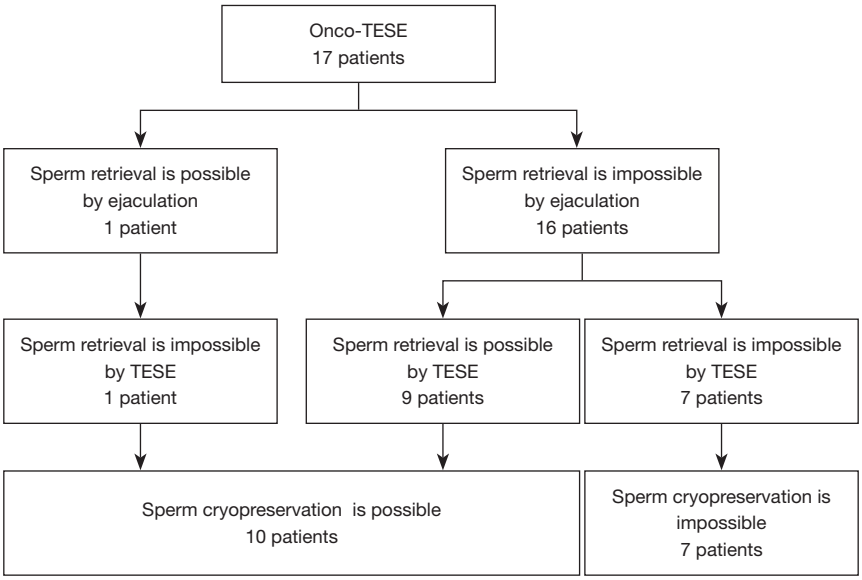

Figure 1 Results of sperm cryopreservation. Sperm cryopreservation by ejaculation was successful in 1 of the 17 cases. Including the 9 cases where sperm could be acquired by TESE, cryopreservation was achived in 10 cases. TESE, testicular sperm extraction.

consent for this retrospective analysis was waived.

Results

The characteristics of the studied patients are presented in *Figure 1*. The patients' mean age was 26.2 [13–40] years old. The primary diseases were testicular tumor in seven cases, leukemia in six cases, myelodysplastic syndrome in one case, pineal tumor in one case, spinal cord tumor in one case, and Ewing sarcoma in one case. The reasons for TESE were azoospermia in 11 cases, severe oligozoospermia in 3 cases, ejaculation difficulties in 2 cases, and necrospermia in one case.

In nine patients, chemotherapy had already been initiated during surgery. Six patients had leukemia, one case had myelodysplastic syndrome, one case had a pineal tumor, and one case had Ewing's sarcoma. Eight patients had not received chemotherapy before surgery.

Overall, motile sperm were successfully retrieved by TESE in 9 out of 17 patients (52.9%). Based on disease, sperm could be acquired by TESE in 5 out of 7 patients (71.4%) with testicular tumors and in 3 out of 6 patients (50%) with leukemia. Based on the presence of preoperative chemotherapy, sperm could be acquired by TESE in 3 out of 9 patients with chemotherapy (33.3%) and 6 out of 8 patients without chemotherapy (75%). Compared with patients receiving preoperative chemotherapy, the number of patients without chemotherapy who achieved successful sperm cryopreservation was significantly larger based on the Fisher's exact test results (P=0.03). Moreover, six of the patients were adolescents. Testicular volume in all patients was >14 mL, except in Patients 16 and 17 whose testicular volume was not measured. Hormone levels were not examined for any of the patients.

The overall picture of the patient is shown in *Table 1*. Sperm cryopreservation was performed in 10 patients (58.8%), including one patient with severe oligozoospermia whose sperm could not be acquired by TESE. The patient had only 4 motile sperm in his ejaculated semen on two occasions, which was considered insufficient. Thus, TESE was performed additionally where no testicular sperm were retrieved. Cryopreserved sperm were used in 2 of the 10 cases, both of who were not undergoing chemotherapy. Pregnancy and live birth were successfully achieved after ICSI in both cases. One patient's wife was 9 years younger than him and had polycystic ovary syndrome. In this case, nine oocytes were retrieved; and a fertilization rate of 4/8 (50.0%), a blastocyst achievement rate of 2/8 (25.0%), and an implantation rate of 1/2 (50.0%) was observed. Another patient was the same age as his wife who had no disease. Seven oocytes were retrieved from her, with a fertilization rate of 3/7 (42.9%), a blastocyst achievement rate of 1/7 (14.3%), and an implantation rate of 1/1 (100.0%). Among the remaining 8 cases, cryopreservation was terminated in 3

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Table 1 Patient characteristics who underwent onco-TESE

Patient number	Age (years)	Primary disease	Indication of onco-TESE	Preoperative chemotherapy	Motile sperm retrieval by TESE	Married	Status/reproductive outcomes
Patient 1	35	Testicular tumor	Azoospermia	No	Yes	Married	Delivery
Patient 2	25	Testicular tumor	Azoospermia	No	Yes	Married	Delivery
Patient 3	35	Testicular tumor	Azoospermia	No	Yes	Married	Under cryopreservation
Patient 4	39	Testicular tumor	Azoospermia	No	Yes	Single	Under cryopreservation
Patient 5	39	Testicular tumor	Severe oligozoospermia	No	Yes	Married	Under cryopreservation
Patient 6	15	Acute lymphoid leukemia	Severe oligozoospermia	Yes	Yes	Single	Under cryopreservation
Patient 7	16	Acute myeloid leukemia	Azoospermia	Yes	Yes	Single	Deceased
Patient 8	15	Acute myeloid leukemia	Azoospermia	Yes	Yes	Single	Discarded
Patient 9	29	Spinal cord tumor	Ejaculation disorder	No	Yes	Single	Deceased
Patient 10	24	Testicular tumor	Severe oligozoospermia	No	No	Single	Under cryopreservation
Patient 11	36	Testicular tumor	Azoospermia	No	No	Married	–
Patient 12	20	Acute lymphoid leukemia	Severe oligozoospermia	Yes	No	Single	–
Patient 13	14	Acute lymphoid leukemia	Severe oligozoospermia	Yes	No	Single	–
Patient 14	38	Chronic myeloid leukemia	Severe oligozoospermia	Yes	No	Single	–
Patient 15	40	Myelodysplastic syndrome	Azoospermia	Yes	No	Married	–
Patient 16	13	Ewing sarcoma	Azoospermia	Yes	No	Single	–
Patient 17	13	Pineal tumor	Ejaculation disorder	Yes	No	Single	–

Overall, 17 patients were included, including 7 with testicular and hematologic tumors. In 2 cases, the babies were delivered by intracytoplasmic sperm injection. Sperm from 5 patients under cryopreservation. TESE, testicular sperm extraction.

cases due to the death of the patient (n=2), and appointment defaulting (n=1). The cause of death in the 2 cases was progression of the primary disease at approximately 18 months after TESE. Patients 2 and 3 requested a postoperative semen analysis, but no sperm were found. Patient 15 too had no sperm. The other patients did not request a semen analysis.

Discussion

Ogouma *et al.* defined onco-TESE as TESE before the start of gonadotoxic treatment in cancer patients. In their systematic review, they cited 15 studies on TESE before gonadotoxic treatment, 18 studies on TESE after gonadotoxic treatment, and one study on TESE both before and after gonadotoxic treatment. Altogether, 96 cases of TESE were performed before gonadotoxic treatment, and the success rate of sperm retrieval ranged from 38.1% to 80%. The use of frozen sperm was described in 10 studies, and 11 ICSI cycles and 10 pregnancies or deliveries were observed in 51 cases. TESE after gonadotoxic treatment was performed in a total of 392 cases, and the success rate of sperm retrieval ranged from 33.3–76.2%. The use of frozen sperm was described in 17 studies, and 338 cycles of ICSI

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and 91 pregnancies and deliveries were observed in 370 cases (6).

In this study, we defined onco-TESE as TESE for fertility preservation in cancer patients with or without the initiation of gonadotoxic treatment; this was because TESE for fertility preservation can be considered even after initiating gonadotoxic treatment. It is important to establish a clear definition of onco-TESE here. In a previous study, TESE before gonadotoxic treatment was performed in a small number of cases and were mainly described as case reports (6). We successfully report 17 cases of TESE for fertility preservation and 8 cases of TESE before gonadotoxic treatment. We performed onco-TESE in two patients with ejaculation disorders: one patient had never ejaculated and the other had difficulty ejaculating due to a spinal tumor. We also considered using electric ejaculation or vibrator devices; however, since these devices were unavailable at our hospital and the opportunities were limited owing to the patients' poor general condition, we performed onco-TESE. The number of patients in the sperm retrieval group by TESE stratified by disease was higher in those with testicular tumors, followed by leukemia and then spinal cord tumors. The patients who received chemotherapy before surgery were only those patients with leukemia. Patients in the sperm non-retrieval group by TESE included those with leukemia, testicular tumor, myelodysplastic syndrome, Ewing's sarcoma, and pineal tumor. Six patients, excluding testicular tumors, had received chemotherapy prior to surgery. The treatment regimens and number of chemotherapy courses were unknown in many cases because all the patients were treated at other hospitals. All but one patient in the chemotherapy-naive group had testicular tumors, and most patients in the chemotherapy-treated group had hematologic tumors. In a previous study, the sperm retrieval rates by TESE in the chemotherapy-treated patients were reported to be 75.5% for testicular tumors, 33.5% for hematologic tumors, and 44.4% for other tumors (6). In this study, the sperm retrieval rates by TESE were 75% and 33.3% in the chemotherapy-naive and chemotherapy-treated groups, respectively, which are not significantly different from those of the previous study. Similarly, our study reported a significantly higher success rate of sperm cryopreservation for patients not receiving chemotherapy. Onco-TESE during chemotherapy may be a controversial option from the viewpoint of cancer drugs' effect on spermatozoa. The Japan Society of Clinical Oncology recommends that fertility preservation therapy should be initiated prior to cancer treatment whenever possible, but if this is not possible, it should be reconsidered when changing the treatment plan (7). However, it would be meaningful for the patients scheduled with high-risk drugs or bone marrow transplantation, considering the possibility of permanent loss of spermatogenesis. Preoperative fertility preservation may not always be indicated for testicular tumors to the point where surgery is needed in a quasi-emergency; moreover, there is a less risk of postoperative azoospermia with a unilateral tumor. However, counseling for hypogonadism and infertility should be provided prior to treatment. The American Urological Association recommends considering preoperative fertility preservation for patients with contralateral testes that are not normal or infertile (8). In the present study, all of the cases in which the sperm could not be retrieved by conventional TESE were those who had started chemotherapy. Therefore, microdissection TESE was not performed considering the patients' general condition. In patients whose sperm could not be acquired by conventional TESE, microdissection TESE may be considered if the patient's general condition allows it.

Spermatogenesis dysfunction may be present in cancer patients even before treatment. The hypothalamic-pituitary-gonadal axis may be affected in patients with testicular tumor, leukemia, lymphomas, and central nervous system tumors (9,10). Additionally, fever may adversely affect spermatogenesis, and cytokines released by the tumor may cause dysfunction in spermatogenesis (11).

Young patients with cancer are often treated with high-dose chemotherapy to achieve curative effects; thus, fertility may be lost with chemotherapy. The ASCO has reported the risk of spermatogenesis dysfunction by gonadotoxic treatment. The high-risk treatment for testicular toxicity includes administration of alkylating agents and irradiation of the testes, cranium, and whole body, whereas the medium-risk treatment includes the use of platinum drugs such as cisplatin and scattered radiation to the testes (12). The testes have a blood-testis barrier, but these drugs may affect spermatogenesis beyond the barrier (13). Alkylating agents inhibit DNA replication by alkylating DNA, and platinum drugs inhibit replication by creating cross-links in DNA double-strands. The inhibition of DNA replication suppresses cell proliferation (14,15). Given that chemotherapy targets rapidly dividing cells, it acts on germ cells undergoing spermatogenesis as well as cancer cells. Among germ cells, differentiated spermatocytes are the most sensitive. Sperm maturation is impaired at approximately 1 month after the start of chemotherapy (16).

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In chemotherapy, spermatogenesis dysfunction occurs in a drug-dependent, volume-dependent manner and affects sperm quality and quantity due to DNA damage. Hence, sperm cryopreservation before starting treatment is recommended (17,18). Additionally, radiation therapy causes DNA damage and inhibits self-renewal of cells, causing them to disappear. Radiation to the testes or scrotal tissue affects spermatocytes and Leydig cells and inhibits spermatogenesis due to the sensitivity of spermatocytes, which replicate more rapidly (19).

The incidence of azoospermia after gonadotoxic treatment was reported to be 46% in patients with leukemia, 59% in those with lymphoma, 12% in those with testicular tumors, and 34% in other malignant tumors (20). In Karunakaran *et al.*'s survey involving hemato-oncologists and patients, a majority of physicians omitted fertility counseling due to a lack of time for discussion, a lack of referral facilities, and a lack of time to start treatment. Some patients did not desire fertility preservation due to its high cost (21). However, if the patient wishes to have a baby or if they would like to hear more about reproductive functions and other issues from a specialist, he should be referred as soon as possible to a reproductive medicine doctor.

Testicular tumors predominantly affect the AYA generation. Patients with testicular tumors often have infertility even before treatment, with 6–24% of these patients having azoospermia and 50% having oligozoospermia (22). The semen findings are reported to be worse in patients with testicular tumors due to the tumor's toxicity and increased blood flow (23,24). However, no consensus has been reached on whether fertility preservation treatment is better before or after orchiectomy. In testicular tumors, germ cell neoplasia *in situ* tends to remain around the tumor. Additionally, spermatogenesis is more likely to be maintained in tubules that are distant from the tumor; in fact, spermatozoa were confirmed in 93% of tubules that were ≥7.5 mm instant from the tumor margin (25). Therefore, in onco-TESE on the affected side of a testicular tumor, it is desirable to collect tubules that are as distant from the tumor as possible. Albers *et al.* have reported that, in cases of bilateral testicular tumors or testicular tumors that develop in a solitary testis, if the preoperative testosterone level is normal and the tumor occupies <30% of the testicular volume, partial orchiectomy should be considered for fertility preservation and testosterone maintenance (26). However, the current standard treatment is still radical inguinal orchiectomy, and onco-TESE is considered extremely important.

The low sperm retrieval rate in the patients undergoing chemotherapy in the present study may be due to the fact that the majority of the patients had hematologic tumors. In addition to the fact that patients with hematologic tumors require early intervention, all patients were referred from other hospitals, which may have increased the number of visits after the start of treatment. It would be desirable to disseminate the usefulness of sperm cryopreservation to cancer center hospitals, expand the number of facilities that can perform sperm cryopreservation, and establish a network to facilitate fertility preservation. Given that sperm retrieval can be performed even after the start of chemotherapy in some patients, the patients should then be referred to a specialist as early as possible.

During counseling, we explained that the safety of pregnancy with sperm cryopreserved before chemotherapy is guaranteed but not with that after chemotherapy. In the present study, cryopreserved sperm were used in only 2 of the 10 patients, and in both cases, babies were delivered by ICSI. No pregnancy loss was observed. The use of cryopreserved sperm is expected to increase in these cases in the future as many patients who have not yet used cryopreserved sperm have recently undergone surgery. The use of cryopreserved sperm has been low in previous studies as well (6). The low utilization rate of the cryopreserved sperm may be due to the prolonged treatment of the primary disease and increasing unmarried rate, in addition to the inadequate observation period. In young patients with cancer, anxiety about the future may also contribute to the low frozen sperm usage rate.

The present study has certain limitations. First, our study included only a small number of patients. Further studies with a larger number of patients are warranted. Second, most patients were included after gonadotoxic treatment was initiated because of the limited number of facilities providing fertility preservation. If fertility preservation is possible at the treating facility itself, interventions can be performed prior to chemotherapy. Third, hormone levels were not checked prior to surgery. The levels of some hormones could have been used to predict spermatogenesis. Nonetheless, considering the fact that onco-TESE has enabled some patients to achieve fertility preservation and have a baby, onco-TESE is considered a valuable option. In the future, establishing a network that can promptly determine the indication for onco-TESE, smoothly refer patients to specialists in reproductive medicine, and share information will be essential. Additionally, we must also focus on the establishment of a system that enables

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emergent surgery when necessary and infertility treatment using frozen sperm.

Conclusions

Fertility preservation is very important as cancer treatment may cause permanent loss of reproductive function among patients. Therefore, patients should be asked if they have a desire to bear a child before initiating gonadotoxic treatment, and a smooth referral to a specialist in reproductive medicine is recommended when needed. Although fertility preservation before starting gonadotoxic treatment is ideal, it can also be discussed after the initiation of such treatment. In the future, creating a society and system more supportive of fertility preservation is essential.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-21/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-21/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-21/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The protocol for this research was approved by a suitably constituted Ethics Committee of Yokohama City University Medical Center (approval No. F211100008). This study was conducted in accordance with the provisions stipulated in the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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