Commentary

Incorporating Fertility Preservation Into the Care of Young Oncology Patients

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As the number of cancer survivors continues to increase, oncologists are faced with the challenge of providing cancer therapy to patients who may 1 day want to have children. Yet, gonadotoxic cancer treatments can compromise future fertility, either temporarily or permanently. There are established means of preserving fertility before cancer treatment; specifically, sperm cryopreservation for men and in vitro fertilization and embryo cryopreservation for women. Several innovative techniques are being actively investigated, including oocyte and ovarian follicle cryopreservation, ovarian tissue transplantation, and in vitro follicle maturation, which may expand the number of fertility preservation choices for young cancer patients. Fertility preservation may also require some modification of cancer therapy; thus, patients' wishes regarding future fertility and available fertility preservation alternatives should be discussed before initiation of therapy. This commentary provides an overview of the range of fertility preservation options currently available and under development, using case-based discussions to illustrate ways in which fertility preservation can be incorporated into oncology care. Cases involving breast cancer, testicular cancer, and rectal cancer are described to illustrate fertility issues experienced by male and female patients, as well as to provide examples of strategies for modifying surgical, medical, and radiation therapy to spare fertility. Current guidelines in oncology and reproductive medicine are also reviewed to underscore the importance of communicating fertility preservation options to young patients with cancer. ***Cancer*** **2011;117:4–10.** *© 2010 American Cancer Society.*

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Cancer continues to be a leading cause of mortality, yet new and effective therapies have led to an increase in the number of cancer survivors. There are over 10 million cancer survivors in the United States alone.[1] Whereas the incidence of many cancers increases with age, 1 in 168 Americans will be diagnosed with a malignancy between the ages of 15 and 30.[2] Greater success in treating cancer brings a new challenge for the oncologist treating younger patients: providing cancer treatment for patients who have a very real possibility of 1 day having children. This requires an expanded perspective on the potential long-term consequences of the cancer itself as well as the impact of intense and often highly toxic therapy on patients' future fertility. To this end, a recent study found patient concerns about future fertility ranked second only to questions about mortality.[3]

Ongoing research efforts have led to expanded fertility preservation options for both men and women diagnosed with cancer, and it is increasingly important for the care offered to younger oncology patients to include discussions about family planning and fertility preservation. As some approaches to fertility preservation may require modification in the timing of a patient's treatment and cannot be implemented once systemic therapy has begun, integration of fertility issues into initial discussions about cancer treatment is essential. Multidisciplinary cancer care requires close communication between surgical oncologists, radiation oncologists, and medical oncologists during the development of a treatment plan.[4-6] This structured interaction should enable incorporation of fertility preservation into cancer management. By briefly reviewing the advances in fertility preservation for cancer patients and using case studies, this commentary will illustrate how fertility planning can be integrated into oncology practice to enhance the lives of cancer survivors.

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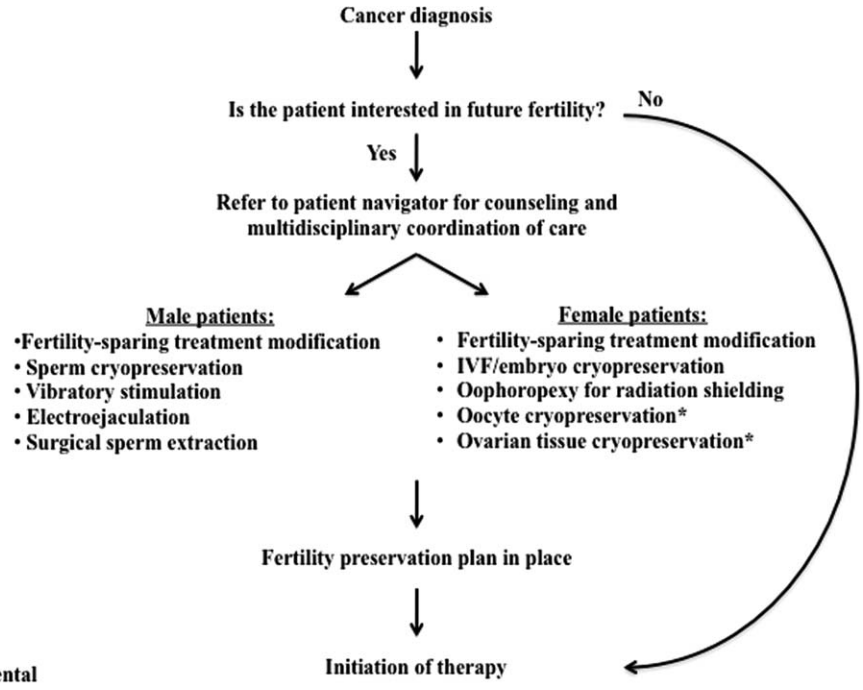

Figure 1. Navigation of the oncofertility treatment path is illustrated. Questions about a young patient's desire for future fertility begin with a cancer diagnosis. If a patient is not interested in fertility preservation, cancer therapy can proceed. However, if a patient is interested in attempting to preserve future fertility, the next steps involve both patient counseling and coordination of care. A fertility preservation plan can be tailored to an individual's circumstances and reflect both established and experimental options. After a treatment plan incorporates both the need to treat a patient's disease and their wishes regarding future fertility, the final step is initiation of cancer therapy.

Fertility Preservation Options

Fertility preservation options can be divided into several categories (Fig. 1). First, germ line cells can be preserved directly. In postpubertal male patients, this involves sperm banking. For younger pubertal male patients, where collection of a semen sample may be more difficult, vibratory stimulation, electroejaculation, or surgical sperm extraction can be attempted.[7,8] Currently, no viable options are in place for prepubertal boys, though this is an area of active investigation. For female patients, the most accepted therapy involves hormonal stimulation, oocyte retrieval, and either oocyte cryopreservation or in vitro fertilization (IVF), followed by embryo cryopreservation before initiating therapy.[9-12] It is critical that the female patient have her baseline fertility assessed before any intervention for fertility preservation, particularly for women over the age of 35, due to the natural reduction in ovarian reserve. At this point, over 500 live births have been achieved using cryopreserved oocytes from young women, yet this technique is still considered experimental.[13] IVF, while often successful, necessitates that patients without partners choose a sperm donor, which can be a highly complex decision. While IVF with embryo cryopreservation remains the option most likely to succeed, ongoing research efforts in artificial reproductive therapy are examining approaches that would expand fertility preservation options. Technologies are being used to remove ovarian tissue, which contains immature oocytes, and cryopreserve strips of cortical tissue or individual follicles before therapy.[11,14-16] Cortical tissue strips can then be reimplanted after cancer therapy has concluded, in an attempt to restore ovarian function. This approach has resulted in 6 reported live births for patients who have completed their cancer treatment, with 5 additional births presented at a recent meeting of the International Society of Fertility Preservation.[14,16-19] However, this technique remains experimental and may carry the risk of reintroduction of cancer cells upon autotransplantation.[15,16,20,21] Laboratory efforts for in vitro maturation of cryopreserved immature follicles have shown promise in animal and human studies.[22-25] Although not yet an option for patients, the ability to cryopreserve immature follicles within ovarian cortical material to mature them at a later date would facilitate fertility preservation for the youngest

female cancer patients not eligible to undergo assisted reproductive techniques.

In addition to direct germ-line preservation, other strategies can be discussed with younger cancer patients who desire children. Male patients who are unable to bank sperm before cancer treatment may consider IVF using a sperm donor. Similarly, for women who do not preserve embryos or oocytes before cancer treatment, but who maintain a functional reproductive tract after therapy, IVF with donor eggs can be used to achieve pregnancy. For those patients who cannot carry a pregnancy, use of a gestational carrier or adoption are also options that can be considered.

Fertility and Cancer Treatment Planning

Modification of surgical protocols can also be part of integrating fertility preservation into cancer therapy. For young women with gynecologic malignancies, standard therapy often involves aggressive surgical resection that makes future pregnancies impossible. However, emerging data suggest that less aggressive resection can be used to successfully treat malignancy while still preserving fertility. Conservative management of endometrial carcinoma or ovarian carcinoma with subsequent fertility in young patients has been reported, while ongoing studies are evaluating the clinical efficacy of fertility-sparing conical excisions in women with cervical cancer.[26-29]

Radiation therapy is gonadotoxic in a dose-dependent manner and has been shown to damage developing sperm as well as decrease ovarian reserve.[30-33] In the case of gastrointestinal tumors, relative proximity to the reproductive tract is a concern, as radiation used to treat the primary tumor may have deleterious secondary effects on future fertility.[34] However, as with other treatment modalities, recognition of this challenge before initiation of gonadotoxic radiation can help preserve fertility in some patients. Sperm cryopreservation can be offered to men, whereas surgical ovarian transposition out of the radiation field and/or oocyte or embryo preservation are options for women undergoing pelvic radiation.[34]

As more data emerge regarding the threat to fertility posed by specific pharmacological agents, chemotherapy protocols may be modified to avoid potentially gonadotoxic side effects in young patients. Chemotherapeutic agents targeting rapidly dividing cells are damaging to germ cells, with alkylating agents having particularly toxic effects on ovarian tissue.[33,35-37] Studies in patients with urological tumors or breast cancer suggest the feasibility of treatment modification to help minimize reproductive tract toxicity; these modified regimens may be preferable for patients diagnosed during their reproductive years.[38,39] However, any change to standard therapy requires discussion between patient and physician on a case-by-case basis. For example, in the setting of colorectal cancer, standard 5-FU therapy does not seem to have deleterious effects on fertility while the use of newer adjuvant agents such as oxaliplatin may introduce more fertility-threatening side effects.[40] Furthermore, the incorporation of improved diagnostics may provide a more accurate assessment of patients who are likely to benefit from chemotherapy. The recently developed Oncotype DX test may help breast cancer patients and clinicians make decisions regarding postsurgery chemotherapy on the basis of tumor molecular markers and the likelihood of disease recurrence.[41] Implementation of new diagnostic tools may allow some younger patients to avoid gonadotoxic chemotherapy altogether.

Data suggest that in certain malignancies, including testicular cancer and Hodgkin disease, compounds produced by the tumor itself can be spermatotoxic before the initiation of therapy, resulting in chromosomal aneuploidy.[42] In addition, chromosomal abnormalities in spermatocytes can be detected up to 24 months after chemotherapy.[42] Fertility discussions with these patients should include the possibility that cryopreserved sperm may not lead to a viable pregnancy. The role of preimplantation genetic diagnosis may also be discussed with this patient population.

A Question of Timing

Conversations about fertility preservation in cancer patients are most effective when they occur before initiation of treatment. Germ line tissue banking for both male and female patients optimally should take place before any cancer-related surgical resection of reproductive tissue and before initiation of chemotherapy. This is particularly relevant for female patients, as the effects of chemotherapy become more pronounced as a woman nears menopause.[43,44] The more subtle challenge facing oncologists is determining in which patients and for how long standard therapy can be delayed to accommodate fertility preservation. It has been proposed that women with breast cancer can delay treatment for up to 1 month to initiate hormonal stimulation and oocyte retrieval for either oocyte or embryo cryopreservation.[8,11,45,46] There is also some evidence suggesting that breast cancer patients who will ultimately undergo a course of tamoxifen treatment can delay this antihormonal therapy until after a pregnancy.[47] Although estrogen receptor-positive tumors are hormo-

nally driven, there is no evidence directly linking pregnancy after breast cancer with an increased incidence of disease recurrence.[48-50]

Case Discussions

As demonstrated by the series of case discussions that follow, incorporating fertility preservation into cancer care requires flexibility on a case-by-case basis to consider a patient's wishes as well as the optimal course of therapy needed to treat the disease.

Fertility preservation and breast cancer

A 34-year-old woman presented with an isolated 4-cm, firm, left breast mass. After visualization by ultrasound and mammogram, core biopsy was performed, which demonstrated estrogen and progesterone receptor-negative and HER2 negative infiltrating ductal carcinoma. Treatment planning was discussed with the patient and included timing of chemotherapy, lumpectomy versus mastectomy, and the use of radiation therapy. The patient opted for primary surgery with lumpectomy, followed by chemotherapy and radiation. Fertility preservation was also discussed, and the patient, who was single and had no children, stated that she would want to pursue as many options as possible to try to have a child after her treatment. After meeting with the surgical oncologist, the patient met with an oncofertility patient navigator, and her case was discussed with the multidisciplinary oncofertility team that included the patient's oncologists, a reproductive endocrinology infertility specialist, and the patient navigator. The patient then met with the reproductive endocrinology infertility specialist who discussed fertility preservation options, including embryo cryopreservation, oocyte cryopreservation, and ovarian tissue cryopreservation. The patient opted for embryo and oocyte cryopreservation, and oral contraceptives were started immediately in preparation for oocyte retrieval after surgery. On final pathology, all lymph nodes and margins were noted to be free of tumor cells. During her 4-week recovery from surgery, the patient underwent successful ovarian stimulation and oocyte harvest, which resulted in the cryopreservation of several oocytes and 4 embryos using an anonymous sperm donor. The patient subsequently began adjuvant chemotherapy to be followed by radiation, and she intends to pursue a pregnancy in the future with her preserved reproductive tissue.

Fertility preservation and testicular cancer

A 28-year-old single male presented to his internist for evaluation of a painless, firm, left testicular lump. A scrotal ultrasound revealed a 3-cm heterogeneous left testicular lesion, prompting a referral to a urologist. Repeat physical examination confirmed the presence of an indurated, nontender, left testicular mass. Serum tumor marker levels revealed normal alpha-fetoprotein, beta-hCG, and LDH levels. At that time, the patient was counseled regarding treatment options, and a recommendation was made for left radical orchiectomy. In addition, he was encouraged to undergo sperm cryopreservation before surgery. He agreed to pursue each of these procedures. The patient noted upon questioning that he was engaged and that he and his fiancee had been trying to achieve a pregnancy for 1 year without success. He also reported that his fiancee had recently seen a reproductive endocrinologist for evaluation of her reproductive health. The oncofertility patient navigator was contacted, and she helped arrange semen analysis testing with concurrent sperm cryopreservation. The patient provided 2 separate semen samples for cryopreservation, each with an appropriate duration of 2-3 days of preceding abstinence. Both semen analyses revealed normal ejaculate volume, severely low sperm concentration (<100,000 sperm per mL), a moderately low percentage of sperm with motility, and a moderately low percentage of sperm with normal morphology. A total of 6 vials of sperm were cryopreserved, and a test thaw revealed that 25% of the sperm had progressive motility post-thaw. The patient's case was subsequently presented at the multidisciplinary oncofertility grand rounds, attended by his urologist, his fiancee's reproductive endocrinologist, and the oncofertility patient navigator. A recommendation was made for the couple to undergo IVF with intracytoplasmic sperm injection (ICSI), given the severe male factor infertility present.

The patient underwent left radical orchiectomy, revealing a nonseminomatous mixed germ cell tumor. Postoperative imaging revealed a normal chest x-ray and no evidence of retroperitoneal lymphadenopathy, consistent with clinical stage I disease. After meeting with a medical oncologist and discussing treatment options, the patient opted for primary platinum-based chemotherapy consisting of 2 cycles of bleomycin, etoposide, and cisplatin. Upon completion of chemotherapy, he underwent serial semen testing every 6 months for 2 years. Each semen analysis showed normal ejaculate volume with azoospermia. Two years after completion of chemotherapy, the couple underwent IVF/ICSI using his cryopreserved sperm, and a singleton pregnancy resulted.

This case accentuates several important points. First, men affected by cancer may not initially volunteer their

efforts to achieve a pregnancy or express their desire for future paternity. It is imperative that the urologist or oncologist discuss the potential effects of cancer and cancer therapy with the patient, preferably before initiation of treatment. Second, many males diagnosed with cancer present concurrently with impaired semen parameters. These changes may derive from a variety of factors, including fever, cytological immune response, hypogonadism, and congenital or acquired testicular abnormalities. Finally, surgical therapy and chemotherapy may result in persistent azoospermia, further highlighting the importance of offering sperm cryopreservation before cancer therapy is begun.

Fertility preservation and rectal cancer

A 38-year-old woman with a history of hemorrhoids noticed bright red blood in her stool for 6 months. When the bleeding did not stop and became associated with abdominal pain and intermittent constipation, she underwent a colonoscopy which revealed a suspicious mass in the rectum. Biopsy results demonstrated high-grade adenocarcinoma, and a CT scan of the chest, abdomen, and pelvis indicated disease had spread to some local lymph nodes. No evidence of disease was seen in other organs. At the time of diagnosis, the patient had a 3-year-old daughter, and she and her husband had been trying to conceive their second child.

Treatment for stage III rectal cancer involves surgery as well as preoperative chemotherapy and radiation to the pelvis. In this case, pelvic radiation was the most significant threat to future fertility, and options, including pretreatment oophoropexy to move the ovaries away from the site of maximum radiation, were discussed with the patient and her husband. In addition, the decision was made to use a 5-FU-based chemotherapy regimen instead of the more gonadotoxic oxaliplatin. After meeting with her surgeon, the patient was referred to the oncofertility team, where additional options for oocyte or embryo cryopreservation were also discussed. The patient opted for oocyte retrieval and embryo cryopreservation before her scheduled oophoropexy and subsequent neoadjuvant chemotherapy and radiation. Dosimetry was specified to minimize exposure of the uterus and ovaries to radiation. At the time of surgery, 8 weeks after chemoradiation, a 22-cm section of distal colon and rectum were removed, and margins were declared free of tumor. Thirteen mesorectal lymph nodes showed no evidence of residual cancer, and the patient recovered without complications. To date, 18 months after the completion of therapy, she has not yet become pregnant, although her periods have returned. The patient and her husband are now discussing the possibility of working with a reproductive endocrinologist to attempt a pregnancy using their cryopreserved embryos. If the patient's uterus is determined to be too fibrotic postradiation to sustain a pregnancy, they have decided not to pursue the use of a surrogate and may instead investigate adoption possibilities.

Practice Guidelines

Each of the above cases illustrates the means by which fertility preservation can be integrated into the care of cancer patients. In all cases, the success of such measures depends upon early and open communication with patients, flexibility in scheduling appointments and procedures for both cancer care and fertility preservation, and the presence of a multidisciplinary oncofertility team that can see patients and discuss their cases on short notice. Current guidelines issued by the professional bodies representing both oncologists and fertility specialists underscore the importance of clear discussion regarding available interventions.[51,52] The 2005 report of the ethics committee of the American Society of Reproductive Medicine (ASRM) states that physicians should inform cancer patients about options for fertility preservation—recognizing that, to date, the only established techniques for doing so include sperm or embryo cryopreservation. The ASRM guidelines further emphasize that experimental techniques, including oocyte or ovarian tissue cryopreservation, should be conducted with the oversight of an Institutional Review Board.[51] In 2006, the American Society of Clinical Oncology (ASCO) Recommendations on Fertility Preservation in Cancer Patients were published.[52] Key to these guidelines was an awareness that cancer patients are interested in information regarding fertility, and that early intervention and discussion are critical to ensure future reproductive success. Similar to the ASRM report, these recommendations also identify sperm and embryo cryopreservation as the options known to be most successful.

As greater numbers of young cancer patients are successfully treated, it is increasingly important for the medical community to address the long-term needs of the cancer survivor. The oncologist has the greatest ability to initiate conversations about disease management, treatment options, and issues related to life after cancer; thus, it is essential that oncologists become familiar with the growing field of fertility preservation. Not only can several distinct options be discussed with patients and incorporated into the multidisciplinary steps of cancer treatment, but doing

so can also immeasurably enrich patients' lives as cancer survivors. To facilitate this goal, the Oncofertility Consortium has been established as a multidisciplinary and multiinstitution research collaboration specifically focused on the research efforts, clinical practice, and social and ethical implications raised by fertility preservation in cancer patients.[43] A recent analysis of several qualitative studies with adult and pediatric oncologists suggests that, despite the ASCO/ASRM guidelines, many oncologists do not discuss fertility preservation with cancer patients.[53] Several factors have been identified to account for this discrepancy, including lack of knowledge, uncertainty about the success of fertility preservation methods, and language/cultural barriers. As cancer care moves into the 21st century, it is our hope that available options for fertility preservation will continue to expand and become part of the conversation between every oncologist and their young patients.

CONFLICT OF INTEREST DISCLOSURES

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