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Preservation of male fertility in patients undergoing pelvic irradiation

Marigdalia K. Ramirez-Fort[1, 2], Mehdi Kardoust-Parizi[4, 5], Ryan Flannigan[2], Phil Bach[2], Nicholas Koch[9], Casey Gilman[1, 3], Paula Suarez[1, 3], Digna V. Fort[1], Shearwood McClelland III[6], Christopher S. Lange[1, 7], John P. Mulhall[8], Migdalia Fort[1], Peter N. Schlegel[2]

[1]Life Sciences & BioDefense, BioFort Corp, Guaynabo, Puerto Rico, United States
[2]Department of Urology, Weill Cornell Medicine, New York, NY, United States
[3]Department of Psychiatry, Mayo Clinic College of Medicine and Science, Rochester, MN, United States
[4]Department of Urology, Medical University of Vienna, Vienna, Austria
[5]Department of Urology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[6]Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, Indiana, United States
[7]Department of Radiation Oncology, SUNY Downstate Health Sciences University, Brooklyn, New York, United States
[8]Department of Sexual and Reproductive Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[9]Department of Medical Physics, CONE Health, Greensboro, NC, United States

ABSTRACT

As the number of cancer survivors increases, so does the demand for preserving male fertility after radiation. It is important for healthcare providers to understand the pathophysiology of radiation-induced testicular injury, the techniques of fertility preservation both before and during radiation, and their role in counseling patients on the risks to their fertility and the means of mitigating these risks.

Impaired spermatogenesis is a known testicular toxicity of radiation in both the acute and the late settings, as rapidly dividing spermatogonial germ cells are exquisitely sensitive to irradiation. The threshold for spermatogonial injury and subsequent impairment in spermatogenesis is ~ 0.1 Gy and the severity of gonadal injury is highly dose-dependent. Total doses < 4 Gy may allow for recovery of spermatogenesis and fertility potential, but with larger doses, recovery may be protracted or impossible.

All patients undergoing gonadotoxic radiation therapy should be counseled on the possibility of future infertility, offered the opportunity for semen cryopreservation, and offered referral to a fertility specialist. In addition to this, every effort should be made to shield the testes (if not expected to contain tumor) during therapy.

Key words: male fertility; semen cryopreservation; penile vibrostimulation; electroejaculation; gonadotoxic radiation

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Introduction

The demand for male fertility preservation in the oncological setting has increased steadily over the past two decades [1]. A population-based study found the annual incidence of new cancer cases for patients aged 20–39 to be 43.3 per 100,000 [2]. As therapeutic options improve, so does the number of cancer survivors, and thus an increasing number of patients who desire fertility post-treat-

Address for correspondence: Marigdalia K. Ramirez-Fort, MD, President & CEO, BioFort, Life Sciences & BioDefense, PR-1 Km 20.6 Bo. Rios, Guaynabo, Puerto Rico, USA 00970, tel: +1 787 246 3671; e-mail: marigdalia@biofort.io

ment. Studies have shown that more than 50% of young male cancer survivors, and up to 75% of adult men who did not have a child at the time of cancer diagnosis, desire post-therapy paternity [3]. Furthermore, less than 60% of patients receive information from healthcare providers regarding post-cancer infertility treatment, and fewer than one-fourth of men without children bank sperm before treatment [4]. Therefore, it is important to identify methods that may preserve reproductive and sexual function, as this translates into an improved quality of life for this survivor population; one study found that feeling healthy enough to be a good parent after cancer was the strongest predictor of emotional well-being [4].

The American Society of Clinical Oncology (ASCO) clinical practice guidelines on fertility preservation for cancer patients emphasize the responsibility of healthcare providers to discuss fertility preservation as a part of the patient education and informed consent process, prior to initiating cancer therapy, including radiotherapy [5]. Therefore, oncological care providers should be encouraged to address the possibility of infertility, discuss fertility preservation options, and refer patients to appropriate reproductive specialists [3, 5, 6]. In settings where the radiation oncologist might be the first physician encounter in the patient's oncological management, this is particularly true (e.g., cancers of the prostate, bladder, anus/rectum, penis, and pelvic/upper thigh sarcomas). Even treatment of diseases of the chest and abdomen may produce significant doses to the testes [7] and, thus, the potential for impairment in spermatogenesis should be discussed with these patients as well.

Special consideration must be given to patients with Hodgkin's Disease and other pediatric malignancies that require irradiation of the pelvis, scrotum, or whole body; an additional patient population to be considered are young adults receiving heterotopic ossification prophylaxis following acetabular fracture, where the scrotum may receive spermatogenesis-impairing dosage [8]. At the time of treatment of pediatric patients, the future reproductive potential of their children should be discussed with the parents, in addition to the full implications of cancer therapy. It is imperative, therefore, that radiation oncologists do not shy away from a discussion of fertility perseveration.

Functional reproductive anatomy and physiology

The testes are predominantly comprised of three cell types: germ, Leydig, and Sertoli cells. Fetal germ cells (gonocytes) transform into adult spermatogonia. Final germ cell transformation occurs at 3–5 years of age to develop primary spermatocytes [9]. Leydig cells release testosterone in response to rises in luteinizing hormone (LH), required for the differentiation of male genitalia and brain masculinization [10], while Sertoli cells play an important role in providing immune protection to the developing germ cells, contributing to the blood-testis barrier, and maintaining developing germ cells [11].

Pathophysiology of radiation-induced gonadotoxicity

Testosterone deficiency

Leydig cells are responsible for androgen production and are relatively radio-resistant, withstanding doses of up to 30 Gy [12], yet testosterone levels are routinely found to be lower, and LH levels elevated up to 350%, in patients, following pelvic irradiation. These findings suggest impaired Leydig cell function, despite these cells being relatively tolerant to ionizing radiation [13]. Furthermore, pelvic radiation therapy has been associated with low sexual function in 14% of young men aged 16–24 years and up to 28% in men aged 55–64 years. Among these affected men, reduced libido occurs in 14.9%, rapid ejaculation in 14.9%, and erectile dysfunction in 12.9% [14]. These adverse changes in sexual function may be a manifestation of Leydig cell impairment.

While some degree of the endocrine dysfunction and oligospermia seen in cancer patients may be stress-induced, there are data to suggest that radiation produces effects above and beyond this physiological response. Several studies have demonstrated that scattered radiation to the testes may result in transient and long-term endocrine dysfunction, which may interfere with fertility [15, 16]. In one such study, 33 men who received prostatic irradiation alone were compared to 55 men after radical prostatectomy (RP). No patients received adjuvant androgen deprivation therapy. Low testosterone levels were seen in the irradiated group up to

eight years after treatment. Furthermore, a mean decrease in testosterone production was seen in these men when compared to those that underwent RP alone. There was a 27% ($p < 0.001$) decrease in total testosterone levels and a 32% ($p < 0.001$) decrease in free testosterone levels. Both luteinizing hormone and follicle-stimulating hormone levels increased by 53% ($p < 0.005$) and 100% ($p < 0.001$), respectively [16].

Impaired spermatogenesis

Conversely, germinal cells are exquisitely radiosensitive, particularly to multi-fractionated regimens [17–19]. Generally, doses of 0.1 to 0.15 Gy may lead to temporary sterility and doses over 4 Gy result in irreversible damage [12]. The earliest changes in spermatogenesis occur with the reduction in the number of leptotene spermatocytes, occurring approximately 14–25 days after radiation, followed by a reduction in pachytene spermatocytes at 25 days post-irradiation [20]. If the man ejaculates, significant decreases in ejaculated sperm concentration may be observed approximately 10 weeks post-radiotherapy [21], and azoospermia has been seen as early as after approximately 18 weeks [18]. The time to recovery of spermatogenesis is dose-dependent. Maximal testis doses of 1 Gy may require 9–18 months to recover spermatogenesis; doses of 2–3 Gy may take 30 months; doses of 4 Gy may take 5 years, and doses of up to 6–8 Gy in 2 Gy fractions may result in complete obliteration of germ cells with resulting permanent sterility [22–24].

Boehmer et al. conducted an elegant dosimetric determination of the unshielded testicular dose during standardly fractionated prostate radiotherapy using calibrated thermoluminescence dosimeters [15]. The calculated projected cumulative dose to the unshielded testes was 2 ± 1.5 Gy. Testicular doses during unshielded prostatic irradiation can therefore be sufficient to cause protracted, if not permanent, impairment of spermatogenesis [15].

Furthermore, there is evidence to suggest that prostatic irradiation results in testicular atrophy. Daniell et al. conducted a histopathological assessment of 78 therapeutic orchiectomy specimens from men without prior androgen deprivation therapy [16]. Measuring the histological testicular volume, they demonstrated a significant incidence of testicular atrophy in men with a history of prostatic irradiation compared to men without prior irradiation (71% *vs.* 28%; p-value < 0.001) [16, 25]. The frequency of post-irradiation testicular atrophy was independent of age [16]. Interestingly, testicular atrophy was more frequent in specimens obtained within three years of irradiation compared to greater than three years (89% *vs.* 53%) ($p < 0.001$), suggesting the possibility of testicular recovery over time [16, 25].

Fertility preservation strategies

Sperm and embryo cryopreservation are considered standard practices for fertility preservation and are widely available. Both ASCO and the American Society for Reproductive Medicine (ASRM) recognize and recommend sperm cryopreservation as an established method of fertility preservation in men [26, 27]. Ideally, patients are encouraged to produce semen specimens that can be cryopreserved prior to the initiation of cancer therapy. If possible, at least three samples should be collected without the use of sperm toxic lubricants [28] and with an abstinence period of 48–96 hours prior to the semen analysis/banking and up to 48 hours between collections in order to maximize the concentration of healthy sperm available for cryopreservation [29–32]. It is generally accepted that with normozoospermic sperm, there is no time limit for the duration of cryopreservation [33]. To prevent delays in cancer treatment, it is important to address the issue of fertility preservation early enough so that it is possible for the patient to collect a specimen. Semen specimens are typically obtained via masturbation, Penile Vibro-Stimulation (PVS), Electro-Ejaculation (EEJ), and Epididymal and Testicular Sperm Extraction.

Masturbation

Masturbation is the preferred technique for semen sampling in nonazoospermic persons without significant complications [34]. It is preferred that the sample is collected after a minimum of 2 days and a maximum of 7 days of sexual abstinence. Where possible, the specimen is collected via masturbation into a wide-mouthed, sterile container of material (e.g., glass or plastic), confirmed to be non-toxic for spermatozoa. Collection may occur at home if there is less than a one-hour delay between the collection of the specimen and presen-

tation at the designated cryopreservation facility. Otherwise, the specimen may be collected at the cryopreservation facility. Any loss of semen during collection must be reported. The specimen container should be kept at ambient temperature, between 20°C and 37°C, to avoid substantial changes in temperature that may affect the spermatozoa post-ejaculation [34].

Penile vibro-stimulation (PVS)

Some men may be unable to provide an ejaculated sample via masturbation due to cultural, psychological, physical, or religious reasons [35]. For these men, PVS or EEJ may be explored as potential methods of obtaining sperm for cryopreservation. Another group that may benefit from PVS is males with spinal cord injuries. Men with an intact ejaculatory reflex arc, which is dependent on the level of spinal cord injury, can experience reflex ejaculation, especially for patients with spinal cord injury (SCI) above the level of T12 or patients with psychogenic anejaculation [36].

PVS involves the placement of a vibrator against the penile frenulum resulting in stimulation of the dorsal penile nerves, resulting in ejaculation. Vibratory stimulation must be individualized for each patient but is best applied to the frenular surface of the penis with a narrow head device. These devices are widely available at commercial outlets and can be used at home. Based on our institutional experience, those who fail PVS, up to 20% will be salvaged with the simultaneous use of two vibrators. In those SCI patients who fail vibratory stimulation alone, the addition of midodrine is thought by some to significantly increase the rate of antegrade ejaculation as well as orgasm [36].

It should be noted that men with SCI above T6, may exhibit autonomic dysreflexia, which may increase the risk of urinary tract infections. Additionally, some men with SCI have poor sperm quality; despite being able to collect ejaculated sperm, they may not be candidates for IUI. In this case, *in vitro* fertilization, and intracytoplasmic sperm injection (IVF/ICSI) are recommended. However, these semen samples may have higher DNA fragmentation rates than normal controls [36].

Electro-ejaculation (EEJ)

Although not preferred in most patients, EEJ is an appropriate method of obtaining semen from patients who have problems with the natural mechanism of ejaculation (e.g., after spinal injury), especially for those who do not respond to PVS or who find masturbation unpalatable. Semen retrieved using EEJ tends to have poor sperm motility and is, therefore, more suited to use with IVF or ICSI rather than IUI [37].

The procedure is performed under general anesthesia for men who are sensate below the waist. The patient is placed in the lateral decubitus position. Anoscopy is performed to confirm that the rectum is empty and that no rectal mucosal abnormalities are present. The rectal probe is inserted completely into the rectum with the electrodes oriented anteriorly over the prostate and seminal vesicles. Stimulation is carried out with a standard electrical stimulation system starting at a maximum energy of 5 V. The stimulation pattern is a "peaked sine wave", 5–7 s apart; with the voltage increasing gradually, followed by a rapid decrease after the peak is reached. The voltage maximum is then increased in a stepwise manner up to 30 V. Throughout the procedure, the patient is monitored for penile tumescence, rectal temperature, and antegrade semen flow. The procedure will continue until seminal emission ceases, the rectal temperature reaches 38°C, or a maximum of 30 V is attained [36, 37].

A post-procedural anoscopy is performed to evaluate for mucosal injury, which is a potential complication of this procedure. The patient is turned supine and two retrograde specimens are obtained via urethral catheterization. The initial retrograde specimen is diluted in human tubal fluid (HTF) buffered with HEPES and plasmanate, pH 7.4, and sent for immediate processing along with the antegrade ejaculate. The bladder is then irrigated with HTF, and this second retrograde specimen is sent for immediate processing as well [36, 38]. ICSI coupled to EEJ, may lead to fertilization rates of 75% per injected oocyte and a clinical pregnancy rate of 55% per fresh semen retrieval attempt. There seems to be little difference in sperm quality for specimens obtained by EEJ versus PVS, although both have higher DNA fragmentation rates than normal masturbation controls [37].

Potential complications can arise in men with spinal cord injuries above T6, who are at a greater risk of autonomic dysreflexia, resulting in urinary tract infections. Anoscopy is performed to ensure

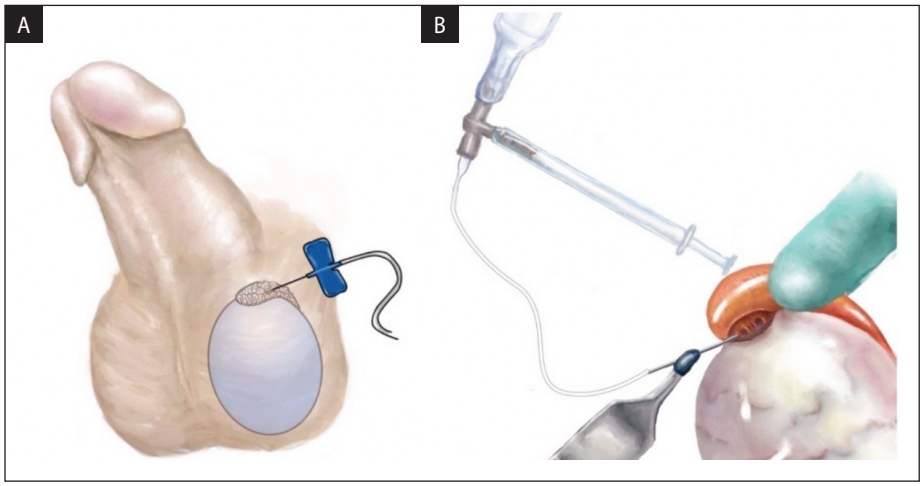

Figure 1. Sperm retrieval techniques. **A.** Percutaneous epididymal sperm aspiration (PESA). The needle is placed into the head of the epididymis as close to the efferent ducts as possible. **B.** Microsurgical epididymal sperm aspiration (MESA). This is the most precise and successful way to retrieve epididymal sperm. Under a general anesthetic, the testicle is delivered from the scrotum and the head of the epididymis is reflected back from the testicle with a finger exposing the efferent ducts draining from the testicle to the epididymis. Here, a single dilated efferent duct is punctured and sperm is aspirated

that there is no rectal mucosal injury. Temporary abdominal discomfort and severe muscle spasms can also occur after electrical stimulation. Other potential risks, especially in patients with underlying cardiovascular problems, include chest infection, pulmonary embolus, stroke, deep vein thrombosis, heart attack, and death [36].

Epididymal and testicular sperm extraction (PESA and MESA)

Unfortunately, up to 15% of men diagnosed with cancer are azoospermic prior to the initiation of oncologic therapy [39]. In these men, referral to a fertility specialist is crucial, as more advanced techniques may be needed to retrieve sperm for cryopreservation. For men found to be azoospermic or with profound oligospermia (i.e., < 5 million sperm/mL of ejaculate) [40], surgical retrieval may be indicated. Sperm may be obtained either from the epididymis or the testis depending on the etiology of azoospermia. For men without non-obstructive azoospermia, epididymal sperm can be obtained either via percutaneous epididymal sperm aspiration (PESA) or by open surgical techniques such as microsurgical epididymal sperm aspiration (MESA).

PESA can be performed in an ambulatory setting under local anesthesia. In short, a 21–26-gauge needle is inserted through the scrotal skin into the caput epididymis to aspirate epididymal fluid (Fig. 1A). PESA sperm retrieval is successful in 61–96% of patients and typically yields thousands to millions of sperm [41–43]. Despite the need for general anesthesia, MESA is the preferred epididymal sperm retrieval technique, with a sperm retrieval rate of 96–100% [29], yielding 15–95 million sperm that are adequate for cryopreservation [41].

With MESA, dilated epididymal tubules are identified and aspirated individually with the assistance of an operating microscope, enabling both minimal trauma to the epididymis and adequate hemostasis (Fig. 1B). Both PESA and MESA yield a higher sperm count with sperm of better quality than EEJ, thus decreasing the chance of needing subsequent sperm retrieval procedures [44]. However, these procedures may be associated with a risk of developing a scrotal hematoma, skin infection, and/or epididymal obstruction.

Testicular sperm aspiration (TESA)

Men with non-obstructive azoospermia, most commonly encountered following radiation therapy, require sperm retrieval directly from the testis either via testicular sperm aspiration (TESA) or surgical extraction (TESE) [41, 42]. Similar to PESA, TESA can be performed in an ambulatory setting under local anesthesia without access to an operating microscope. Using a 19-23-gauge butterfly needle attached to a syringe, the testicle is punctured percutaneously through approximately

30 passes. The testis is stabilized between the surgeon's thumb and forefinger, and a needle is inserted along the long axis of the testis [42]. The needle is withdrawn slightly and redirected to disrupt the testicular architecture [42]. The procedure is repeated until adequate testicular material has been aspirated [42]. A Franzen needle holder can be used to provide negative pressure for needle aspiration [42]. Sperm is aspirated from the testicular tissue in 52–100% of cases [41].Associated risks and complications include the development of scrotal and testicular hematoma, skin infection, testicular damage, and atrophy [41].

TESE (microTESE)

In contrast to TESA, TESE is an open testicular biopsy performed with the assistance of an operating microscope. Testicular tissue is retrieved from several regions of the testis and the microscope is used to identify dilated seminiferous tubules that are more likely to harbor viable sperm, thereby guiding sperm retrieval within the specimen. This approach, more accurately termed microdissection testicular sperm extraction (microTESE), enhances hemostasis, reduces the quantity of testicular tissue harvested, and increases sperm yield (Fig. 2) [45]. MicroTESE results in successful sperm retrieval for 45–63% of non-obstructive azoospermic men with 70-fold less tissue excised compared to conventional TESE [46]. Sperm retrieval is also possible for men that are azoospermic after having undergone radiation therapy, with sperm retrieval rates dependent upon the dose and temporal relationship with radiotherapy [47].

Since the testicular blood supply is distributed over the surface of the testis before it penetrates the testicular parenchyma, multiple blind biopsies can interrupt the testicular blood supply and devascularize the testis if all branches of the testicular artery are divided. Therefore, it is important to avoid

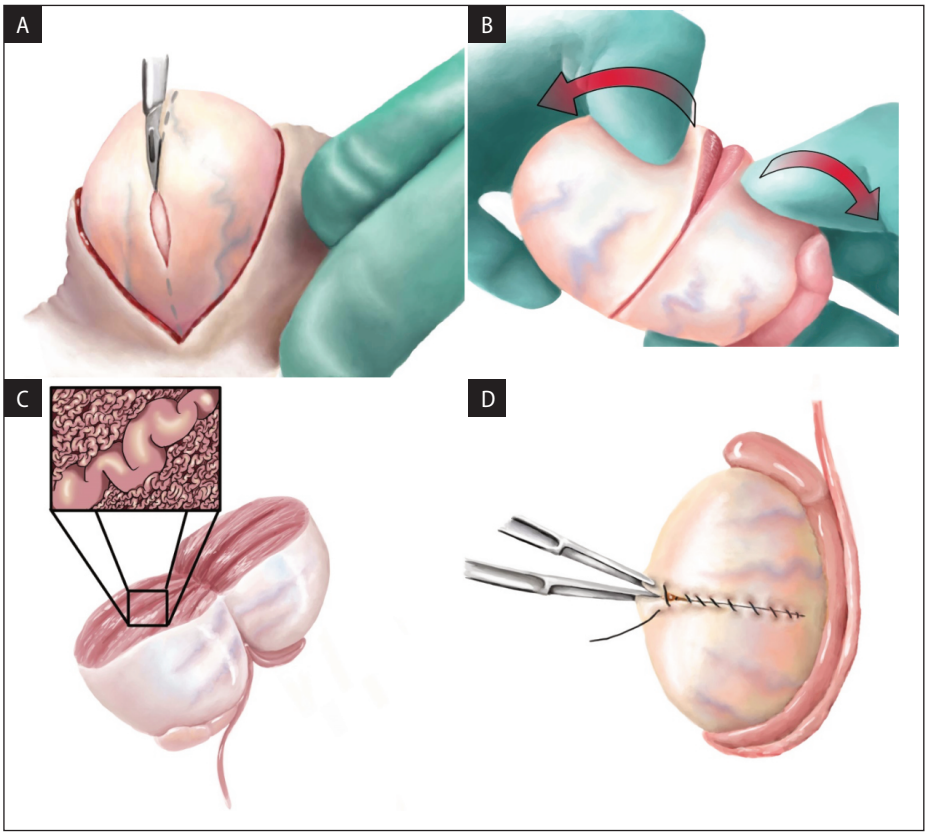

Figure 2. Microdissection testicular sperm extraction (microTESE). **A.** Under a general anesthetic, the testicle is delivered through a scrotal incision. An equatorial incision is made in the tunica albuginea; **B.** The testicle is bi-valved exposing the seminiferous tubules; **C.** The seminiferous tubules are carefully searched under an operating microscope until a dilated tubule is identified. These dilated tubules are more likely to contain sperm and should be harvested. The tissue is then placed in sperm transport media, minced then examined under a microscope by the embryology team for the presence of sperm; **D.** Once the microTESE is complete, hemostasis is achieved with bipolar cautery and the tunica albuginea is closed

subtunical testicular vessels during testicular biopsy procedures, especially if large or multiple biopsies are performed [48]. An increased number of biopsies is always counter-balanced by greater risk of damage to the vascularity of the testis, so the surgeon must be constantly aware of this. In addition, the identification of regions of the testis that have sperm production cannot be reliably evaluated prior to the biopsy. Multiple random biopsies may lead to the removal of large volumes of testicular tissue with uncertain results of sperm retrieval [49].

Strategies for reducing out-of-field dose

Three sources of X-ray scatter contribute to patient dose outside the treatment field: scatter originating from within the patient, scatter off the field collimators, and leakage radiation through the head of the linear accelerator that fills the room with low-energy X-rays [50]. At an increasing distance from the field edge, the total dose decreases somewhat exponentially; near the field edge, the component of patient scattered radiation increases with the volume of tissue irradiated and prescription dose [50]. This component dominates out to roughly 20 cm, where gantry head leakage becomes the dominant source [51]. The collimator scatter and gantry head leakage components increase with the number of monitor units (MU) delivered in the plan. Compared to a conformal 3D plan, modulated treatments (such as IMRT and VMAT) require the utilization of more MUs and are therefore less efficient in delivering the prescription dose, which consequently results in proportional increases in collimator scatter and head leakage [50]. However, if flattening-filter-free (FFF) beams are used, MUs will increase but gantry head leakage will decrease owing to the absence of the flattening filter, a major contributor to head leakage [52]. With the exception of neutron contribution, out-of-field doses vary little with beam energy or depth in the patient, except at the patient's surface near the field edge [50]. Dibs et al. demonstrated meaningful gonadal sparing with the use of helical tomotherapy for patients undergoing total body irradiation for nonmalignant indications [52].

Neutrons are another source of out-of-field dose to the patient and become a concern for treatment beam energies above 10 MV [53]. Neutrons are generated in the head of the linear accelerator when high-energy photons interact with head shielding and beamline components [54]. For one vendor of linear accelerators, the number of neutrons produced increases roughly 10-fold from 10 MV to 15 MV and by 20-fold from 15 MV to 18 MV beam energies [51]. The neutron dose out of the field is proportional to the total plan MUs for a given beam energy, yet the photon scatter still contributes the majority of out-of-field dose [55].

Shielding techniques with high-Z material minimize photon scatter and leakage [56]. The classically used shielding device for the testes, is colloquially called a *clamshell* (Lead Testicle Shield, Radiation Products Design, Inc, Albertville, MN). It is a divided, hollow sphere, made of lead that surrounds the testicles during radiotherapy (Fig. 3). Studies that looked at testicular dose measurements with and without shielding material have demonstrated that gonadal shielding can reduce the testicular dose 3 to 10-fold [57, 58]. Specifically, mean testicular dose per fraction from para-aortic and ipsilateral iliac fields of 25–36 Gy with and without testicular shielding have been measured as 1.48 ± 0.5 cGy and 3.89 ± 1.44 cGy ($p < 0.001$), respectively [7]. The mean testicular dose from para-aortic irradiation alone was measured as 0.65 ± 0.35 cGy with shielding and 1.86 ± 0.86 cGy without shielding [7]. Unfortunately, lead is not an effective shield against secondary neutrons; however, neutrons can be avoided through use of beam energies 10 MV and lower [59].

During treatment simulation, patient positioning should be reproducible and include the clamshell in the setup. Due to the image artifacts caused by the highly attenuating lead shield, a rubber dummy clamshell is also available. If the setup is not reproducible, deformation of the target during treatment setup caused by the placement of the clamshell can result in a geometric miss [60]. Treatment through the clamshell should be avoided with certainty.

Post-radiation management

The ideal time for sperm cryopreservation is prior to the initiation of gonadotoxic therapy and every effort should be made to complete sperm banking prior to treatment. For patients who have already begun therapy, the decision on whether to cryopreserve sperm is controversial, as radiation may be teratogenic. Men who have recently started gonadotoxic

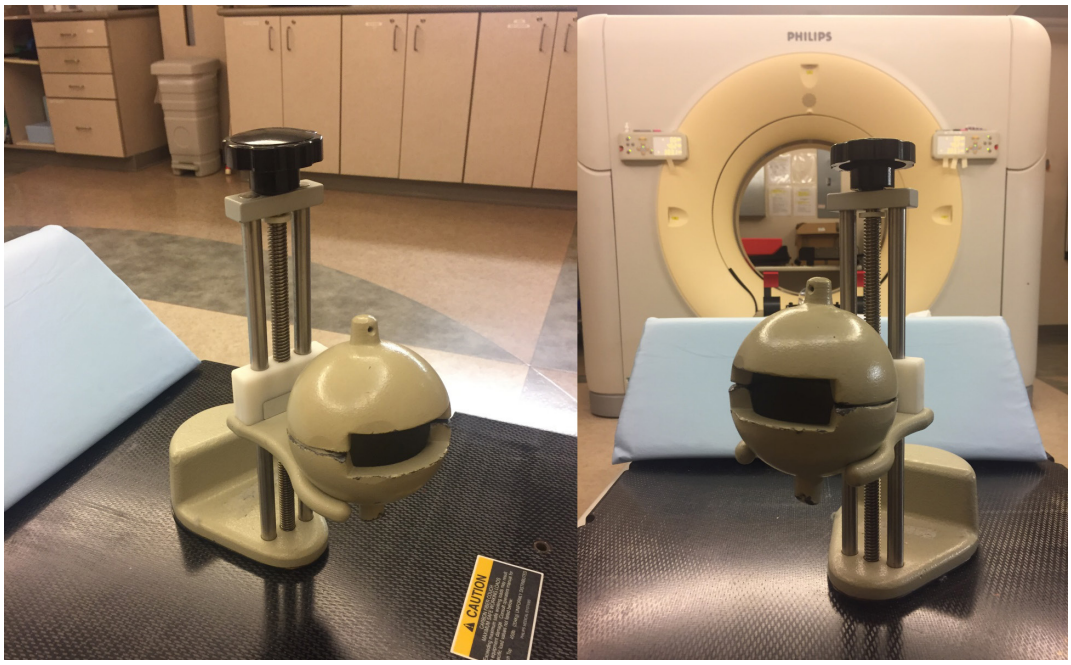

Figure 3. Clamshell, designed to reduce scatter radiation to the testes. It consists of a spherical lead cup with a wall thickness of 0.5 inches (1.27 cm). The open sector allows for comfortable attachment to the patient and the adjustable stand allows for increased patient comfort

therapies are unlikely to be azoospermic and some advocate proceeding with sperm banking [61]. However, animal models have shown that the offspring produced by males actively undergoing gonadotoxic therapy tend to have many genetic mutations [62]. Because of radiation therapy's known adverse effects on sperm quality and offspring conceived, patients undergoing treatment should be counseled to use contraception to minimize unintended pregnancies. In the azoospermic man who has already started gonadotoxic therapy prior to sperm cryopreservation, a discussion of the potential risks of using the retrieved sperm is important.

If a patient has already completed radiotherapy, he should be counseled to wait at least 18 months before attempting to father a child, as studies have shown increased chromosomal and other genetic abnormalities in sperm up to 18 months after gonadotoxic therapy [63]. The fertility management of the patient after 18 months can then be directed by his reproductive potential as determined by semen analysis and serum testosterone and FSH levels.

Conclusion

All men undergoing potentially gonadotoxic radiation therapy should be counseled on the possibility of future infertility, offered the opportunity for semen cryopreservation, and offered referral to a fertility specialist. Available male fertility experts can be listed through the Society for male reproduction and urology of ASRM (SMRU.org). In addition to this, every effort should be made to shield the testes during therapy with the use of a clamshell. Clamshell phantoms should be utilized during the simulation process to preserve a replicable PTV and achieve adequate dose coverage. Scattered radiation to the testes is associated with chromosomal disorders in sperm that may increase the risks of genetic abnormality in the offspring of the irradiated patient. Therefore, it is advised to wait 18 months after irradiation to procreate to avoid this risk of genetic abnormalities.

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Conflict of interest

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Competing interests

N/A.

Ethical approval

N/A.

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