ORIGINAL PAPER

Nagoya J. Med. Sci. **82**. 677–684, 2020
doi:10.18999/nagjms.82.4.677

Male infertility treatment for cancer survivors: does anticancer treatment affect infertility treatment?

Hatsuki Hibi[1], Miho Sugie[1], Tadashi Ohori[1], Noritaka Fukunaga[2], Megumi Sonohara[2] and Yoshimasa Asada[2]

[1]*Department of Urology, Kyoritsu General Hospital, Nagoya, Japan*
[2]*Asada Ladies Clinic, Nagoya, Japan*

ABSTRACT

We investigated the impact of prior anticancer treatments such as chemotherapy and radiotherapy on subsequent infertility treatment in cancer survivors who consulted our male infertility division. Of 1,525 male infertility patients who consulted our division between 2008 and 2018, 56 (3.7%) were cancer survivors. Of these, 32 received anticancer treatment (group A) and 24 were treated with surgery alone or were seen before anticancer treatment (group B). Semen analysis revealed that azoospermia in 26 subjects (81.3%) and 14 (58.3%) in groups A and B respectively. Ejaculatory dysfunction was observed 1 in group A and in 2 group B subjects. Sperm cryopreservation before anticancer treatment was performed 4 subjects. Sperm retrieval surgery for intracytoplasmic sperm injection (ICSI) was performed in 13 cases in group A and 10 in group B. Motile sperm were recovered in 7 subjects and in 8 subjects in group A and B respectively. Overall pregnancies and deliveries with ICSI were achieved for 7 subjects (21.9%) in group A, and 9 (37.5%) in group B. Successful sperm retrieval may not be affected by prior anticancer treatment as shown in this study. However, some patients abandoned infertility treatment due to the cost of testing and sperm retrieval surgery. Support for the cost of infertility treatment in cancer survivors is necessary.

Keywords: cancer survivor, male infertility, anti-cancer treatment, sperm retrieval surgery, ICSI outcome

INTRODUCTION

Cancer incidence in young men has been increasing and about 11,000 men aged 15–39 years are diagnosed with cancer every year in Japan.[1] There is however an increase in the survival rate of those men still within the reproductive age due to recent advances cancer therapies. It is well known that cytotoxic chemotherapy and radiotherapy is associated with dramatic gonadal damage in men. Timely cryopreservation of semen which can be used for assisted reproductive technology (ART) is the best modality to ensure fertility. However, in the subjects with germ

Received: February 17, 2020; accepted: April 15, 2020

Corresponding Author: Hatsuki Hibi, MD
Department of Urology, Kyoritsu General Hospital, 4-33 Goban-cho, Atsuta-ward, Nagoya 456-8611, Japan
Tel: +81-52-654-2211, Fax: +81-52-651-7210, E-mail: hibih@quartz.ocn.ne.jp

*This paper was presented at Annual Meeting of European Society of Human Reproduction and Embryology held at Vienna, 23-26 June, 2019.

cell tumors, sperm quality is already abnormal at the time of diagnosis. In approximately 12% of men, no viable spermatozoa are present for cryopreservation before the start of treatment.[2] In this study we investigated whether prior anticancer treatments such as chemotherapy and radiotherapy impact the outcome of infertility treatment in cancer survivors who consulted at our male infertility division

MATERIALS AND METHODS

Patients

Of 1,525 male infertility patients who consulted our division between 2008 and 2018, 56 (3.7%) were cancer survivors who desired to have their own genetic offspring. Of these, 32 received anticancer treatment (group A) and 24 were treated with surgery alone or were seen before anticancer treatment (group B). Patient characteristics in each group is shown in Table 1. Pathologic findings in group A included hematologic cancer (11 cases; acute lymphocytic leukemia (ALL): 4; acute myeloblastic leukemia (AML): 2; malignant lymphoma (ML): 5), testicular (8 cases; semimona: 6, non-seminomatous germ cell tumor (NSGCT): 2), colorectal (4), osteosarcoma (3), extragonadal germ cell (2), parotid gland (1), adrenal glioblastoma (1), rhabdomyosarcoma (1), and prostate (1). Total body irradiation (TBI) and bone marrow transplantation (BMT) from siblings was carried out in 3 subjects with ALL. Three ML subjects received radiation therapy following chemotherapy. One osteosarcoma patient received hemodialysis due to chemotherapy related renal failure. Group B consisted of testicular cancer (11; seminoma: 9, NSGCT: 2), colorectal (4), kidney (3), extragonadal germ cell (2), lung (1), gallbladder (1), thymus (1), and ALL (1), (see Table 2). Semen analyses in each group are shown in Table 3. In group A, 26 subjects showed azoospermia, oligoasthenozoospermia in 4, and cryptozoospermia in 1, respectively. In group B, 14 subjects had azoospermia, 3 had normospermia and oligoasthenozoospermia, and 2 cryptozoospermia, respectively. Ejaculatory dysfunction (EjD) was observed in 1 NSGCT subject after retroperitoneal lymph node dissection in group A, and in group B there were 2 (one had rectal cancer requiring rectal amputation, and another kidney cancer due to unidentified EjD). Although chromosomal analysis should be recommended to those with azoospermia and cryptozoospermia, some patients did not have analysis due to cost. Chromosomal G band was checked in 24 subjects (75% of group A), and 15 (62.5%) in group B, respectively. Y chromosomal microdeletion was evaluated in only 21 subjects (37.5%) in group A and B.

Methods

One patient with oligoasthenozoospermia and three with normospermia in group B underwent cryopreservation of semen before anticancer treatments. For the azoospermia or EjD subjects, surgical sperm retrieval for intracytoplasmic sperm injection (ICSI) was performed under spinal or local anesthesia with spermatic block and usage of sedative during surgery upon patient's request. In group A, retrograde vasal sperm aspiration (ReVSA)[3] was undertaken in one subject for EjD, microscopic epididymal sperm aspiration (MESA) in one and microscopic testicular sperm extraction (micro-TESE) in 11, respectively. In group B, ReVSA was performed in two subjects, MESA in one, and micro-TESE in 7, respectively. Aspirated or extracted samples were transferred into modified human tubal fluid and sent to the in vitro fertilization (IVF) laboratory for cryopreservation. On the other hand, for the patients with azoospermia, 14 subjects of 26 (53.8%) in group A and 6 of 14 (42.9%) in group B did not have sperm retrieval surgery and terminated fertility treatment due to cost.

Table 1 Patients characteristics

	Group A (n=32)	Group B (n=24)
Age	34.0 (27–52)	36.0 (27–61)
Spouse age	31.5 (25–40)	34.0 (25–40)
Duration of infertility (year)	2.0 (0.5–8)	2.5 (1–13)
Testicular size right/left (mL)	10 (resected-24) / 11 (resected-26)	14 (resected-20) / 14 (resected-26)
LH (mIU/mL)	6.2 (1.8–17.9)	4.2 (0.1–18.4)
FSH (mIU/mL)	14.8 (1.5–44.3)	11.8 (0.1–53.4)
Testosterone (ng/mL)	4.52 (0.41–17.46)	4.20 (0.64–8.37)
Free testosterone (pg/mL)	11.4 (3.7–17.1)	10.6 (1.6–38.4)
Body mass index	22.1 (17.9–33.1)	22.6 (18.6–24.5)

Table 2 Type of cancer in each group

	Group A (n=32)	Group B (n=24)
Hematologic	11	1
Testicular	8	11
Colorectal	4	4
Osteosarcoma	3	–
Extragonadal germ cell	2	2
Parotid	1	–
Adrenal glioblastoma	1	–
Rhabdomyosarcoma	1	–
Prostate	1	–
Kidney	–	3
Lung	–	1
Gallbladder	–	1
Thymus	–	1

Table 3 Findings of semen analysis

	Group A (n=32)	Group B (n=24)
Normospermia	–	3 (cryopreserved)
Oligoasthenozoospermia	4	3 (cryopreserved in 1)
Cryptozoospermia	1	2
Azoospermia	26	14
Ejaculatory dysfunction	1	2

RESULTS

There was no difference between group A and B regarding age, spouse age, endocrine panel, and body mass index (BMI). Normal karyotype of 46XY was observed in 22 subjects (84.6%) in group A and 14 (93.3%) in group B (Table 4). Two subjects showed 46XX after BMT, and one subject had Klinefelter's syndrome. Y chromosomal microdeletion was not observed except in a case of BMT. Successful sperm cryopreservation before anticancer treatment in group B was performed for testicular, colorectal, lung, and thymus cancer cases. In group A, anticancer treatment was carried out before puberty in 6 (18.5%) subjects. The cancer type for these cases

Table 4 Chromosomal examination

	Group A (n=26)	Group B (n=15)
46 XY	22	14
46 XY inv	2	–
46 XX	2 (bone marrow transplanted)	–
47 XXY	–	1

was ALL in 4, adrenal glioblastoma in 1, and rhabdomyosarcoma in 1, respectively. The mean duration from anticancer treatments was 12 years (range; 2–29) except in two cases of during chemotherapy where we were unable to evaluate the actual regimen and dose of chemotherapy.

In cases of azoospermia and ejaculatory dysfunction, sperm retrieval surgery was performed in 13 cases (40.6%) in group A and 10 (41.7%) cases in group B. In group A, motile sperm recovery was 100% by ReVSA and MESA, 45.4% (5/11 cases) by micro-TESE, respectively. In group B, three subjects had motile sperm retrieved by ReVSA and MESA, 71.4% (5/7 cases) by micro-TESE. Immotile sperm were recovered in three subjects (osteosarcoma: 1, ML: 2) in group A by micro-TESE. Successful motile sperm recovery in group A was obtained in testicular (4), colorectal (1), ALL (1), osteosarcoma (1), and in group B was testicular (6), colorectal (1), kidney (1), respectively.

Pregnancies and healthy deliveries by using surgically retrieved sperm for ICSI were observed in testicular (seminoma: 2, NSGCT: 2), ALL (1), colorectal (1), and osteosarcoma (1) in group A, respectively. In group B, pregnancy and healthy delivery were achieved in testicular (seminoma: 2, NSGCT: 2), colorectal (1), and kidney (1), respectively. Three pregnancies and healthy deliveries using ejaculated sperm were obtained in group B. (seminoma: 2, colorectal: 1) Whereas in three subjects where only immotile sperm were recovered, no pregnancy was achieved. No statistical difference was observed between group A and B (P=0.21), overall pregnancies and deliveries were observed in 7 subjects (21.9%) in group A, and 9 (37.5%) in group B.

DISCUSSION

Cryopreservation of sperm

Fertility preservation in males is the process of recovering spermatozoa or testis tissue with the aim of providing a future opportunity to father biological children. It is well known that cytotoxic chemotherapy and radiotherapy as anticancer treatments are associated with dramatic gonadal damage in men. The standard fertility preservation technique is cryopreservation of ejaculated semen. Timely cryopreservation of semen which can be used for ART is considered to be the best modality to ensure fertility. Although this is a highly important method to preserve fertility, this is not always possible such as in pediatric or pre-pubertal patients. Fertility preservation in such patients is considered to be a challenging. Sometimes the boy is unwilling to discuss experiences with ejaculation and nocturnal emissions. Since anticancer treatment is mandatory to reduce the negative impact on life expectancy, semen cryopreservation has not been increased.[4] Muller et al reported that of the 898 patients who had cryopreserved semen, only 96 (10.7%) used the samples for ART. The live birth rates for intra-uterine insemination (IUI), IVF, ICSI were 13%, 29%, 32%, respectively.[5] Kobayashi et al also reported the low usage rate of cryopreserved sperm in 122 Japanese men during the recent decade.[6] This low usage may be due to patient survival, retained or recovered fertility, no paternity wish or to achieve a completed family. In particular, the ability to conceive spontaneously without burdensome fertility treatment seems an

important reason for this low usage rate.

Health problems of cancer survivor

In accordance to a large scaled cohort analysis, cancer survivors were eight times as likely as their siblings to have severe or life-threatening chronic health conditions.[7] Survivors especially of bone tumors, central nervous system (CNS) tumors, and Hodgkin's disease are in particular high risk groups. For example, bone tumor survivors may have associated musculoskeletal problems, congestive heart failure, and hearing loss. CNS tumor survivors have cognitive dysfunction, and endocrinological disorders. Hodgkin's disease survivors developed cardiovascular disease, secondary cancers (particularly breast cancer in women), lung disease, and thyroid disorders. The incidence of health conditions reported by this population increases with time and does not appear to plateau. Oeffinger et al emphasized that the monitoring of survivors is an important part of their overall health care.[7] Bone tumor and ML subjects in group A were fortunately in a healthy condition. Following a mean duration of 12 years after anticancer treatments, it was still unclear what the precise diagnosis Hodgkin's disease or non-Hodgkin's.

Surgery

The cryopreservation of semen is a safe and effective way of preserving fertility for adolescent and adult males. For adult azoospermia, sperm retrieval surgery is necessary and TESE is indicated for harvesting sperm.[8] There is no doubt that micro-TESE has become a standard surgery for use in non-obstructive azoospermic (NOA) patients.[9] However, sperm retrieval surgery does not always mean TESE. Although the number of patients were small in each group, two patients showed obstructive azoospermia (OA). We previously emphasized superior pregnancy and clinical delivery were observed in MESA following ICSI without testicular surgical damage.[10] Careful observation should be paid during surgery under operative microscope to avoid unnecessary testicular damage.

ICSI results according to the cancer type

Anticancer treatments have potential to cause germline mutation that may increase the risk of cancer in the offspring of former cancer patients. However, according to the Finnish nationwide survey, offspring of cancer patients are not at an increased risk of cancer except in cases with a hereditary cancer syndrome.[11] Alkylating agents, such as cyclophosphamide and procarbazine, are the most common agents implicated. Whereas cisplatin-based chemotherapy for testicular cancer results in temporary azoospermia in most men, recovery of spermatogenesis occurs in about 50% after 2 years, and 80% after 5 years.[12] Spermatogenesis may still continue over several years if the spermatogonial cell population is not completely depleted. If a population of these germ stem cells remains after cancer treatment, the regeneration of spermatozoa may continue for years.[13] Thus, spermatogenesis can recover in some patients depending on the type of cancer and the dose and duration of treatment received, but such recovery is still clinically unpredictable. Muller et al reported that no pregnancy occurred by using the sperm from patients with cancers other than lymphoma or testicular tumors.[5] Kobayashi et al also reported the use of semen cryopreservation as an onco-fertility treatment, whilst pregnancy was achieved in subjects with hematologic and testicular cancers, no pregnancy occurred from patients with digestive and or other cancer type.[6] In our series, 7 pregnancies and delivery were achieved in group A; four in testicular, and one in ALL, colorectal, and osteosarcoma, respectively. The relationship of cancer type and successful sperm retrieval remained unclear.

Issues for prepuberty

For prepuberty boys, there are no proven successful options to preserve future fertility. Patients and their families require to be counseled before cancer treatments by a specialist in order to carry out fertility preservation. Genetic damage following anticancer treatments has been reported. Increased aneuploid frequency has been observed in human sperm, and an increase in chromosomal abnormalities after chemotherapy.[14]

A recent study demonstrated that iPS cells generate haploid spermatotid.[15] Advances have since been made in the derivation of differentiated male germ cells from mouse or human ES cells. Transcription factors were used to reprogram somatic cells to iPSA cells in a 2006 study.[16] However, harvesting testicular tissue is still considered to be an experimental modality. Several medical and ethical risks are associated with this procedure; it is uncertain how much testicular damage will occur in these boys after removing testicular tissue, which could limit the testicular capability to recover from anticancer treatments.[2]

Lack of precise cancer registration and needs for governmental support

National clinical database (NCD) systems have been running since 2011 in mainly surgical departments in Japan. The nationwide cancer registration systems were started from 2016. However, each patient received anticancer agents however the actual dose was difficult to evaluate retrospectively. Prospective and accurate registration systems for anticancer treatments is necessary in order to better understand the subsequent health condition and to incorporate a fertility evaluation for cancer survivors.

From April 2019 in Japan, the financial support for the sperm retrieval surgery was raised to from 150,000 yen to 300,000 yen. Although successful sperm retrieval is considered just as a start of fertility treatment, this support is limited by the income of the couple and depending on the local government. Infertility couples consequently require to undergo fertility treatment such as ICSI, and hence this limitation should be reconsidered. The Japanese population is decreasing and newborn births was lowest ever experienced in 2019.[17] In this study, 50% of azoospermic subjects abandoned subsequent fertility treatment due to cost. We emphasize that more governmental support is needed for infertility treatment, and social attitudes to fertility treatment should be changed.

In conclusion, motile sperm recovery was achieved by sperm retrieval surgery in 7 subjects (53.8%) group A and in 8 (80%) group B. Overall, seven healthy deliveries were obtained in group A, and nine in group B. Since actual kind and the dose of anticancer agent could not evaluate, the influence on motile sperm recovery did not become clear. However, if motile sperm recovery was obtained, ICSI can be contributed to high pregnancy rate. Anticancer treatment may not affect the clinical pregnancy and delivery in this study. Although the number of patients was small, pregnancies and healthy deliveries were achieved for some couples. On the other hand, there were patients who abandoned infertility treatment due to the cost of testing and sperm retrieval surgery. Support for the cost of infertility treatment in cancer survivors should be considered.

ACKNOWLEDGEMENT

The authors thank all of the members of the IVF Laboratory team of the Asada Ladies Clinic and the staff of the Asada Fertility Research Center, Nagoya, Japan.

DISCLOSURES

Human rights and informed consent statements: All procedures completed were dome 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 patients for the purpose of inclusion in this study.

Animal rights statements: This article does not contain any studies with animal subjects performed by any of the authors.

ETHICAL APPROVAL

The protocol for this research project, including its use of human subjects, was approved by a suitably constituted Ethics Committee.

CONFLICT OF INTEREST

Each author has no COI with regard to this manuscript.

REFERENCES

1. https://ganjoho.jp/reg_stat/statistics/stat/child_aya.html [in Japanese]. accessed 30 Jan. 2020.
2. Dohle GR. Male infertility in cancer patients: Review of the literature. *Int J Urol*. 2010;17(4):327–331. doi:10.1111/j.1442-2042.2010.02484.x
3. Hibi H, Ohori T, Yamada Y, Honda N, Hashiba Y, Asada Y. Retrograde vasal sperm aspiration in anejaculatory patients with spinal cord injury. *Reprod Med Biol*. 2008;7(3):115–118. doi: 10.1111/j.1447-0578.2008.00207.x
4. Lass A, Akagbosu F, Brinsden P. Sperm banking and assisted reproduction treatment for couples following cancer treatment of the male partner. *Hun Reprod Update*. 2001;7(4):370–377. doi: 10.1093/humupd/7.4.370
5. Muller I, Oude Ophuis RJ, Broekmans FJM, Lock TM. Semen cryopreservation and usage rate for assisted reproductive technology in 898 men with cancer. *Reprod BioMed Online*. 2016;32(2):147–153. doi: 10.1016/j.rbmo.2015.11.005
6. Kobayashi H, Tamura K, Tai T, Nagao K, Nakajima K. Semen cryopreservation as an oncofertility treatment in 122 Japanese men with cancer: A decade-long study. *Reprod Med Biol*. 2017;16(4):320–324. doi: 10.1002/rmb2.12044
7. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355(15):1572–1582. doi: 10.1056/NEJMsa060185
8. Hibi H, Ohori T, Yamada Y, Honda N, Hashiba Y, Asada Y. Testicular sperm extraction and ICSI in patients with post-chemotherapy non-obstructive azoospermia. *Arch Androl*. 2007;53(2):63–65. doi: 10.1080/01485010600915152
9. Schlegel PN. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. *Hum Reprod*. 1999;14(1):131–135. doi: 10.1093/humrep/14.1.131
10. Hibi H, Sumitomo M, Fukunaga N, Sonohara M, Asada Y. Superior clinical pregnancy rates after micro-surgery epididymal sperm aspiration. *Reprod Med Biol*. 2017;17(1):59–63. doi:10.1002/rmb2.12069
11. Laura-Maria S, Madanat-Harjuoja, Malila N, et al. Risk of cancer among children of cancer patients- a nationwide study in Finland. *Int J Cancer*. 2010;126(5);1196–1205. doi: 10.1002/ijc.24856
12. Howell SJ, and Shalet SM. Spermatogenesis after cancer treatment: Damage and recovery. *J Natl Cancer Monogr Inst*. 2005;34;12–17. doi: 10.1093/jncimonographs/lgi003
13. Pacey AA. Fertility issues in survivors from adolescent cancers. *Cancer Treat Rev*. 2007;33(7):646–655. doi: 10.1016/j.ctrv.2007.02.001
14. Genesca A, Benet J, Caballin MR, Miro R, Germa JR, Egozcue J. Significance of structural chromosome aberrations in human sperm: analysis of induced aberrations. *Hum Genet*. 1990;85(5);495–499. doi: 10.1007/

bf00194223

15. Yang S, Bo J, Hu H, et al. Deprivation of male germ cells from induced pluripotential stem cells in vitro and reconstituted seminiferous tubules. *Cell Prolif*. 2012;45(2):91–100. doi:10.111/j.1365-2184.2012.00811.x
16. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126(4):663–76. doi: 10.1016/j.cell.2006.07.024
17. https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suikei19/index.html. accessed 30 Jan. 2020.