Clinical guidelines for sperm cryopreservation in cancer patients

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No clear clinical guidelines exist on how to counsel male cancer patients about fertility preservation. Detailed counseling is recommended before treatment when issues of collection and storage need to be highlighted. Concern about the quality of sperm collected before and/or after treatment in terms of assisted reproduction is needed, and the potential outcomes should be discussed early as part of cancer survivorship. The discussion should be sensitive and tailored to the ethical situation based on the age of the patient, the severity of the illness, the need to initiate treatment, and genetic risk. Cryopreservation should be attempted/achieved before cancer treatment is initiated. Cryopreservation should not be performed during treatment or for some time after treatment because of the chromosomal and structural damage to sperm from cancer treatment. Contraception should be instigated during this period. (Fertil Steril® 2013;100:1203–9. ©2013 by American Society for Reproductive Medicine.)

Key Words: Cancer treatment, chemotherapy, fertility preservation, guidelines, radiation, sperm cryopreservation

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Fertility preservation for male cancer patients is an important aspect of cancer management and survivorship. A survey of 904 men from a multi-institutional study in 2002 found that 51% to 70% of young male cancer survivors wanted children in the future, including 77% who were childless at the time of cancer diagnosis (1). Only 24% of the young male cancer patients, which included 37% of childless men, actually banked sperm. The most common reason was found to be lack of information (1). Another study by Schrover et al. (2) in 2002 looked at oncologists' attitudes and practices regarding banking of sperm before cancer treatment and found 91% of the 718 oncologists consulted agreed sperm banking should be offered to all men before treatment. Forty-eight percent of the oncologists never brought up the topic or mentioned it to less than 25% of eligible men. The main reasons cited were the lack of time for the discussion, high costs, and lack of convenient facilities. Since that time, the America Society of Clinical Oncologists (ASCO) in 2006, and later in 2013, recommended that oncologists counsel cancer patients about fertility preservation as part of their cancer treatment plan (3, 4). In 2010, the Survey for Adolescent Reproduction (SPARE) assessed pediatric oncology specialists' attitudes and practice patterns toward fertility preservation since the introduction of the 2006 ASCO recommendations. They showed only 46% respondents reported that they refer male pubertal cancer patients to a fertility specialist before cancer treatment >50% of the time. Although 44% of respondents were familiar with the 2006 ASCO recommendations, only 39% used them to guide decision-making in more than half of their patients (5).

Oncologist need to have a rudimentary understanding of fertility preservation or at minimum should contact a specialist center for advice about specific details. Many oncologists may not feel comfortable discussing basic important facts such as the methods and indications for assisted reproductive technology (ART) that might be needed in the future (e.g., intrauterine insemination [IUI] vs. in vitro fertilization [IVF]). It is incumbent on specialists in the field of male and female reproduction to educate their oncologic colleagues on this issue (6). However, there are no clinical guidelines to help providers with the issues that are involved with the process of counseling patients on sperm cryopreservation, and how it is arranged and when to use or not to use the sperm.

Ideally, counseling needs to be framed in the form of before, during, and after cancer treatment. This can be a very challenging counseling session in situations when patients are often trying to come to terms with their

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cancer diagnosis; have constitutional symptoms of their disease to make informed decision making and semen collection difficult; and when cancer treatment often needs to be initiated very soon, sometimes within hours. Ethical dilemmas like this need to be addressed with patients and families (6). It cannot be forgotten or ignored, that despite the improved survivorship rates from cancer, a number of patients will die from their cancer. Hallak et al. (7) showed that 37% of the cryopreserved sperm discarded was due to death of the patient. This reiterates the need to discuss the proviso for using or discarding stored sperm in the event of death before the planned cryopreservation (8).

This is a difficult and sensitive discussion when patients are worried about their own mortality, but it cannot be avoided. The issue of a named partner who may be allowed to use the sperm posthumously needs to be explicit. If there is no named partner, the ethics and legalities of who has permission to acquire the specimens and who can use the specimens becomes an issue. This is especially important with minors who need parental written permission to proceed with cryopreservation. The rules of individual institutions, states, and countries will dictate this issue (8). These important issues and dilemmas should be discussed with patients and oncologists alike during the different stages of cancer care/treatment.

PRETHERAPY CLINICAL GUIDANCE

Number of Samples to Cryopreserve

The question of how many samples to freeze is determined by the quality of sperm provided (9). This depends on the health of the patient and the type of cancer. It has been shown that the semen parameters of oncology patients before cancer treatment (both before freezing and after thawing) are worse than those of healthy donors (10, 11). Hotaling et al. (11) demonstrated that of the cancers evaluated, prostate cancer had the best prefreeze total motile count (TMC) and lymphoid leukemia had the worst. Of all parameters, motility has been shown to be affected most in cancer patients compared with controls (11, 12). This pathophysiologic behavior of sperm before and after cryopreservation allows for subtle and specialized counseling for different types of cancer, as well as the need to possibly cryopreserve more vials for certain cancers (e.g., testicular cancer and leukemia) (11, 13, 14). Sperm quality also depends on the abstinence period between semen collections. When the cancer treatment needs to start quickly, a change in the normal abstinence paradigm of 2 to 5 days for sperm collection can be replaced with a more frequent collection schedule, although this may affect the quality of the sperm cryopreserved. In a study involving cancer patients, Agarwal et al. (15) showed semen collection for cryopreservation after 24 to $\leq$48 hours of abstinence resulted in post-thaw quality comparable to that after an abstinence of 48 to $\leq$72 hours or longer (15).

The andrology laboratory plays an important role in determining the patient's future fertility fate and the type of ART that will be needed. Sperm quality will determine the cryopreservation process, especially the number of sperm per vial and the number of vials cryopreserved. This in turn will predict the potential future use of each vial for IUI or IVF and intracytoplasmic sperm injection (ICSI). The concept of ART may seem very abstract at the pretreatment stage for cancer, especially when the sperm parameters are not yet known and patients are overwhelmed with their potential options. However, patients need to understand which potential method of ART may be needed in the future because the cost of freezing and the type of ART are often financially prohibitive. Patients do not always have a chance to think about or understand the economic benefits of pretreatment cryopreservation versus costly sperm recovery and more expensive ART alternatives after treatment. Overall this can be difficult to discuss during early pretreatment counseling for cancer, as fertility may not be the first priority of the patient, partner, or family. Many providers and andrology laboratories may freeze initially to spare patients this discussion at a difficult time, then provide them with financial counseling at a later date, which requires delicacy.

Cryopreservation for IUI or ICSI

The method of cryopreservation (slow freeze vs. vitrification) will affect sperm recovery; historically, approximately 50% of sperm survive from the freezing process (16–20). However, sperm from cancer patients appears to behave differently. Myeloid leukemia has been shown to have the lowest postthaw TMC and the largest reduction in TMC after cryopreservation (89%). Testicular cancer and both myeloid and lymphoid leukemias have statistically significant lower sperm survival (viability) rates (44.8%, 32.1%, and 35.1%, respectively) compared with a procreative management (control) group (11). Multivariate analysis of the different oncologic diagnoses has shown testicular cancer has the lowest chance of a postthaw TMC $>$5 million (11). Improvement and maximizing sperm recovery from cryopreservation techniques is important. Newer data support vitrification for low sperm concentration to improve postthaw survival (20, 21). As candidates for IUI before freezing may become candidates for IVF after thawing, recoverability of more viable sperm from such samples can have huge implications for couples in terms of the level of medical intervention, ethical considerations, and ART costs.

In terms of the number of sperm required for successful IUI, the literature is mixed. It depends on multiple factors both male and female. The evidence suggests that a 5–10 million processed total motile count (PTMC) should be used for IUI (9,22–24). In a comparative study of six different PTMC ranges, the lowest pregnancy rates were observed when the PTMC was $<$2 million compared with the other groups. This was to be expected, but the investigators did not find a statistically significant difference between the other PTMC stratifications, which ranged from a PTMC of 2.1–4 million to $>$10 million (25). That study was not performed specifically in cancer patients. Byrd et al. (26) in 1990 showed optimal pregnancy rates achieved by IUI occurred if the number of motile sperm inseminated was between 6 and 15 million/mL. They also showed if the postthaw motility was $<$30% of the prethaw motility, the

pregnancy rate was only 5.5% compared with 15.4% and 27.2% if the post-thaw motility was 30% to 50% and >50%, respectively.

As a rule of thumb, with a 50% sperm survival rate quoted from conventional cryopreservation, many laboratories would consider a prefreeze PTMC of 10 million sperm necessary to result in approximately 5 million sperm after thawing and to obtain adequate IUI (22–24). This number would ideally be frozen per vial so each vial could be used with each subsequent IUI. As indicated earlier, some cancers may have a worse than 50% survival rate, which needs to be taken into consideration for the postthaw TMC for IUI (11). A number similar to IUI is needed to freeze for conventional IVF. If the sperm count or other parameters are lower than this, the samples should be divided into numerous aliquots for ICSI. Some clinics will use frozen sperm as a criterion for ICSI when performing IVF. This is not necessarily the standard of care, but it is a common practice.

Another consideration for IUI is the number of IUI attempts required to achieve a pregnancy as well as the number of pregnancies desired. This is certainly not a discrete number; the number of IUI attempts to obtain a successful pregnancy depends on multiple factors, including the female partner's age and fertility testing results. In a younger population, IUI success rates can range from 8% to 15% (27). One consideration is most IUI data are based on a male and/or female infertile population, and thus, often are not applicable to cancer survivors whose female partner may otherwise be fertile. However, given these data, it is reasonable to expect that as many as six IUI attempts may be needed to achieve a pregnancy. Thus, the number of vials available to accommodate a suitable number of IUI cycles vs. saving a vial or two for IVF-ICSI should be considered very carefully, especially when a man is azoospermic after cancer treatment. Anticipating future plans in such situations is important because of the limited amount of cryopreserved sperm and the need to avoid wasting samples.

In addition, the cost of numerous ART cycles can be prohibitive for couples, even more so when no biologic sperm specimens remain and they must consider microdissection of the testicles (microTESE), or needle testicular sperm extraction for sperm retrieval before ICSI. In a randomized trial, Reindollar et al. (28) showed that an accelerated protocol proceeding to IVF after fewer IUI cycles (bypassing the gonadotropin IUI cycles) was more cost effective and successful in achieving live births. This study focused on idiopathic infertility, with men having >15 million TMC or >5 million postwash TMC. Although the study did not specifically pertain to cancer patients who might have potentially decreased sperm parameters and did not examine the use of cryopreserved sperm, the results could be extrapolated, reiterating that it may be more efficacious to proceed to IVF sooner. Some would advocate ICSI in borderline IUI or conventional IVF cases when there are few vials with good sperm. Note that refreezing thawed sperm when not used and/or when the stock of biologic sperm is low/depleting has been performed but remains controversial (29). It is interesting that specimens from cancer patients appear to resist cryoinjury from a refreeze similar to those of noncancer controls (29, 30).

Sperm Retrieval

It is also important for providers to understand and devise guidance on methods of sperm retrieval for men with cancer, especially those who have physiologic, anatomic, or constitutional limitations. Obtaining samples by ejaculation is the conventional, simplest, and most noninvasive method. However, ejaculation may be a challenge for a man who is weak from his cancer, has significant constitutional symptoms, or has limited movement due to conditions such as recent lymph node biopsies/cancer surgery, or port placements or lines.

The age of the patient and pubertal status are also potential dilemmas. Very young males may never have masturbated, and discussion of this issue needs to be in consultation, with the parents aware and informed. Management of prepubertal males is beyond the scope of this review, but in brief may involve testicular biopsy or even orchiectomy for spermatogonia (stem cell) recovery and cryopreservation and later transplantation/stimulation (31, 32). This is still experimental (33–35).

In postpubertal males who potentially are too weak or are otherwise unable to collect samples through masturbation, vibratory stimulation and/or electroejaculation (EEJ) may be an option (36). Electroejaculation for patients with normal sensory status requires them to undergo general anesthesia, so the patient's health will determine whether he is able to undergo the procedure. If the patient is too sick to undergo anesthesia, bedside sperm retrieval with local anesthesia may be considered, involving percutaneous epididymal sperm aspiration (PESA), needle testicular sperm extraction (TESE), or testicular sperm aspiration (TESA).

Whether a patient undergoes general anesthesia, electroejaculation, open testis biopsy, or microscopic epididymal sperm aspiration (MESA) should be considered before any cancer treatments. Sometimes such procedures can be performed at the time of port placement, but this remains at the discretion of the general surgeon and oncologist, who may be concerned about infection of the port with hematologic bacteria from scrotal surgery.

Testicular cancer is a unique situation in that sperm can be retrieved from the removed testicle itself via bench dissection of the tissue. After the pathologist has ensured that the tissue is opened in accordance with the requirements for pathologic diagnosis and margin evaluation, often sperm can be retrieved from the testicular tissue surrounding a testis tumor or via epididymal aspiration. This type of testicular sperm extraction is often referred to as onco-TESE.

After a radical orchiectomy for testis cancer, approximately 9% of men who have a normal contralateral testis become azoospermic thereafter. This reiterates the importance of obtaining an ejaculated specimen before the orchiectomy or retrieving sperm from the testis at the time of surgery (37), as this may be the last opportunity for biologic sperm retrieval in these patients. When the patient has a testis cancer in a solitary testis, a preoperative attempt at cryopreservation using ejaculated sperm is encouraged along with the recovery of sperm from the removed solitary testis (as described previously). Note that testicular biopsies and/or onco-TESE with microTESE have also been performed successfully in men with other cancers who were azoospermic before the cancer treatment (38).

Some patients may be coagulopathic, especially those with hematologic cancers, which can lead to increased risks from the biopsy and may complicate their recovery. The risk/benefit profile must be determined at the time of presentation, and ethical dilemmas such as these must be addressed with the patients and families (6).

Testing of Sperm for Cryopreservation

It is important to understand the requirements for testing specimens for transmittable infections before storage as well as in the context of a present or future female partner, and to guide both providers and patients on these aspects. In 2005, the U.S. Food and Drug Administration (FDA) began enforcing a comprehensive set of new regulations designed to improve the safety of human cellular and tissue-based products. These regulations (21 CFR 1271) expanded the regulatory requirements on the tissue products that previously had been regulated, including reproductive tissue. Note that federal requirements are often lower than state requirements or the recommendations by the American Society of Reproductive Medicine (ASRM). In 2012, ASRM updated their, "Recommendations of Gamete and Embryo Donation," to incorporate the optimal screening and testing practices laid out by the FDA and other tissue bank agencies for sexually transmitted infections (STIs) (39, 40). This includes serologic testing for human immunodeficiency virus (HIV) type 1 antibody (AB) and nucleic acid testing (NAT); HIV-2 AB and NAT, and the HIV group 0 AB; hepatitis C AB and NAT; hepatitis B surface antigen; hepatitis B core antibody (IgG and IgM); serology for syphilis, human T-lymphotropic virus (HTLV) types 1 and 2; and *Neisseria gonorrhea* and *Chlamydia trachomatis*. Cytomegalovirus (CMV) also is becoming an important pathogen because of the possible risk of transmission via sperm sample to partners who may be immunosuppressed or have a transplant.

A number of commercial consulting companies exist to help fertility centers set up rigid screening protocols that comply with high standards. Because cancer patients are not considered an anonymous or directed donation, mandatory testing is usually not needed. The patient's relationship status with a partner also may be a factor; intimate partners can be exempted from the testing and may sign a waiver accepting a risk of transmission if they have unprotected intercourse together before cryopreservation. If there is no named partner at the time of cancer sperm cryopreservation and the donation is to be used autologously at a later date, baseline screening usually is not needed, especially if the couple were having unprotected intercourse before the use of the cryopreserved sperm. Infectious disease testing should be offered and be part of the informed consent discussion, but mandatory testing is not necessarily a part of care guidelines with cancer patients, except in rare cases such as the need for a gestational carrier.

CLINICAL GUIDANCE DURING CANCER TREATMENT

Unfortunately, oncologists and male cancer patients alike often do not consider sperm cryopreservation until after the cancer treatment has begun, often in the early phases. Because later stages of spermatogenesis have already completed, spermatocytes and above have already been formed; the patient's sperm counts may not decline in the first 2 months after initiation of cytotoxic treatment (41). However, cryopreservation and pregnancy should be discouraged during any cancer treatment phases, early or otherwise: cell damage and cell death during treatment place these sperm at risk for structural DNA damage and chromosomal abnormalities (42–44). Animal studies have shown that later stage spermatogenic cells are susceptible to the induction of mutagenic damage and can transmit mutations to the next generation (45). The counseling of men who are stable enough to continue sexual intercourse during the induction and active phases of cancer treatment must include a discussion of contraception.

As with general contraception, continued use of female birth control and/or male birth control in the form of condoms is required. The failure rate of contraceptive methods needs to be considered. Condoms, when used alone, have a failure rate of 2% for perfect use, up to 18% for "typical use", and a breakage or slippage rate of 2% to 9% (46–49). Female birth control failure when used alone depends on the method, with a 0.05% failure rate with levonorgestrel implants, 0.2% to 0.8% with an intrauterine device (IUD), 6% for birth control pills, 22% with the withdrawal method, and 24% for abstinence during the potential fertile window (48, 50). Note that these percentages indicate the number out of every 100 women who experienced an unintended pregnancy within the first year of typical use of each contraceptive method; therefore, many advocate the use of two contraceptive methods during the cancer treatment.

CLINICAL GUIDANCE AFTER CANCER TREATMENT

Reevaluation of the patient and his situation for ART or natural conception through intercourse during the survivorship phase of recovery is important. At this stage, the cancer has either been cured or is in significant remission, so the patient will be able to think more clearly about his future and fertility. At this point, return or maintenance of spermatogenesis may occur, along with the possible use or discard of the previously collected specimen(s). Among the reasons for cryopreserved sperm being discarded after cancer treatment, Hallak et al. (7) found regaining fertility but no plans for more children in 41% of men, good sperm quality in 14%, and no plans to have children in 7%. The patients in their study were similar in age, number of specimens, and interval between diagnosis and treatment, but they showed significant differences in type of treatment and time in the program. The cost of cryopreservation and specimen storage was not cited.

One issue that is often poorly understood by patients is how long sperm can remain cryopreserved before use. In 2004, a case report described a successful birth using sperm from a man with cancer who had cryopreserved sperm 21 years earlier (51). It is advisable to recommend that men not discard sperm until they are certain that they have returned

to normal fertility, have completed their family, or do not plan to have children.

After cancer treatment has been completed, the evaluation of semen quality can determine the need for either continued storage of pretreatment sperm or the use of posttreatment sperm. Many times, patients/couples will ask about the quality of the sperm and whether use of pretreatment sperm is preferred to posttreatment sperm. This brings into question again the pretreatment status of the patient, the type of cancer involved, and whether the patient was constitutionally sick and potentially produced poor quality sperm. The cancer treatment used and the amount of time that has passed since the last cancer treatment factor into the determination about posttreatment sperm. Evaluating the quality of the sperm from before and after treatment with this information is important for advising patients on the types of ART that might be needed and the potential for success. For example, would IVF be better or worse for a patient if he had a low sperm count before treatment while he was sick vs. his similar low sperm count 3 years after treatment when he is feeling better? This is a dilemma. Also, when is it safe to resume unprotected intercourse and/or attempt to conceive after treatment; is there ongoing damage to dividing cells (i.e., sperm) with an associated potential risk of miscarriages and potential fetal abnormalities?

The issue of continued sperm damage or structural chromosomal abnormalities after cancer treatment has been well reviewed in the literature but is limited by the fact that many cancer agents and combinations of drugs have not been studied in animal or human fertilization studies or in a longitudinal manner (43, 52). We have already outlined the potential for damage during treatment. Recovery of spermatogenesis after treatment depends on the drug used, dose used, combination of agents used, number of cycles of treatment, and radiation vs. chemotherapy or in combination. The amount of radiation and overall dose used also play a role. Use of other potentially gonadotoxic agents such as immunosuppression drugs for bone marrow transplant patients is also important and are often continued in the posttreatment period. These factors will determine the stages of spermatogenesis suppressed and the duration of suppression.

Suppression or damage to the spermatogonial stem cells may have longer lasting effects, not just on the return of sperm but also as persistent genetic damage throughout the life of the cancer survivor. Damage to later stages (spermatocytes and spermatids) may be transient and reversible with no long-term genetic consequences as long as a cycle of spermatogenesis has been allowed to occur and the damaged late-stage spermatogenesis is cleared with the toxic agent. It is difficult to determine whether prolonged sperm damage and risk to offspring can occur from induced damage to stem cells after cancer treatment that continues to propagate into all future cycles of spermatogenesis onward. Alternative etiologies include the role of advancing male age alone on the efficiency of cell division or the affect of the cancer genetics on sperm function (33, 41). In testicular cancer, sperm abnormalities are not seen more often than in normal controls before chemotherapy (53). However, chemotherapy-induced sperm diploidy has been seen in sperm in men who have received platinum, etoposide, and bleomycin (PEB) combination treatment for testis cancer up to 2 years after completion of treatment, suggesting a direct role of the chemotherapy. Structural chromosome damage in sperm has been reported in men receiving chemotherapy ± radiotherapy for sarcoma and Wilm's tumor 5 to 18 years after completion of treatment (54). However, these are case studies, and no longitudinal large cohort studies with long-term follow-up evaluation of sperm have been performed to date. As a result, when sperm damage or structural chromosomal abnormalities minimize with time remains unclear, with no clear guidance on the subject.

The time line depends on the type of cancer and cancer treatment combination used. As a result, it is very difficult to ascribe a specific time to recovery of "normal sperm" (53–56). In the absence of strong data, many recommend 18 to 24 months of continued contraception before couples either resume unprotected intercourse or attempt to conceive spontaneously. In cases where transient and late-stage spermatogenesis are affected, and sperm return does not become azoospermic or returns quickly, it has been suggested that 1 year may be adequate. This may be a reasonable margin for recovery, with four full cycles of spermatogenesis having passed. Again this is in the absence of good basic science data though. If a man does become azoospermic, then this suggests early stages of spermatogenesis have been affected, and it may take several cycles of spermatogenesis to allow for sperm return, if it returns at all. In these cases, it would probably be best to wait the 2 years before advising the use of posttreatment sperm for spontaneous conception or ART.

Unfortunately, as a disclaimer, when damage is seen as far out as 18 years from treatment, patients/couples need to be advised that even after a significant period of time a finite and continued risk of sperm structural or DNA damage could be likely. That being said, we as providers have to be careful in how we counsel couples. Although there is evidence that DNA damage persists in some cases and it is linked potentially with lower fertilization and/or implantation rates, there is no clear evidence that birth defects occur in such situations (57). The primary responsibility of oncologists is to achieve remission and cure, although the increasing range of effective anticancer treatments does require better discussion about male fertility preservation and the effect of treatment on germ cells and potential gene mutations. Long-term effects in this generation and the next remain unclear at the moment. In the current and future era of ART, preimplantation genetic testing may have a role in certain cases of inheritable cancers (6).

In conclusion, detailed counseling is recommended before cancer treatment, when issues of cell damage, contraception, and storage need to be highlighted. Cryopreservation should be attempted/achieved before treatment is initiated. Cryopreservation should not be performed during treatment or for some time after treatment. Contraception should be instigated during this period. Concern about the quality of sperm collected in terms of the type of ART required and the potential outcomes should be discussed early as part of cancer survivorship. The discussion should be sensitive, tailored to the ethical situation, and based on the age of the

patient, the severity of the illness, the need to initiate treatment, and the genetic risks (6, 58).

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