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Fertility Among Testicular Cancer Survivors at a Male Infertility Clinic

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Introduction: Sperm quality is often abnormal at the time of testicular cancer diagnosis. Anti-cancer treatment has detrimental effects on spermatogenesis, and inevitably results in a single testicle after treatment; thus, subsequent fertility is a concern. We evaluated fertility among testicular cancer survivors at our male infertility clinic.

Materials and methods: From 2014 April to 2023 March, 1,750 male infertility patients consulted our division, 53 (3.0%) of whom had a history of cancer treatment. A total of 18 patients diagnosed with testicular cancer were evaluated for cancer treatment, semen findings, and infertility treatment.

Results: Ten patients were followed up with a high orchidectomy alone. Eight patients were treated with orchidectomy followed by chemotherapy, and six patients received subsequent retroperitoneal lymph node dissection. Two patients underwent cryopreservation of ejaculated sperm before cancer treatment. Eight patients showed motile sperm in their ejaculates, and ten patients showed azoospermia. Sperm retrieval surgery was attempted in six participants with azoospermia, four of whom achieved successful motile sperm recovery. Four healthy girls were delivered through intracytoplasmic sperm injection (ICSI); subsequently one healthy boy was delivered after frozen thawed embryo transfer.

Conclusions: Cryopreservation of ejaculated sperm before cancer treatment is essential, however it is not so commonly performed. Testicular cancer survivors, even those with azoospermia, can achieve fatherhood through ICSI, after precise evaluation and appropriate sperm retrieval surgery.

Key words: testicular cancer survivor, sperm retrieval surgery, testicular sperm extraction (TESE), microscopic sperm aspiration (MESA), intracytoplasmic sperm injection (ICSI)

INTRODUCTION

General improvements in the prognosis of patients with cancer have been achieved through recent advances in surgery, radiotherapy, and chemotherapy treatments, thus increasing the number of patients surviving therapy. However, cancer treatments can have irreversible detrimental effects on spermatogenesis. In patients with testicular cancer, sperm quality is often already abnormal at the time of diagnosis, and testicular cancer inevitably results in a single testicle remaining after treatment; conse-

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quently, subsequent fertility is a concern. Although cryopreservation of ejaculated sperm before cancer treatment should be performed, it does not commonly occur in practice. Even in infertility units, only about 10% of patients undergo cryopreservation of ejaculated sperm during treatment. In contrast, the use of cryopreserved ejaculated sperm for infertility treatment actually occurs in only 10% of patients[1]. Here, we retrospectively evaluated the fertility status and treatment of testicular cancer survivors at our male infertility clinic.

MATERIALS AND METHODS

Study design, size, and duration

From April 2014 to March 2023, 1,750 male infertility patients our clinic, 53 (3.0%) of whom had a history of cancer treatment. Eighteen patients diagnosed with testicular cancer were evaluated for cancer treatment, semen findings, and infertility treatment.

Patients and setting

The median patient age was 36 years (interquartile range; 31, 38), and the median spousal age was 33 years (32, 35). The median duration from termination of cancer treatment was 5.5 years (3.0, 7.0), and the median duration of infertility was 3.0 years (1.8, 4.3). Testicular volume was judged by punched-out orchidometer. The median testicular volume was 16 mL (7, 20) in the right testicle and 15 mL (10, 18) in the left testicle. The median levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone were 4.70 mIU/mL (4.13, 6.68), 9.45 mIU/mL (7.30, 18.35), and 5.28 ng/mL (3.56, 6.68), respectively.

RESULTS

Testicular cancer type and treatment

Seminoma was observed in 16 participants, and non-seminomatous germ cell tumor (NSGCT) was observed in two patients. Ten patients with seminoma diagnosed as pT1N0M0 were followed up with a high orchidectomy alone. One patient with seminoma diagnosed as pT1N1M0 underwent orchidectomy followed by combination chemotherapy comprising bleomycin, etoposide, and cisplatin (BEP). Five patients with seminoma diagnosed as pT1N2M0 in one, pT2N0M0 in three, and pT3N1M0 in one, were treated with orchidectomy followed by chemotherapy, and subsequent retroperitoneal lymph node dissection (RPLND), respectively. One NSGCT (embryonal/yolk sac/immature teratoma) diagnosed as pT2N0M0 was treated with orchidectomy followed by BEP, and another NSGCT (embryonal) diagnosed as pT3N0M0 underwent orchidectomy, BEP, and RPLND.

Semen analyses and cancer type

Two patients underwent cryopreservation of ejaculated motile sperm before cancer treatment. Semen analyses did not reveal normozoospermia in any participants. Azoospermia was diagnosed in ten participants, and oligoasthenozoospermia was diagnosed in eight participants. Among the patients with oligoasthenozoospermia, the median sperm count and motility were 4.5×10^{6}/mL (1.6, 6.1) and 24% (15, 31), respectively.

Among the ten patients with azoospermia, eight were diagnosed as having pT1N0M0 seminoma. In contrast, among patients with oligoasthenozoospermia, six were diagnosed as having an advanced pathological stage and/or lymph node metastasis. Details of semen analysis and cancer type, stage, and treatment were shown in Table 1. Cancer stage was expressed according to the Union for International Cancer Control (UICC) 8the edition.

Two seminoma pT2N0M0 participants who received RPLND showed ejaculatory dys-

function. Fortunately, they were able to ejaculate after oral administration of daily 50 mg amoxapine daily. Their sperm counts were 37 $\times 10^6$/mL and 6.5 $\times 10^6$/mL, and their sperm motility 17% and 7%.

The differences in each parameter between participants with sperm present and absent are shown in Table 2. When spermatogenesis was

Table 1. Semen analysis and cancer type, stage, and treatment

Cancer type and stage/following treatment	age	Sperm count $\times 10^6$/mL	Sperm motility (%)
Seminoma pT1N0M0/WW	30	0	0
Seminoma pT1N0M0/WW	37	4	50
Seminoma pT1N0M0/WW	31	2	44
Seminoma pT1N0M0/WW	31	0	0
Seminoma pT1N0M0/WW	31	0	0
Seminoma pT1N0M0/WW	32	0	0
Seminoma pT1N0M0/WW	32	0	0
Seminoma pT1N0M0/WW	38	0	0
Seminoma pT1N0M0/WW	44	0	0
Seminoma pT1N0M0/WW	45	0	0
Seminoma pT1N1M0/BEP	40	5	5
Seminoma pT1N2M0/BEP/RPLND	36	0	0
Seminoma pT2N0M0/BEP/RPLND	42	6.5	7
Seminoma pT2N0M0/BEP/RPLND	34	0.2	26
Seminoma pT2N0M0/BEP/RPLND	34	37	17
NCGCT (embryonal/yolk sac/immature teratoma) pT2N0M0/BEP*	28	6	21
NSGCT (embryonal) pT3N0M0/BEP/RPLND*	36	0.25	26
Seminoma pT3N1M0/BEP/RPLND	29	0	0

WW: watchful waiting
BEP: combination chemotherapy of bleomycin/etoposide/cisplatin
RPLND: retroperitoneal lymph node dissection
*These patients received cryopreservation of sperm before treatment.

Table 2. Differences in each parameter between patients with sperm presence or absence

	Sperm (+) n=10	Sperm (−) n=8	P value
Age (y)	33 (32, 38)	32 (31, 38)	0.317
Spouse age (y)	33 (29, 35)	32 (31, 37)	0.742
Duration from latest cancer treatment (y)	3.0 (1.6, 6.3)	2.5 (1.3, 3.8)	0.974
Right testis volume (mL)	16 (16, 20)	8 (7, 16)	0.352
Left testis volume (mL)	18 (16, 18)	10 (8, 16)	0.053
LH (mIU/mL)	4.2 (4.1, 4.4)	6.3 (4.7, 17.9)	0.004
FSH (mIU/mL)	8.1 (7.3, 9.9)	14.3 (7.3, 19.7)	0.001
Testosterone (ng/mL)	5.86 (3.73, 6.59)	5.28 (3.55, 6.71)	0.788
Zinc (ng/mL)	81 (76, 87)	65 (64, 65)	0.058
Body mass index (kg/m^2)	22.9 (20.6, 24.5)	22.0 (21.5, 26.4)	0.701

Data are shown as median (interquartile range)
Mann-Whitney U test was used.

present, the serum gonadotropin value was significantly lower than that in patients demonstrating no spermatogenesis.

Sperm retrieval surgery

Sperm retrieval surgery was attempted in six participants with azoospermia. Three participants underwent microscopic sperm extraction (micro-TESE), two participants received onco-TESE, and one patient was by microscopic sperm aspiration (MESA). Onco-TESE was defined as a micro-TESE procedure performed at a sufficient distance from the tumor under ex-vivo conditions.

Four of six patients with azoospermia obtained motile sperm through sperm retrieval surgery. Onco-TESE was performed on two seminomas. One case was pT3N1M0, and the contralateral testis was not clear on palpation and imaging. Another one case with a contralateral testis was orchiectomized because of pT1N0M0 seminoma 3 years prior. Both participants showed successful motile sperm recovery. One of three patients with pT1N0M0 seminoma who received micro-TESE had motile sperm. One patient with pT1N0M0 seminoma underwent motile sperm recovery through MESA. His endocrine panel and residual testicular volume were normal (LH/FSH =2.9/3.6 mIU/mL, testosterone=8.37 ng/mL, left testicular volume=26 mL). This patient was considered as having obstructive azoospermia rather than impaired spermatogenesis caused by testicular cancer.

Pregnancy results

Ejaculated or surgically retrieved sperm were used for intracytoplasmic sperm injection (ICSI) to achieve pregnancy. One participant with pT1N0M0 seminoma had a healthy girl born through ICSI using ejaculated sperm. Three healthy girls were also delivered through MESA-ICSI (1), and onco-TESE-ICSI (2). One participant subsequently had a healthy boy born through frozen thawed embryo transfer.

Statement of ethics

The protocol for this research project, including the use of human participants, was approved by the Ethical Committee of Kyoritsu General Hospital. (approval number: 2022-10, approval date: 2023/02/20).

DISCUSSION

With advances in cancer treatment, the numbers of cancer survivors are increasing. Fertility is particularly important for members of the adolescent and young adult (AYA) generation, who would like to have families. Most cancers in the AYA generation are classified as rare. Although the incidence of testicular cancer is also rare, it is the most common solid cancer among men of ages at which fertility is a concern. Approximately 20,000 new cancer patients per year are in the AYA generation, thus accounting for 2.5% of all patients with cancer in Japan[2]. This proportion was similar to the proportion of patients who visited our male infertility division who were cancer survivors.

Among testicular cancer survivors, surgery and chemotherapy can affect spermatogenesis, hormone production, and sperm transport, thus resulting in testicular dysfunction. In addition, anti-cancer agents decrease the number of spermatogonia and cause permanent spermatogenic dysfunction in the early stages of treatment, when the total amount used is high. Patients with testicular cancer often have abnormal semen quality, and treatment results in the preservation of a single testicle; therefore, subsequent fertility is a concern. Although cryopreservation of ejaculated sperm before cancer treatment should be used, this procedure is rarely performed, as observed in this study. In general, cancer survivors frequently

have diminished testicular function after cancer treatment, and most cases of azoospermia are considered non-obstructive azoospermia (NOA). For patients with NOA, TESE is currently considered the standard surgery for obtaining motile sperm. We have previously reported that post-chemotherapy cancer survivors with NOA can achieve fatherhood through micro-TESE with ICSI[3].

In this study, eight of ten patients with azoospermia had pT1N0M0 seminoma and had not received any cancer treatment other than high orchidectomy. In contrast, six of the eight patients with oligoasthenozoospermia had advanced testicular cancer at pT2 or higher or lymph node metastasis, and four patients also underwent RPLND. Thus, the fertility of the testicular cancer survivors might not have been dependent on cancer treatment.

The two patients with ejaculation dysfunction due to RPLND were able to ejaculate after oral administration of amoxapine. However, in September 2022, the Ministry of Health, Labor and Welfare of Japan issued an administrative notice describing detection of N-nitrosoamoxapine, a potentially carcinogenic substance, in amoxapine. Currently, amoxapine cannot be used in Japan, and we have been required to instead use imipramine or other treatments, despite their lower efficacy than that of amoxapine[4].

Watchful waiting (surveillance) for patients with early-stage testicular cancer patients has been used. In contrast, BEP is the standard treatment for advanced testicular cancer. The testicular toxicity of cisplatin, the main drug in BEP, is considered moderate. To estimate the long-term effects of chemotherapy on fertility, Pont and Albrecht have conducted a prospective study comparing patients who received chemotherapy with those who did not, and have concluded that a cumulative cisplatin dose <400 mg/m^2 is unlikely to cause irreversible damage to fertility[5]. Levine et al. have reported an increased risk of testicular toxicity when cisplatin is administered at doses greater than 500 mg/m^2 [6]. BEP is usually administered in three courses[7]. When cisplatin is used in a regimen for 20 mg/m^2 from day 1 through day 5, the total cisplatin amount administered in three courses of BEP would be 300 mg/m^2, which does not high toxicity risk.

In this study, six of the eight patients treated with chemotherapy showed motile sperm in their ejaculate, despite poor sperm quality. Of the ten cases with azoospermia, motile sperm were recovered in four of six patients who underwent sperm retrieval surgery. In a retrospective study, spermatozoa have been found after TESE in 15 (65.2%) of 23 men[8]. The predominant histopathology pattern observed was Sertoli cells only (47.8%), followed by hypospermatogenesis (30.4%), mixed (17.4%), and late maturation arrest (4.3%). Suzuki et al., in a study of 45 patients with testicular cancer treated with BEP, have reported that 44 recovered spermatogenesis[9]. However, the recovery of spermatogenesis was delayed according to the number of BEP cycles administered. In groups of patients receiving one or two, three, and four 4 cycles, the recovery rates of spermatogenesis within 2 years were 83.3, 80.0, and 66.7%, respectively. In the group receiving five or six cycles of BEP or high dose chemotherapy, spermatogenesis required more than 2 years to recover. The age and semen parameters before chemotherapy were not found to be useful as predictors of spermatogenesis recovery[9].

Shin et al. have reported a live birth rate of 27% in fathers with post-chemotherapy azoospermia, including hematopoietic cancer[10]. They have observed no significant differences in the

sperm retrieval rate, clinical pregnancy, and live birth rate between fathers with testicular cancer and hematopoietic cancer. Moreover, they have detected no predictive variables associated with successful sperm retrieval.

According to self-reported paternity after testicular cancer treatment with two to four cycles of cis-platin based chemotherapy, 80% (85 of 106) patients successfully achieved post-treatment paternity at a median 12-year follow-up[11].

Thus, the sperm recovery rate in testicular cancer survivors through TESE reported herein was relatively good. However, irreversible damage may occur when anticancer drugs are used in high doses. In contrast, studies exploring additional BEP regimen adjustments to further decrease toxicity have shown that the lower threshold of efficacy has been reached, thus potentially compromising the efficacy of the chemotherapy[7]. Therefore, weighing the effectiveness of chemotherapy against cancer and the testicular damage caused by adverse effects poses a dilemma.

Cirigliano et al. have reported successful sperm recovery was obtained in 33.3% of cases by onco-TESE[12]. In our series, motile spermatozoa were collected by onco-TESE in patients with pT3N1M0 seminoma of a single testicle or pT1N0M0 seminoma after contralateral orchidectomy due to seminoma. In contrast, for patients with pT1N0M0 seminoma with normal hormone levels, assumed to be due to obstructive azoospermia, we were able to recover a sufficient amount of motile sperm through MESA. However, the cause of obstruction was unclear. In general, sperm retrieval is often performed with TESE. However, we have been advocating for the use of MESA, because it causes less postoperative pain for patients, has no effect on testosterone, is less burdensome for the embryologists, and is associated with good pregnancy and live birth rates[13][14].

Although no clear criteria are available, our study might suggest that a low FSH value indicates the possibility of obstructive azoospermia even in testicular cancer survivors after treatment. A high FSH value is associated with a greater number of chemotherapy cycles[11]. As observed in this case series, retrieval of motile sperm through MESA may be possible, even among cancer survivors. Because testicular cancer survivors have a single testicle, sperm retrieval has a significant effect on testosterone. Sperm retrieval should not be considered feasible though only TESE. Surgeons performing the sperm retrieval must carefully consider the disadvantages of the surgery.

Four healthy girls and one healthy boy were born through ICSI by using ejaculated or surgically retrieved sperm in this study. Live birth rate was achieved for 5 of 18 (27.7%) participants. Thus, testicular cancer survivors with appropriate treatment have a good chance of becoming fathers, as previously reported[8][9][10].

Among testicular cancer survivors, evidence of sperm in semen is not necessarily associated with the use of chemotherapy. In this study, preservation of spermatogenesis among testicular cancer survivors appeared to depend on the patient's potential, regardless of the presence or absence of chemotherapy. Even testicular cancer survivors with azoospermia can undergo sperm retrieval with appropriate surgery and can father children after assisted reproductive technology procedure.

Limitations and reasons for caution

Although patients with azoospermia were informed of the need for sperm retrieval surgery, several participants did not choose to undergo the operation. One participant who had cryopreserved sperm, does not plan to marry.

Because of a lack of information about pregnancy among participants with oligoasthenozoospermia, we cannot draw conclusions regarding their fertility status.

All patients in this study received cancer treatment at other hospital. Although the information of cancer stage and treatments had obtained from referring hospital, the precise doses of each drug of chemotherapy remained unclear.

Wider implications of the findings

Testicular cancer inevitably results in the presence of a single testicle after treatment; however, motile sperm recovery without TESE may possible. Surgeons should carefully assess using operative microscopy to determine the most appropriate recovery method, other than TESE, which can cause damage to the testis.

CONCLUSIONS

Testicular cancer survivors even if they have azoospermia, can be fatherhood through proper diagnosis, appropriate surgery, and the use of ICSI.

Disclosures

Human rights and informed consent statements: 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. Written informed consent was obtained from the participants to participate in the current study.

Statement of ethics

The protocol for this research project, including its use of human subjects, was approved by a suitably constituted the Ethical Committee of Kyoritsu General Hospital. (approval number: 2022-10, approval date: 2/20/2023)

Data availability statement

We cannot share data openly to protect the privacy of research participants.

Conflicts of interest

Each author has no COI regarding this manuscript.

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