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Sperm Banking for Male Cancer Patients: Social and Semen Profiles

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ABSTRACT

Purpose: Report the characteristics of cryopreserved semen from a cohort of male cancer patients, attitudes towards cryopreservation and outcomes of semen samples based on a 12-year cryopreservation program.
Material and Methods: Data from 98 male cancer patients whose sperm samples were banked were evaluated. Demographic parameters, semen characteristics, destination of sperm banked samples and questionnaires answered by the patients regarding cryopreservation time were evaluated.
Results: The cancer diagnoses were testicle (56.1%), prostate (15.3%), Hodgkin's lymphomas (9.2%), non-Hodgkin's lymphomas (7.1%), leukemia (3.1%) and other malignancies (9.2%). The patients with testicular cancer presented lower sperm concentration ($p < 0.001$); however, there were no differences with the percentage of normozoospermic patients among cancer type groups ($p = 0.185$). A shorter time between cancer diagnosis and sperm banking was observed for testicular and prostate cancer patients ($p < 0.001$). Most of the patients (89.5%) favored sperm banking as a fertility preservation method.
Conclusions: Although less than 20% of banked sperm samples were disposed of, the majority of patients related sperm banking with safe for fertility preservation. Our results show that all male cancer patients of reproductive age facing cancer treatment could be offered sperm banking.

Key words: *cancer; fertility; semen; sperm banks*
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INTRODUCTION

Cancer is the leading cause of death in the world, accounting for 7.6 million mortality cases in 2005. Cancer treatments (surgery, radiotherapy and chemotherapy) are undertaken to remove malignancies, prolong the patient's life and improve their quality of life. Some types of cancer have higher cure rates than others. When detected early and treated according to best practices, one-third of cancer cases can be cured (1).

The cure rate of malignancies among patients with testicular cancer, Hodgkin's disease, lymphoma, or leukemia can be as high as 90%. However, depending on the underlying disease, age, type and dose of therapeutic agent used, and duration of treatment, these patients might present a post-therapy reproductive dysfunction, with 15-30% remaining sterile in the long term (2-4). With approximately 15% of male cancer patients at less than 55 years of age when first diagnosed (5), the impairment of fertility among surviving young cancer patients who

have not yet started a family has gained increasing clinical importance.

Cytostatic chemotherapy targets cells outside the G0 phase mainly destroy the rapidly proliferating spermatogonias. It is often following such treatments that the majority of male cancer patients develop azoospermia (2). The time for recovery of spermatogenesis is dose dependent and consequently difficult to predict. It has been reported that, while male cancer patients receiving low doses of cytostatic agents may expect recovery of spermatogenesis around 12 weeks after chemotherapy, permanent azoospermia occur in more than 50% of the patients receiving high doses (6).

High-dose radiotherapy to the pelvic region is another important treatment modality in patients with carcinoma in situ of the testis or cancer of the prostate, rectum and bladder, exposing patients to high risks of developing permanent infertility. The impairment of spermatogenesis after radiotherapy is also site- and dose-dependent (7).

Cancer surgery affecting the genital or pelvic organs can also have adverse consequences for fertility, namely, reduced sperm concentration (following unilateral orchiectomy for testicular cancer) (8), erectile dysfunction (after prostatectomy performed in prostate cancer patients) (9), or dry ejaculation (from radical retroperitoneal lymph-node dissections) (10).

Moreover, important alterations of spermatogenesis can be detected prior to treatment in the majority of young patients with testicular cancer or lymphoma and are thus unrelated to cytotoxic chemotherapy (7). Patients should be made aware of the possibility that up to 15% of male patients will already be azoospermic before they have had any chemotherapy or radiotherapy treatment (11).

Early reports on sperm banking for oncological patients showed that few patients had semen samples compatible with successful cryopreservation employed in intra-uterine insemination (12), and pregnancy rates remained very poor (13). As a result, many oncologists considered semen cryopreservation an ineffective, expensive and time consuming fertility strategy for cancer patients.

However, with the introduction of intracytoplasmic sperm injection (ICSI), surviving male cancer patients may now have a better chance of fathering children who are genetically their own, even with the poorest semen samples (14,15).

Furthermore, recent reports have shown that DNA fragmentation in sperm samples from oncological patients before undergoing surgery, chemotherapy or radiotherapy treatments are comparable to those of infertile male partners in assisted reproduction programs and of men with proven fertility (16,17).

Currently, the sperm banking and the assisted reproduction techniques, before and after the treatment respectively, can be successfully offered to male cancer patients. Ideally, semen cryopreservation should be performed before cancer treatment is started, and, if possible, multiples samples should be preserved. The decision to offer each technique is based on the semen quality pre-freeze and post-thaw. Where adequate amounts of spermatozoa have been banked and semen quality allows, intra-uterine insemination using the thawed spermatozoa could be considered, and in vitro fertilization (IVF) techniques including ICSI are generally recommended where the quantity of sperm available is small or as deemed necessary per female pathology (18).

In this study, our specific aims were examining the pre-freeze semen quality and discussing the social importance of sperm banking to male cancer patients. In particular, we report the characteristics of cryopreserved semen from a cohort of male cancer patients, the patients' attitudes toward semen cryopreservation, and tracking of sperm samples from a 12-year cryopreservation program.

MATERIALS AND METHODS

Between July 1996 and January 2008, 98 male cancer patients were referred to our center for sperm banking before receiving potential gonadotoxic therapy, chemotherapy, and/or radiotherapy. All patients received complete information regarding options for future use of sperm samples and the IVF program.

This study was approved by the Institutional Review Board. Patients gave written informed consent for the study procedures and the use of their clinical and biological data for research purposes.

Patients were asked to collect ejaculated semen samples a minimum of three times, except for those patients who started chemotherapy immediately after enrolment into the sperm cryopreservation program; those in the latter category collected only one or two samples. A brief medical history including their diagnosed cancer type was obtained from all patients and blood samples were screened for infectious diseases.

The initially collected semen samples were analyzed according to World Health Organization guidelines for concentration and motility (19) and strictly according to Kruger et al. criteria for morphology (20).

The semen sample was cryopreserved only if motile spermatozoa were found regardless of its concentration. Upon assessment, the semen sample was diluted 1:1 with cryoprotectant (test-yolk buffer with glycerol). Aliquots of 1 mL were transferred to screw-top plastic vials and subjected to a slow cooling rate process. Then, the mixture was frozen at -20ºC for 10 minutes and suspended in vapor phase nitrogen for 2 hours before being stored in liquid nitrogen until required.

A 200 µL aliquot was separately cryopreserved in the same way for post-thaw analysis 24 hours after. To conduct the post-thaw analysis, samples were thawed at room temperature for 5 minutes, followed by 37ºC incubation for 5 to 10 minutes. The samples were washed with culture medium, and the concentration and motility were evaluated according to WHO guidelines for concentration and motility (19).

Data collected from 98 male cancer patients whose sperm samples were banked at our center consisted of the following: (i) Recorded parameters routinely inserted into our center's data bank (male age, marriage and parental status, type of cancer and treatment, period from cancer diagnosis to sample cryopreservation), (ii) The semen characteristics, (iii) The destinations of sperm banked samples (disposed of, thawed for our own use, or continuous cryopreservation), and (iv) Questionnaire responses provided by the volunteers themselves regarding their worries of fertility preservation and concerns about sperm banking.

Statistical analysis of the data was performed using the statistical package SPSS v14. The continuous data were expressed by mean ± standard error of the mean (SE) and compared between two groups using the Mann-Whitney test, or for multiple groups, analysis of variance (ANOVA). Categorical data were analyzed using frequencies and the chi-square estimation. P values < 0.05 were considered statistically significant.

RESULTS

Ninety-eight patients were referred for sperm banking before gonadotoxic therapy. The mean age was 33 years (range: 16-69 years) at the time of cryopreservation. The higher percentage of patients forming this cohort were diagnosed with testicular cancer (56.1%, n = 55), followed by prostate cancer (15.3%, n = 15), Hodgkin's lymphomas (9.2%, n = 9), non-Hodgkin's lymphomas (7.1%, n = 7), leukemia (3.1%, n = 3) and other malignancies (9.2%, n = 9), which included bladder, stomach, rectum, bone and lung cancers. All semen samples provided motile spermatozoa and therefore were suitable for cryopreservation.

Semen characteristics at the time of cryopreservation for the complete group were as follows: mean sperm concentration (45.4 million/mL, range 0.1-368 million/mL), mean of sperm with progressive motility (43.8%, range 6-84%), and mean of sperm with normal Kruger's morphology (3.5%, range 0-11%). The post-thaw test showed mean of motile sperm recuperation at 28.5%.

Patient ages and semen features along with cancer type are shown in Table-1. The patients with prostate cancer were older than patients of other groups. The semen analysis of patients in the testicular cancer group presented lower sperm concentration than patients in other groups, except those with non-Hodgkin's lymphoma.

The overall mean time between cancer diagnosis and sperm cryopreservation was 4.5 months. Although we had not observed a statistical significance, a shorter time between diagnosis and semen cryopreservation was observed for patients with testicular and prostate cancers (Table-1).

Also, the patients were classified according to sperm concentration as normozoospermia (defined

Table 1 *– Semen characteristics among male cancer patients prior to therapeutic treatments.*

Semen Characteristics	Testicular Cancer	Prostate Cancer	Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Leukemia	Other Malignancies
N	55	15	9	7	3	9
Age (years)	28.9 ± 0.9 [a]	54.5 ± 2.9 [a,b,c,d,e]	27.3 ± 3.7 [b]	28.4 ± 1.3 [c]	28.3 ± 2.9 [d]	32.2 ± 3.7 [e]
Time between cancer diagnosis and sperm cryopreservation (months)	1.6 ± 0.3	1.8 ± 0.5	4.5 ± 4.4	5.1 ± 4.3	2.6 ± 1.7	2.6 ± 1.0
Sperm concentration (million/mL)	26.1 ± 3.2 [f, g, h]	71.7 ± 18.5 [f]	101.8 ± 43.3 [g]	48.3 ± 8.3	59.3 ± 11.8 [h]	57.6 ± 32.0
Total motility (%)	58.02 ± 2.0	50.9 ± 4.2	62.8 ± 3.8	66.4 ± 4.7	50.0 ± 21.5	48.8 ± 5.9
Progressive motility (%)	44.9 ± 2.3	35.9 ± 4.6	51.5 ± 5.1	54.7 ± 6.5	43.0 ± 18.3	34.8 ± 6.4
Kruger morphology (%)	3.3 ± 0.3	3.2 ± 0.6	3.6 ± 1.4	4.8 ± 0.8	4.7 ± 2.0	3.4 ± 1.4
Motile sperm recuperation post-thaw (%)	29.8 ± 3.6	19.6 ± 3.5	38.9 ± 11.4	36.8 ± 11.3	31.3 ± 20.4	16.1 ± 8.4

Values are mean ± standard error of the mean (SE). Mann-Whitney test = a, b, c, e: $p < 0.001$, d: $p = 0.011$, f: $p = 0.042$, g: $p = 0.016$, h: $p = 0.041$.

as sperm count ≥ 20 million/mL; 59.2%), oligozoospermia (defined as sperm count > 5 million/mL and < 20 million/mL, 20.4%), or severe oligozoospermia (defined as sperm count ≤ 5 million/mL, 20.4%). However, there was no difference as regards distribution of study patients grouped by cancer types ($p = 0.185$).

The social characteristics of patients showed that only 20.0% of them were married and had children, 28.0% were married and did not have children, and 52.0% were single and did not have children at the time of sperm cryopreservation. The prostate cancer group had a higher percentage of patients who were married (73.3%) and had children (50%).

After sperm cryopreservation, 39.0% of the patients received chemotherapy and/or radiotherapy treatment, 35.4% underwent surgery, and 25.6% had surgery followed by chemotherapy or radiotherapy.

The analysis of responses to the questionnaire item on cryopreservation time revealed that 78.8% of patients were aware of their fertility status. The group who expressed being the least concerned with fertility was the prostate cancer group (46.2%), while 84.7% of the patients in the other categories expressed aware-

ness of their fertility status (p = 0.002). This observed difference may be attributed to prostate cancer patients being older (80% were 55 and older) and who already had children (50% of prostate cancer group).

Overall, 86.9% of the study patients ranked fertility as an important issue following cancer treatment. While many of them already had children, 86.6% of all the study patients still reported infertility a post-treatment concern. Furthermore, 89.5% of them mentioned that they felt comfortable with semen cryopreservation regardless of the type of cancer with which they were diagnosed (p = 0.205).

The sperm samples were cryopreserved for a mean time of 52.7 months. At the time this report was drafted, 80 samples (81.6%) remain cryopreserved in our sperm bank. Sperm storage was discontinued for 18 patients (18.4%) upon the request of either the patient or his wife. At any time, study patients were able to request their own semen samples from our center for use in assisted fertilization techniques.

Between 1996 and 1999, 14 cancer patients agreed to sperm cryopreservation at our center. Since then, an average of 10.1 cancer patients cryopreserved sperm in our centre per year.

COMMENTS

In the present study, we retrospectively evaluated the semen characteristics and attitudes of male cancer patients who had sperm banked before cancer treatment.

Evidence suggested that cancer patients have an intrinsic suppression of spermatogenesis due to disease as oligozoospermia was more frequently observed. The exact mechanism for this suppression is not well established (21). On the other hand, the patients who suffer from testicular cancer showed higher semen abnormalities, probably related to the neoplasm itself (4,11).

Although many studies have reported azoospermia in cancer patients (11,22), all the patients in the present study provided motile spermatozoa and therefore were suitable for cryopreservation. Our findings also demonstrated that the percentage of oligozoospermia in male cancer patients was high (40.8%) independently of cancer type. However, an examination of the sperm concentration revealed that it is significantly lower among testicular cancer patients; thus, this finding supports our hypothesis that the cancer itself influences spermatogenesis generally and is amplified in testicular cancer patients.

The decline in semen quality following thawing is dependent on its initial quality before freezing, but some studies have demonstrated that the cryopreservation process itself does not affect spermatozoa of cancer patients any more than that of healthy donors (23). In this study, we observed a mean post-thaw recuperation rate of 28.5%.

In 2008, it was estimated that there will be 238,860 new cases of male cancer in Brazil, and 120,330 in the State of Sao Paulo state (24). Our center serves the State of Sao Paulo. Over a period of 12 years, only 98 cancer patients cryopreserved semen samples before cancer treatment. This is, in fact, representative of sperm banking in Brazil where the number of centers offering sperm banking is small, and only a limited minority of patients ask for sperm banking.

In our study, testicular cancer patients more frequently requested sperm cryopreservation, followed by prostate cancer patients. Also, we found that the mean time from diagnosis of cancer to the semen collection to cryopreservation was 4.5 months, but this period for testicular and prostate cancer patients was shorter. Reasons for this observed difference may be a higher level of awareness of the need for sperm banking by the medical team treating patients with cancer of the reproductive organs, or by the patient himself, who then influences the awareness level of the cancer site regarding fertility issues.

Some authors have raised doubts about the justification and necessity of providing the facilities for banking spermatozoa before chemotherapy (25), specially for the reason that the relatively small number of men making use of it following completion of treatment is less than 10% (26). The lack of sperm banking that was offered may be explained by several reasons: recovery or waiting for possible recovery of gonadal function, short period from original illness, anxiety regarding potential risks for the children and uncertainty about their long-term health and therefore their suitability to be parents (18).

In addition, a lack of discussion time, presumed high cost, unavailability of adequate facilities and overestimation of the limitations of sperm quality were the most reported reasons why sperm banking was not suggested (27).

At our center, the cost of sperm banking, including three samples of semen, is approximately U$ 500.00, with additional U$ 140.00 per semester for maintaining the cryopreserved sample; and for Brazilian patients, these costs are high.

Cancer patients can 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 cancer, thus diminishing the likelihood of sperm banking (28).

The most common reason for failing to bank sperm is a lack of awareness that such an option exists. Instead, many patients are left with significant anxieties over reproductive health concerns (28). On the other hand, assuring a patient that his fertility potential is secured by sperm banking could help in the emotional battle against cancer (29).

In this study, we found that most of the study patients were aware of fertility issues, that they expressed post-treatment infertility as an important concern, and that they were comforted by sperm banking as a means of fertility preservation.

Increasing awareness and the use of assisted reproductive technologies need to be promoted by an interdisciplinary team of experts caring for adolescents and young adults, as sperm cryopreservation is an efficacious method for preserving future fertility (30). All male cancer patients of reproductive age who will have treatment that may affect testicular function should have their sperm cryopreserved before the initiation of therapy.

Among the study cohort, less than 20% of banked sperm samples were disposed of upon the request of either the patients or their spouses. Reasons for disposal of sperm sample were patient death, no plans for more children, and recovery of fertility. However, at our center, we do not actively follow-up patients after completion of their cancer treatment; therefore, we do not have data on their survival or whether they have been able to conceive spontaneously.

While fertility preservation for post-pubertal male cancer patients has been well established (with sperm banking and techniques of assisted reproduction), there is little agreement regarding appropriate indications for and methods of gamete preservation in pre-pubertal boys (31). For pre-pubertal boys, the prevention of sterility in childhood cancer survivors given the existing practices is a clinical challenge since no active spermatogenesis is yet present. A promising advancement that has been proposed in the scientific community is cryobanking of testicular tissue as an acceptable strategy (32). However, this proposal faces a wall of ethical research debates regarding the conduct of experimentation on pre-pubertal individuals.

Comprehensive cancer treatment planning is needed to help oncologists offer sperm banking as an option to all men at risk of infertility, due to cancer itself or its treatment. The improvement in cancer treatment and life expectancy, combined with greater awareness for fertility options, careful reassurance of the survivors regarding the safety of their children, the possibility of infertility treatment by assisted reproductive technology, and the beneficial contribution in the emotional battle against cancer all lend support to routinely offering sperm banking to all cancer patients, especially those who are interested in having children with their partners.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The article by Bonetti and colleagues highlights the importance of understanding and awareness of the benefits of sperm cryopreservation in a multi-disciplinary team of health care professionals. Our experience in Canada from a retrospective chart review (1) illuminated the fact that we needed to address the multi-disciplinary team to negate the gap in complimentary service between health care professionals in both cancer and fertility specialties.

Our research partnership aimed at increasing the use of fertility preservation strategies. Following an extensive literature review we formed our framework. The need for heightened awareness of the opportunities for patients to preserve their fertility then became our focus. It was quickly determined that we needed to have a two-pronged approach to solving this dearth of information. One would focus on the allied health care professionals while the other would focus on the patient.

The first step in this process focused on empowering staff to ensure referrals were made to the Fertility Clinic. An algorithm for identifying patients was developed to aid in the identification of candidates for fertility preservation sooner rather than later in treatment. This afforded the patient the appropriate time to consider his fertility preservation option(s) and still have the time to bank samples prior to treatment. In addition, creating a standard referral approach facilitated staffs' discussions and eased their discomfort about discussing sperm banking, especially among younger patients. Increased awareness and more rigorous clinical approach including the use of the Referral Form resulted in a 71% increase in sperm cryopreservation referrals compared to the previous year.

A further project investigated Nurses' perception(s) of discussions with patients regarding the patients' future fertility (2). An underlying purpose of this study was to determine any communication barriers and to ascertain what type of educational materials would be beneficial.

Since the use of sperm banking, as part of the treatment protocol for adolescent and young adult (AYA) males with cancer, requires the expertise and cooperation of a multidisciplinary team of oncology and fertility experts nurses' have a primary contact with patients, their role in effective communication information to patients is crucial. Therefore, patients' awareness and understanding of sperm banking is a key element to success. Patients need to make in-

formed decisions at a time when they are inundated with treatment information.

A parallel consideration is the fact that the ability for a cancer survivor to one-day has their own family is of paramount importance to their quality of life during and after treatment. With this in mind, "plain language" education materials were developed to adequately inform male AYA oncology patients about sperm banking prior to cancer treatment (3). The project involved a collaborative partnership among health professionals from both the cancer and fertility clinics.

The educational brochures are beneficial for initiating discussion with the patient. Using the educational brochure as a teaching tool has led to the development of expertise and high comfort level among staff and expertise in facilitating these sensitive discussions. The key points in this process are listed below, and have become part of the routine standard of care: 1) Ensure that the health care provider gives all the appropriate information to the patient so that the patient can make an informed decision and be successful in providing an ejaculate for banking, 2) Ease the discomfort that is often felt by health care providers when discussing sperm banking, 3) Provide a timely referral to the fertility clinic.

Adolescents and young adults with cancer are a unique group. Due to many external factors and changes that take place during this time in their lives the diagnosis of cancer can be overwhelming. Providing AYAs with evidence-based information about fertility preservation by staff trained to impart this information allows them to make informed decisions about their fertility preservation options. Our framework for coordinating efforts in providing fertility preservation options to patients undergoing treatment for cancer encourages the use of effective multi-disciplinary teams that include: oncologists; nurses in both specialties of oncology and infertility, social work, reproductive endocrinology and infertility specialists, andrologists, and embryologists are required to work together in order to achieve success. The result of this unique team approach is not only a cancer survivor but one that is able to round out their quality of life by being able to have a family of their own.

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