Chapter 47
What is the impact of cytotoxic and surgical therapy on sperm and fertility preservation in cancer patients?

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Approximately half of men will receive a cancer diagnosis in their lifetime. Due to advancements in therapeutic options, a majority of patients will survive their cancer, with 5-year survival rates of 76% for males up to 40 years of age and 85% for males up to 19 years of age. These outstanding survival outcomes have led to a greater emphasis on patient survivorship issues in the wake of cancer treatment, which can cause irreversible damage to spermatogenesis and male fertility potential. These considerations, along with the increasing frequency of men pursuing biological parenthood later in life, have collectively led to the emergence of fertility preservation as an essential consideration when planning oncologic therapy.

Even prior to the initiation of cancer treatment, male fertility is often impaired. Authors from the CECOS network in France have shown that males with testicular cancer as well as those with lymphoma have lower semen parameters at the time of cancer diagnosis, including lower sperm concentration, sperm motility, and total motile sperm count compared to fertile controls. Williams et al. reported that prior to treatment, 52% of males with testicular cancer and up to 30% of males with other types of cancer were oligospermic upon presentation. Spermatogenesis and normal fertility requires an intact hypothalamic-pituitary-gonadal (HPG) axis, which can be disrupted through endocrine, inflammatory, and other immune responses to malignancy. This subfertility at baseline can be worsened by systemic processes, including malnutrition and fever, that oncologic patients often endure.

Oncologic Therapies Overview

While their mode of action varies, both chemotherapy and radiation induce DNA damage or slow replication, preferentially targeting rapidly dividing cell lines. Within the testes A (pale) spermatogonia are the progenitors of spermatogenesis and under constant turnover (Chapter 9). A (dark) cells are more quiescent, serving as a reserve pool during times of significant stress or toxicity. This process allows a natural resilience to testicular insults, but with sufficient dosages, both lines can be depleted leading to permanent infertility. In contrast to spermatogonia, Leydig cells have a low rate of division leading to their resilience to such therapies. Though cytotoxic agents can ultimately cause hypogonadism, the relative sensitivities of these cell types result in a disproportionate effect on fertility over testosterone deficiency. For decades the notion of fertility preservation was unattended to in the course of cancer therapies, leaving many patients cured of their cancer but permanently infertile as a side effect. An abundance of literature shows that most patients of reproductive age will survive their cancer therapies and desire the option to pursue biological paternity at some point after treatment. Those patients who have lost their fertility potential in the wake of cancer treatment and who did not undergo sperm cryopreservation report high levels of regret and anxiety related to this outcome. Therefore, it is imperative to understand the impacts of cytotoxic therapy on fertility to appropriately manage patient care and survivorship.

Radiation Therapy

Radiation is a cornerstone of cancer treatment. Worsening reproductive outcomes are associated with fractionated therapy (vs. non-fractionated therapy), increasing radiation dosage, increasing patient age, and the concurrent administration of other therapies. Patients at highest risk are those receiving direct testicular radiation or whole-body radiation. Interestingly, the Leydig cells are typically spared functionally until up to 20-30 Gy of radiation has been administered. However, the lineages of cells involved in spermatogenesis are much more radiosensitive, with testicular radiation dosages < 0.8 Gy commonly causing transient oligozoospermia, 0.9 -2.0 Gy typically resulting in transient azoospermia, and dosages ≥ 2.0 Gy commonly resulting in permanent and irreversible azoospermia. The nadir in sperm production for a given patient typically occurs 3-6 months after the initiation of radiation therapy, and recovery usually occurs over 1-

3 years, with lower testicular radiation dosages being associated with faster recovery of spermatogenesis.

Radiotherapy (XRT) is employed for a variety of solid tumor and hematologic malignancies in addition to preparation for bone marrow transplantation. Direct exposure to the testes, scatter from nearby radiation, and disruption of the hypothalamic-pituitary-gonadal axis through cranial radiation can all impair fertility.

Cumulative XRT is not the only determinant of gonadotoxicity; the manner in which radiation is delivered is also important. Fractionated dosing has a lower threshold for injury. It is hypothesized that the chronic damage from lower doses of XRT is insufficiently repaired, allowing more mutations to accumulate, leading to enhanced apoptosis. In addition to the radiation therapy schedule, the rate of delivery also can impact fertility. One study paradoxically showed low dose rates of radiation lead to more testicular damage compared to high dose rates. Likewise, a recent study showed that ultra-high dose rate (FLASH) radiotherapy (>40 Gy/s) demonstrated remarkable sparing of normal tissue. This tissue sparing effect (TSE) can also be influenced by the method of delivery. Microbeam radiotherapy creates this TSE in various organs through spatial and periodic alternation of the radiation dose.

Chemotherapy

The overall impact of chemotherapy on fertility is dependent upon the specific medication regimen and dosage administered. Many different classes of chemotherapeutic agents are available to clinicians, and these drugs are typically categorized as "high," "intermediate," and "low" risk for causing fertility impairment. Alkylating agents (cyclophosphamide, procarbazine, busulfan) are examples of high-risk agents, and vincristine is an example of a low-risk chemotherapeutic drug (Chapter 42).

Alkylating agents deserve further discussion. They disrupt DNA through base pair alkylation, leading to abnormal cross-bridge formation and mispaired nucleotides. Cyclophosphamide exhibits a dose-dependent effect, with dosages of 7.5-9 g/m^2 leading to impaired fertility, >10 g/m^2 gonadal injury, and > 20 g/m^2 usually causing permanent sterility. Green et al. have attempted to define levels of cyclophosphamide exposure below which azoospermia would not be seen. They coined the term "cyclophosphamide equivalent dosage (CED)," with the hope of providing patients with prognostic information about the effects of chemotherapy on

fertility. However, the authors found that there was no CED below which azoospermia was not seen in their cohort. Azoospermia has been found in 10% of those receiving a cyclophosphamide equivalent dose (CED) of < 4 g/m^2. The effects of alkylating agents can be long-lasting, with 25% remaining azoospermic, 28% oligozoospermic, and only 48% normozoospermic after 21-year follow-up, with each cumulative increase in CED of 1 g/m^2 being associated with worse recovery potential in reproductive status.

Platinum analogues similarly damage DNA and can interfere with replication, leading to equivalent rates of gonadotoxicty, yet their effects may be less permanent. Normozoospermic patients undergoing cisplatin therapy for testicular cancer had normozoospermia (64%), oligozoospermia (16%), and azoospermia (20%) posttreatment, but 80% recovered normal spermatogenesis by 5 years post-therapy. Carboplatin has similar effects, with one study of men undergoing multiagent BEC (bleomycin, etoposide, carboplatin) chemotherapy for testicular cancer revealing a 93% and an 83% chance of recovering of normozoospermia after 2 and 4 cycles respectively. Antimetabolites, vinca alkaloids, and topoisomerase inhibitors can have some gonadotoxicity, but their impact is more attenuated.

In addition to the individual drugs discussed above, multiagent regimens can also have a significantly adverse impact on fertility. MOPP therapy (mechlorethamine, oncovin, procarbazine, prednisone) in the setting of Hodgkin lymphoma typically leads to azoospermia in 85-90% of patients undergoing >3 courses, with additional common sequalae of low testosterone and gynecomastia. COPP therapy (cyclophosphamide, oncovin, procarbazine,) was found to have similar fertility effects in one study, with 100% of azoospermic men persisting up to 11 years post treatment. Due to their toxicity, ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) has been utilized instead, resulting in 90% recovery of semen parameters at 24 months with no azoospermia compared to alkylating agents. BEP (bleomycin, etoposide, platinum, prednisone) is a common combination therapy for treatment of testicular cancer. Semen parameters typically decrease following treatment, with one study showing less than half of patients recovering to normozoospermia at 24 months. Only 2% of patients remained azoospermic following therapy, with a history of receiving >2 cycles, abnormal baseline parameters, and concurrent radiation treatment all being predictive of poor recovery.

Surgical Therapy

Along with cytotoxic therapy, surgery can also be an iatrogenic cause of infertility. Surgery involving excision of testicular tissue, as is routinely performed on patients with testicular cancer, can result in loss of germ cell mass and reproductive potential. Oncologic pelvic surgery involving excision of the prostate gland or bladder results in a disruption of the excurrent ductal system and male infertility. Retroperitoneal surgery for colon cancer and retroperitoneal lymph node dissection (RPLND) surgical procedures can result in disruption of the lumbar sympathetic structures as well as the hypogastric/pelvic plexus that contain the sympathetic outputs driving seminal emission and ejaculatory function. RPLND for testicular cancer is a significant offender due to damage incurred to the hypogastric plexus, which leads to retrograde or anejaculation in 89% of cases. However, nerve sparing protocols have improved antegrade ejaculation outcomes up to 99% in chemotherapy-naïve patients and up to 89% of those patients who received chemotherapy. Pelvic surgery for prostate, bladder, and colorectal cancers can also damage parasympathetic nerves causing either temporary or permanent erectile dysfunction. The vas deferens is also intimately intertwined with this anatomy and can be unintentionally injured during these surgical cases. Even if spermatogenesis remains unimpaired, this injury can result in an obstructive azoospermia. Thus, regardless of the need of cytotoxic anti-cancer therapy, surgery alone can inadvertently lead to erectile dysfunction, resulting in impaired ejaculation and insufficient sperm counts.

Fertility Preservation

Due to the impact that chemotherapy, radiation, and surgery have on future fertility, both the American Society of Clinical Oncology (ASCO) 2018 guidelines, and the American Urological Association/American Society for Reproductive Medicine (AUA/ASRM) 2021 combined guidelines recommend sperm cryopreservation prior to the initiation of gonadotoxic therapy. This is imperative, as even a single dose of chemotherapy can compromise spermatic DNA quality and the overall quality of the sample. Most adult male patients, as well as adolescents, are capable of producing a sufficient semen sample for fertility preservation by masturbation. Semen collection can usually be successfully completed by patients, with proper coordination of care and

assurances of patient privacy at the time of collection. Given the improved access to IVF/ICSI, only very small numbers of viable sperm are required to help ensure fertility preservation. Peripubertal boys can be evaluated for the presence of Tanner stage II development, nocturnal emission, and testicular volume of 10-12 ml as indicators for the onset of spermatogenesis and their ability to provide a specimen (Chapter28).

Retrograde ejaculation may hamper the successful attainment of an ejaculated semen sample and should be suspected in men with histories of retroperitoneal surgery, low ejaculate volumes and neuropathy. A post-ejaculation urinalysis (PEU) can confirm the diagnosis with the presence of sperm in the urine. Alpha agonists such as pseudoephedrine and tricyclic antidepressants such as imipramine have a sympathomimetic effect and can be trialed in an attempt to restore antegrade function through improvement of bladder neck contraction. Sperm can also be collected from the bladder through trans-urethral catheterization, which is usually accomplished by first instilling sperm wash media into the bladder immediately before collection.

Patients with anejaculation present additional therapeutic challenges. Penile vibratory stimulation (PVS) involves application of a non-invasive vibratory device to the frenulum to facilitate induction of a spinal ejaculatory reflex. If PVS is unsuccessful, electroejaculation (EEJ), which involves electrical stimulation to the pelvis delivered via transrectal probe, can be trialed. This approach results in the nonspecific application of direct electrical current to the prostate gland and seminal vesicles to induce ejaculation. EEJ is significantly more invasive than PVS and must be conducted under general anesthesia in patients who are neurologically intact.

Patients who remain persistently anejaculatory, aspermic, or azoospermic despite the above interventions are candidates for oncologic testicular sperm extraction (onco-TESE). This approach, first describe by Schrader et al, involves surgical extraction of testicular tissue for the purpose of fertility preservation. Onco-TESE is also considered an invasive surgical approach, with sperm extraction success rates at approximately 50% based on several studies. Unfortunately, fertility preservation options for pre-pubertal cancer patients are limited and reliant upon clinical trials to develop investigative approaches (Chapter 46).

Barriers

While barriers to fertility preservation include financial, logistical, and cultural factors, one of the most glaring factors is the role of a provider. The greatest predictor of preservation is a physician recommendation. The diagnosis of cancer coincides with significant stress and a focus on the diagnosis and initiation of oncologic treatment. This focus can lead oncologists to be less likely to refer patients for fertility preservation care, particularly in the setting of an aggressive cancer. Physician, nurse practitioner, and nurse discomfort in discussing fertility preservation with patients can also lead to low patient referral rates for sperm cryopreservation. Provider bias may also play a role, as patients with lower median income, worse prognosis, or more advanced age are all less likely to be provided counseling.

Patient factors can also play a role in fertility preservation. Assisted reproductive techniques (ART) can be expensive processes and can dissuade those without sufficient financial resources to preserve their fertility. Access to a facility where appropriate sperm cryopreservation in the midst of acute oncologic care can also present a physical barrier to care—this is particularly true at some rural and pediatric hospitals. Finally, some patients have religious or cultural beliefs that can result in objections to masturbation, sperm cryopreservation, or other facets of assisted reproductive techniques.

Fertility Preservation Programs

Despite the numerous barriers that exist, patient counseling can have a dramatic impact on rates of cryopreservation. Dedicated fertility preservation programs consist of multidisciplinary teams of oncologists, urologists, reproductive endocrinologists, geneticists, nurses, social workers, and mental health professionals providing fertility services to these patients. The implementation of formalized programs has been shown to increase consultation rates by 2.4-fold, with one study even showing a 6-fold increase in fertility preservation. A patient navigator acting as a single point of contact can also help patients access and receive fertility preservation care more efficiently while minimizing patient stress in the process.

Conclusions

The cytotoxic and surgical management of cancer can drastically impact fertility potential. While effective means for sperm cryopreservation exist, significant barriers continue to limit patient access. The establishment of dedicated, multi-disciplinary fertility preservation teams can help mitigate these barriers and facilitate successful implementation of fertility preservation care.

Suggested reading

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