

Initial 10-year Experience of Sperm Cryopreservation Services for Cancer Patients

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Offering sperm cryopreservation to preserve the fertility of male cancer patients is a relatively recent service in Asia. This study analyzed the types of cancer, timing of collection, sperm quality, and utilization for reproductive services by patients during a 10-year period at a medical center in Taiwan. A total of 75 oncology patients elected to freeze sperm for fertility preservation at our medical center during the initial 10 years of the availability of this service. The mean age of the patients was 25.7 years. Storage was discontinued in 13 (17%) patients and their survival duration was 13.1 ± 11.1 months. The utilization rate of sperm cryopreservation was 2.8% (75/2642). The types of cancer varied, with leukemia (35%), lymphoma (25%), and testicular cancer (13%) comprising the largest groups. A significantly lower sperm count was found in patients with chronic myelogenous leukemia, suggesting the need for earlier sperm collection after initiation of cancer treatment. Only three (4%) patients utilized their specimens for reproductive purposes. There was no clinical pregnancy during the study period, although one biochemical pregnancy was achieved. The low rates of sperm cryostorage for fertility preservation in cancer patients in this study suggest that there is a need for greater emphasis of this option for male oncology patients whose fertility is likely to be affected by chemotherapeutic treatment. [*J Formos Med Assoc* 2006;105(12):1022–1026]

Key Words: cancer, chemotherapy, cryopreservation, male infertility, sperm

Improvements in diagnosis and therapy in oncology have led to a significantly increased survival of young males affected by cancer.¹ Depending on the chemotherapeutic agent and the duration of treatment, however, 45–80% of patients will develop permanent testicular dysfunction resulting in azoospermia. Although the side effects of radiation therapy have been ameliorated by the advent of computerized radiography techniques, and higher dosages can now be delivered accurately to the target tumor, dosages of radiation treatment > 1–2 Gy are still destructive to germinal epithelium. Thus, impairment of

spermatogenesis is an inevitable consequence following chemotherapy and/or radiotherapy.^{2,3} Fertility preservation has been included in the complete treatment plan for every new cancer patient in our hospital for 10 years. Our medical center now offers the service of sperm cryopreservation for any male cancer patient hoping to preserve his fertility.

This retrospective study analyzed the results of this service during the initial 10 years of its availability, including cancer type, rates of patient death, timing of collection, sperm quality and specimen disposal.

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Methods

Since 1995, our andrology laboratory has provided a sperm cryopreservation service for oncology patients. From 1995 to 2004, 112 cancer patients were referred to our andrology laboratory and 75 patients completed sperm collection for cryobanking. The initial evaluation consisted of collecting complete information about medical, surgical and family history. The medical history included cancer diagnosis, any previous or recent medication related to spermatogenesis, and general physical condition. Information collected on surgical history consisted of previous surgical intervention for the cancer such as biopsy, tumor resection, and port-A catheter implantation. Information on marital status, prior fertility and family relationships were included in the family history. For patients requiring emergent consultation from an oncologist for acute leukemia, the procedure of evaluation was completed as soon as possible. A signed detailed consent form that described the benefits of freezing, future disposal and the potential risks (i.e. sperm survival or no guarantee of pregnancy) was collected from all participants.

Semen specimens were collected in a sterile wide-opening container by masturbation. Two days abstinence of ejaculation prior to semen collection was suggested to patients who did not have a hurried oncology treatment schedule. Upon collection, each semen sample was allowed to liquefy. The pre-freeze semen sample was analyzed according to the 1992 WHO guidelines. The SQA II (Medical Electronic Systems Ltd., Caesarea, Israel), a desktop instrument that combines optical detection with an internal computer, was used to provide a quantitative evaluation of semen quality.

Sperm cryopreservation was performed according to the manufacturer's recommendations. Briefly, both the semen sample and the sperm freezing medium (MediCult, Jyllinge, Denmark) were kept at room temperature. The semen was diluted 1:1 (v/v) with the sperm freezing medium. The medium was added drop-wise to the semen and the solution carefully mixed after each addition. The resultant mixture was left at

room temperature for a minimum of 10 minutes. Cryo-tubes were filled with the diluted semen and sealed according to the manufacturer's recommendations. The cryo-tubes were attached to a cane and suspended just above the surface of the liquid nitrogen for 30 minutes. Finally, the cryo-tubes were submerged in the liquid nitrogen for final storage. The quality of the sperm freezing procedure was considered satisfactory if >40% of the original motility was maintained after thawing.

Statistical analysis

Statistical analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). Mean \pm standard deviation were calculated for all variables. Continuous variables were compared among groups using Student's *t* test to compare two groups, or using analysis of variance (ANOVA) to compare multiple groups. All statistical tests were two-sided, and a value of $p < 0.01$ was considered to indicate statistical significance.

Results

From 1995 to 2004, a total of 2642 new male patients aged 13–45 years at diagnosis were recorded in the cancer registry of National Taiwan University Hospital (NTUH). We defined 13–45 years as the reproductive age range during which a patient was most likely to have the potential for and desire to preserve fertility. Only 75 (2.9%) of the registered new male patients preserved their sperm prior to or during their cancer treatment. The characteristics of these patients are listed in Table 1. The majority of patients had leukemia (35%), testicular cancer (13%) or lymphoma (13%). Comparison of the age distribution between each cancer category by ANOVA revealed no significant difference of mean age ($p = 0.29$).

There were 69 (92%) patients whose sperm was collected prior to initiation of chemotherapy or radiation therapy. Only six (8%) patients were referred for sperm cryopreservation after more than one treatment session, one of these patients

had acute myelogenous leukemia (AML) and five had chronic myelogenous leukemia (CML).

Mean sperm count of the 75 patients was $56.3 \pm 4.3 \times 10^6/\text{mL}$, and mean sperm motility was $42.1 \pm 1.8\%$. Compared with these mean values of all 75 cases, analysis with Student's *t* test revealed a significantly lower sperm count in patients with CML and patients with extragonadal germ cell tumor, and a higher sperm count in the sarcoma group. The motility in the extragonadal germ cell group was significantly less than the average value of the total cases.

The percentages of patients with oligospermia (defined as sperm count $< 40 \times 10^6/\text{mL}$) and asthenospermia (defined as motility $< 40\%$) are shown in Table 1. Both sperm count and motility were impaired in more than 50% of patients with CML, extragonadal germ cell tumor, and testicular cancer. In patients with Hodgkin's disease, sperm motility was greatly affected but there was no impairment in sperm count.

Storage was discontinued due to death in a total of 13 (17%) patients (Table 2). The mean duration of storage for this group was 13.1 ± 11.1

Table 1. Patient characteristics and semen parameters according to cancer type

Cancer type	Patients, <i>n</i> (%)	Age (yr) at freeze (range)	Sperm count ($\times 10^6/\text{mL}$)	Motility (%)	Oligospermia* (%)	Asthenospermia* (%)
Leukemia						
AML	12 (16)	26.9 ± 8.1 (17–44)	69.3 ± 9.4	45.2 ± 3.7	8	25
ALL	8 (11)	22.7 ± 6.4 (15–33)	51.6 ± 5.4	41.2 ± 3.5	25	37
CML	6 (8)	30.3 ± 3.7 (24–33)	$19.5 \pm 1.7^\dagger$	36.1 ± 3.8	83	80
Testicular cancer	10 (13)	26.3 ± 8.5 (18–45)	41.8 ± 9.1	32.8 ± 5.3	50	70
Non-Hodgkin's lymphoma	10 (13)	25.6 ± 7.7 (15–38)	66.0 ± 12.3	50.8 ± 4.4	20	10
Hodgkin's disease	9 (12)	23.3 ± 6.1 (19–39)	55.7 ± 8.2	36.2 ± 3.3	22	88
Sarcoma	5 (7)	29.8 ± 7.3 (18–36)	$90.6 \pm 9.8^\dagger$	50.4 ± 11.0	0	20
Extragonadal germ cell tumor	5 (7)	27.0 ± 5.4 (23–36)	$17.6 \pm 3.9^\dagger$	$27.2 \pm 1.2^\dagger$	100	100
Other [‡]	10 (13)	20.8 ± 6.3 (13–30)	74.6 ± 18.3	51.7 ± 7.0		
<i>p</i> [§]		0.29				
Total	75	25.7 ± 7.4 (13–45)	56.3 ± 4.3	42.1 ± 1.8		

*Oligospermia is defined as sperm count $< 40 \times 10^6/\text{mL}$ and asthenospermia as sperm motility $< 40\%$; [†] $p < 0.01$ compared with total number of cases (Student's *t* test); [‡]those cancer categories for which the case number was less than five are summarized in this group (included aplastic anemia, brain tumor, nasopharyngeal cancer, bladder and prostate cancer); [§]*p* values calculated by analysis of variance. AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; CML = chronic myelogenous leukemia.

Table 2. Characteristics of patients with discontinuation of sperm cryopreservation due to death

Cancer type	<i>n</i>	Age (yr) at sperm freezing (range)	Duration of freezing (mo)
AML	5	30.4 ± 10.9 (17–44)	16.1 ± 16.6 (2.5–44.1)
ALL	4	22.7 ± 7.1 (15–31)	9.8 ± 5.7 (3.2–17.2)
Aplastic anemia	1	30	11
Hodgkin's disease	1	23	11
Non-Hodgkin's lymphoma	1	24	8
Bladder cancer	1	28	28
Total	13	26.5 ± 7.9 (15–47)	13.1 ± 11.1 (2.5–44.1)

AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia.

months (range, 2.5–44.1 months). The major types of cancers in these patients were AML and acute lymphoblastic leukemia.

Only three patients utilized their cryopreserved sperm for reproductive purposes. A total of two insemination cycles and three *in vitro* fertilization (IVF) attempts resulted in only one biochemical pregnancy. There was no clinical pregnancy or live birth during the study period.

Discussion

All men who are about to receive cancer treatment that could impair fertility should be counseled about such side effects and given adequate information to make an informed decision about sperm cryopreservation.^{4,5} The percentage of cancer patients with sperm cryopreservation in this study (2.9%) is within the 2.6–7.7% range of previous reports.^{6–8} Almost all of them would need IVF with intracytoplasmic sperm injection to overcome poor sperm quality.

In the present study, oligospermia was common in patients with testicular cancer, CML, Hodgkin's disease and extragonadal germ cell tumor. Previous studies have attributed low sperm quality to the effects of the tumor on spermatogenesis and the production of β -human chorionic gonadotropin by some cancer histotypes.^{9,10} Semen quality tended to be poorer in men with higher testicular cancer stages.

CML has a rather good prognosis, but >80% of the semen collected from our patients were oligospermic and asthenospermic. In this series, 83% (5/6) of CML patients collected sperm for cryopreservation after the initiation of more than one cancer treatment. Sperm storage was not considered as a necessary management until the disease went into a blast crisis or accelerated phase. The delay in fertility consultation in CML may explain why the sperm quality of these patients was poorer than in other reports.

The detrimental effect of lymphomas and their treatment on spermatogenesis is well established.¹¹ In the present study, we also

demonstrated that these patients had reduced pretreatment sperm concentrations. Oligospermia (defined as values $<40 \times 10^6/\text{mL}$) was found in 22% of patients with Hodgkin's disease and 20% with non-Hodgkin's lymphoma in this series. Previous studies have found abnormal spermatogenesis in 40–70% of patients with Hodgkin's disease before therapy.^{12,13} It has been suggested that this impairment is related to the presence of constitutional symptoms and general stress associated with tumoral illness (fever, weight loss).^{14–16}

In the past decade, overall 5-year survival rates (based on cancer registry data from the Office of Medical Records at NTUH) for male cancer patients aged <45 years of age have gradually improved to 54.7%, but remain lower than in the United States (79%).¹⁷ An epidemiologic review concluded that sperm cryostorage for fertility preservation in cancer patients is under-utilized in the United States.¹⁸ Lack of discussion time, presumed high cost, unavailability of adequate facilities and overestimation of the limitations of sperm quality were reported as the most common reasons that sperm banking was not suggested.^{4,5} From 1995 to 2004, a total of 2642 male patients <45 years old had a diagnosis of cancer in our hospital, but only <2.9% of these patients had sperm cryopreservation.

The low overall 5-year survival rate may be only one of the factors responsible for the low percentage of cancer patients selecting the option of sperm preservation in Taiwan. The majority of cancer patients lose interest in preserving fertility when they are faced with an unpredictable and unfavorable prognosis. The collection of ejaculate is often difficult due to poor general health condition. The oncologist may also take a pessimistic view of survival rate for patients with aggressive tumors, which impedes the likelihood of sperm banking.

Comprehensive cancer treatment planning is needed to help oncologists offer sperm banking as an option to all men at risk of infertility because of their cancer or its treatment. Even men with poor prognosis should be provided with

the option of cryostorage as a form of psychological reassurance and planning for recovery.

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