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REVIEW ARTICLE

Radiation effects on male fertility

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SUMMARY

Background: Spermatogenesis is a process of dynamic cell differentiation. Ionizing radiation impairs spermatogenesis, and spermatogonia are more radiosensitive than spermatocytes or spermatids. Consistent with this assumption and due to improvement in tumor curability, nowadays, fertility preservation represents a public health need.

Objectives: To discuss radiotherapy-induced risk to male fertility and raise oncologic awareness of male fertility in daily clinical practice.

Materials and Methods: PubMed and Clinicaltrials.gov databases were searched for papers in English.

Results: We provide an overview of clinical landscape. Four main issues were proposed: (i) spermatogenesis and radiobiological general concepts; (ii) impairment of spermatogenesis; (iii) impairment of testosterone-producing Leydig cells; (iv) clinical radiotherapy evidence in oncology.

Conclusion: This review can be useful in daily clinical work and offer some directions for future research.

INTRODUCTION

Male gonadal toxicity represents a common complication of modern anticancer treatments (Dillon & Gracia, 2012). Germinal epithelial damage, resulting in oligospermia or azoospermia, is a recognized consequence of radiation therapy (RT) (Stewart *et al.*, 2012). In fact, testis is one of the most radiosensitive tissues, with very low doses of radiation causing significant impairment of its function. Damage may be caused during direct irradiation of the testis or, more commonly, from scattered radiation during treatment to surrounding tissues. Although the effective cancer treatment is of paramount importance, the potential gonadal damage could be a source of considerable distress for patients, especially in those of reproductive age (Dillon & Gracia, 2012).

The aim of this review was to assess radiation effects on male fertility, with a special focus on the main treatment decisions that could negatively impact on patients' quality of life (QoL). The gonadotoxic effects of ionizing radiation are briefly described in an attempt to provide a means of understanding how it relates specifically to the daily clinical practice.

METHODS

Literature search

A non-systematic review of the literature was carried out. We examined current literature describing RT-related gonadal toxicity. PubMed and Clinicaltrials.gov databases were searched for electronic publications, written in English. The following combination of research terms was used: 'male', 'fertility', 'oligospermia', 'azoospermia', 'sperm', 'gonad', 'late', 'toxicity', 'side effects', 'radiation therapy', 'radiation', 'ionizing', 'radioprotection'. In addition, consensus guidelines of fertility preservation were analyzed. Reference lists of selected studies and review papers were manually searched for additional relevant publications. Search strategy was performed up to May 2018.

Study selection

The literature search identified a total of 571 potentially relevant articles, including national and international guidelines. Articles were mainly excluded because the subject matter was not related to our aim or the article was not published in English. Twenty-two papers were retained for review.

RESULTS

We organized results into four sections: (i) spermatogenesis and radiobiological general concepts; (ii) impairment of spermatogenesis; (iii) impairment of testosterone-producing Leydig cells; and (iv) clinical evidence in human.

Spermatogenesis and radiobiological general concepts

Understanding physiological spermatogenesis process, as well as knowing basic radiobiological issues, is paramount to establish a link between RT and testis function. Detailed analysis of these concepts is beyond the aim of this review; thus, we only briefly described their main characteristics.

On one hand, spermatogenesis is a complex process of dynamic cell differentiation by which diploid germ cell spermatogonia undergo proliferation and differentiation into mature haploid spermatozoa. In physiological conditions, it takes around 70 days. Spermatogonial stem cells are able both to self-renew to maintain stem cell populations and to generate progenitor cells that proceed through mitosis, meiosis, and finally morphological transformation of the haploid cells into spermatozoa (Fukunaga *et al.*, 2017). Failure of the spermatogonial stem cell population to function properly results ultimately in spermatogenesis failure.

On the other hand, the therapeutic use of local ionizing radiation is mainly based on the rational foundation provided by the five traditional Rs of radiobiology (repair, repopulation, redistribution, reoxygenation, and radiosensitivity) and the normal tissues proper architecture and reserve capacity (De Felice *et al.*, 2018a). Based on the law of Bergonié and Tribondeau—the radiosensitivity of a tissue is directly proportional to its reproductive capacity and inversely proportional to its degree of differentiation—spermatogonial stem cells are more radiosensitive than mature cells and globally testis tissue is highly radiosensitive due to its high proliferation and growth rate (Vogin & Foray, 2013). RT can damage gonadal tissue at all ages and result in long-term or permanent sterility.

Impairment of spermatogenesis

The onset of radiation injury in the testis is complex. The degree and persistence of gonadal damage depend on a variety of factors, including dose, target volume, fraction size, and the specific target cell population, as well as its architecture and its reserve capacity (De Felice *et al.*, 2016a). Based on United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1977 report, it is well accepted that sterile period is a direct consequence of spermatogonial cell killing (UNSCEAR, 1977). It should be pointed out that the following evidence mainly derived from histological and labeling studies carried out with x-irradiated mouse testis. The amount of direct information on man is still very limited. According to the Oakberg-Huckins model of stem cell renewal and the Clermont and Buston-Obergon two-stem-cell model, two cell populations should be assumed: (i) stem-cell spermatogonia (As) that occur as single isolated cells and are responsible for the repopulation of the germinal epithelium after radiation exposure; (ii) groups of differentiating spermatogonia which constitute the initial step in spermatogenesis (UNSCEAR, 1977). The model can be diagrammatically shown in the following scheme:

A_s spermatogonia cells are in continuous cycle and have a long cell cycle. A_s spermatogonia cells are the most resistant cells of the spermatogonial types. Differentiating cells are distributed at random over the tubules. After irradiation, the repopulation index (RI), which indicates the fraction of repopulated seminiferous tubules, is directly proportional to the number of surviving stem cells (UNSCEAR, 1977). The form of the dose-effect curve is characteristic with an ascending part with total doses below 6 Gy, a plateau at 6–8 Gy, and a descending part with high total dose such as 10 Gy. This humped dose-effect relationship suggests that later doses have less effect than earlier ones, due to progression of the spermatogonial cell population into a more resistant stage (UNSCEAR, 1977). On the other hand, it should be noted that there is a reverse fractionation effect. Dose fractionation decreases the number of surviving A_s spermatogonia. After first dose irradiation, stem cells pass to a more sensitive cell cycle stage, assuming cell synchronization. At this point, the surviving A_s spermatogonia cells are more sensitive than formerly, both to killing and genetic damage (UNSCEAR, 1977). Therefore, a period of sterility is a direct consequence of stem cell killing and dose fractionation determines a detectable delay in the rate of repopulation of germinal epithelium.

At 1.8 Gy per fraction, whole *A* spermatogonia (A_s and A_1–A_4) shows an initial decrease—within the first weeks of irradiation—due to A_1–A_4 reduction, followed by a new level of steady-state growth, since the A_s spermatogonia remain at near-control levels during the entire 7 weeks of RT (UNSCEAR, 1977). Spermatocytes and spermatid are damaged after receiving a 2–3 Gy and 4–6 Gy dose, respectively. These doses can determine permanent damage to spermatogenesis (Maltaris *et al.*, 2006). Considering that physiologically spermatocyte and spermatid lifetime is 46 days and that globally the time needed for spermatogenesis is approximately 70 days, the sperm count is dramatically reduced even to azoospermia after that period. A dose of 8 Gy produces azoospermia in nearly all men. Figure 1 depicts radiation effect on spermatogenesis.

After RT, seminiferous epithelium repopulation is supported by an increase in A_s cell proliferation. Return to fertility is a slow process, and it is dependent on the radiation dose (Maltaris *et al.*, 2006). Usually, following dose of 2–3 Gy, recovery occurs in 10–24 months, whereas at doses of 4–6 Gy, it may required up to 10 years (Biedka *et al.*, 2016). Despite recovery of the sperm count, infertility may occur due to low-quality sperm production or genetic anomalies. After 6 Gy, there is a high risk of permanent sterility. Table 1 summarizes sensitivity of gonadal tissues following single dose irradiation and time to recovery. Doses of irradiation >0.35 Gy cause azoospermia, which may be reversible. The time taken for recovery increases with larger doses; complete recovery takes place within 9–18 months following radiation with <1 Gy, but doses in excess of 2–6 Gy may result in permanent azoospermia.

Stem-cell spermatogonia (A_s) → stem-cell spermatogonia (A_s)
Stem-cell spermatogonia (A_s) → A-paired spermatogonia (A_{pr}) → A-chains aligned spermatogonia (A_{al}) → A_1 spermatogonia → A_2 spermatogonia → A_3 spermatogonia → A_4 spermatogonia → intermediate spermatogonia → B-spermatogonia → primary spermatocytes (I) → secondary spermatocytes (II) → spermatids → sperm cells

Figure 1 Radiation effect on spermatogenesis.

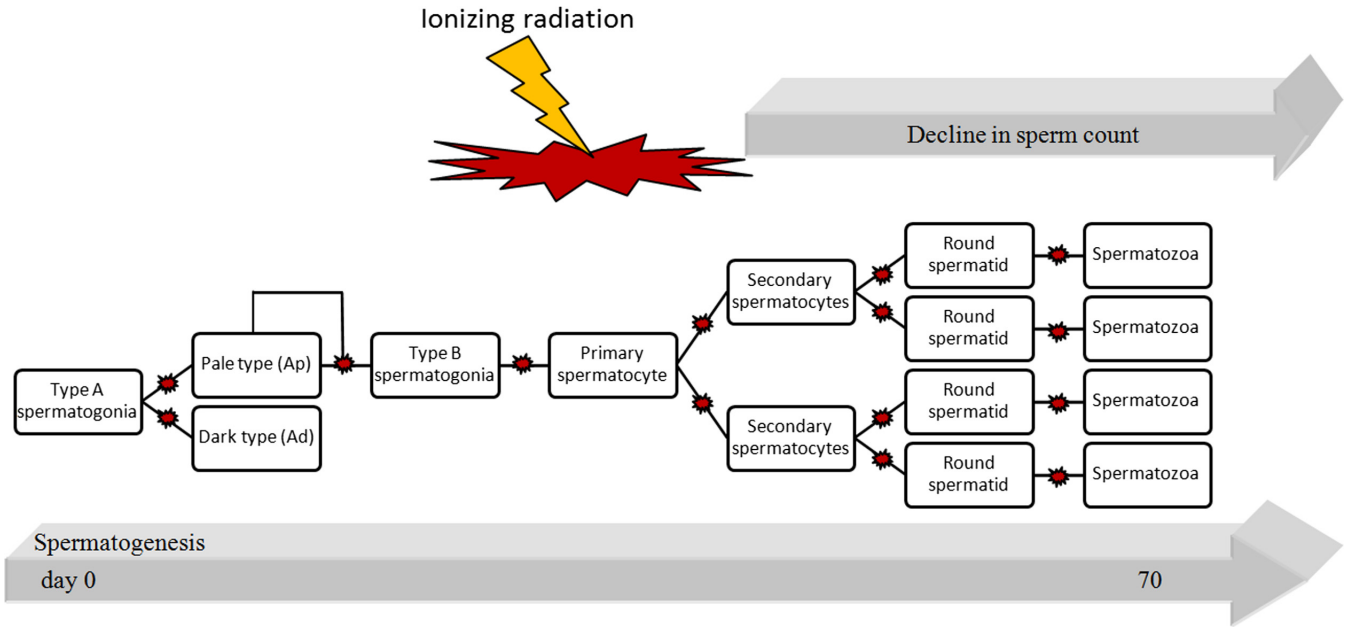


Table 1 Sensitivity of gonadal tissues following single dose irradiation and time to recovery

Cell	Radiation dose	Toxicity	Recovery
Spermatogonia	≤1 Gy	Oligospermia	9–18 months
Spermatocytes	1–3 Gy	Azoospermia	10–30 months
Spermatids	>3 Gy	Azoospermia	>60 months

Gy, Gray.

Table 2 Clinical conditions describing male fertility complication after irradiation

Clinical condition	Degree of exposure	Complication
Testis direct irradiation		
Seminoma (stage I)	High (>3 Gy)	Permanent infertility
Acute lymphoblastic leukemia (testicular relapse)		
Soft tissue sarcoma (deep and high-grade)		
Bone marrow transplantation		
Testis scattered irradiation		
Prostate cancer	Moderate (1.5–3 Gy)	Permanent infertility
Rectal cancer		
Anal canal carcinoma		
Bladder cancer		
Testicular cancer		
Hodgkin lymphoma		
Hypothalamic–pituitary axis dysfunction		
Pituitary gland cancer	High (>24 Gy)	Hypothalamic/ pituitary dysfunction
Acute leukemia (prophylactic cranial irradiation)	Moderate (<24 Gy)	

Impairment of testosterone-producing Leydig cells

The Leydig cells of the testis are remarkably more radioresistant than germinal epithelium and are only injured by high therapeutic radiation doses (Izard, 1995). They are more sensitive in childhood than adult age. Leydig cell function is usually preserved up to 20 Gy in prepubertal boys and 30 Gy in sexually mature men. Due to their function to secrete testosterone, the effect of radiation upon the Leydig cell may determine hypogonadism—loss of body and facial hair, alteration in muscle mass, redistribution of body fat to a more feminine pattern, atrophy of the testis, as well as changes in personality, with loss of motivation, energy and libido, depression, and anxiety (Izard, 1995). Leydig cell function can be monitored by both testosterone and LH serum levels. Normal testosterone value and elevated LH levels are indicative of Leydig cell damage, with a compensatory increase in gonadotropin production.

Clinical evidence in human

How RT can exactly affect fertility in men is still a hot topic. Ionizing radiations can interfere with some parts of the reproductive process, and infertility represents one of the most frequent RT-related late complications. Direct data on ionizing radiation effects on human fertility came from (i) accidental irradiation, such as nuclear accident and occupational irradiation; (ii) experimental irradiation of volunteers; and (iii) clinical irradiation due to RT cancer treatment (Table 2).

Accidental irradiation

Chernobyl nuclear accident in 1986 represents the largest accidental irradiation in human history, resulting in deterministic effects. Significant spermatogenesis disorders were recorded in people working at the cleanup of Chernobyl nuclear accident (Cheburakov & Cheburakova, 1993). Workers were irradiated by doses up to 0.25 Gy and presented changes in sperm count and morphology. Maximal changes were observed in those workers exposed by dose more than 0.1 Gy.

But, as in all radiation accident reports, the main limit was that doses were not accurately known, as well as data fertility before accidental irradiation. However, after Chernobyl accident,

there was much public concern over environmental radiation contamination and occupational exposures and effects on human male fertility (Fukunaga *et al.*, 2017). Recently, the International Commission on Radiological Protection (ICRP) updated the guidance on the control of exposure from radiation sources, based on the latest available scientific information of the atomic bomb survivors with 40–50 years of follow-up (Stewart *et al.*, 2012). The document provided a review of early and late effects of radiation in normal tissues, including testis, with respect to radiation protection. Estimates of the threshold doses for temporary and permanent sterility in adults were 0.15 Gy and 3–6 Gy, respectively.

Experimental irradiation

Data from experimental irradiation of human testis consisted of controlled experiment of healthy volunteers receiving graded radiation doses to the testes (Ash, 1980). In late 1960s and early 1970s, an experimental study was conducted in volunteers of the Oregon State Penitentiary (Ash, 1980). A total of 67 prisoners agreed to have their testicles irradiated with doses ranging from 0.08 to 6 Gy. Both sperm count and morphology were assessed before and after irradiation. Results showed that 0.1 Gy caused significant suppression of sperm count while permanent sterility was observed at doses of 3–5 Gy. Type B spermatogonia were found to be the most radiosensitive cell type, showing changes after all doses. Spermatocytes and spermatids appeared to be damaged after 2–3 and 4–6 Gy, respectively. Complete recovery to pre-irradiation sperm count took place within 9–18 months after <1 Gy, 30 months for 2–3 Gy, and ≥5 after 4–6 Gy.

Clinical irradiation

In recent clinical practice, testicular function can be impaired by both testicular irradiation and hypothalamic–pituitary axis irradiation. Moreover, in case of testicular irradiation, there are two potential clinical conditions: testis direct irradiation and testis scattered irradiation. Here, we provide a comprehensive picture of the main RT indications that could negatively impact on male fertility.

Testis direct irradiation. Fractionated RT could represent a valid treatment option in several cancer therapies, including seminoma, acute lymphoblastic leukemia, sarcoma, and bone marrow transplantation. Patients with stage I seminoma can be adequately managed with 20 Gy to the testis (National Comprehensive Cancer Network, 2018a). Testicular irradiation for stage I disease results in permanent infertility with a significant risk of hypogonadism which increases with time. Testicular irradiation requires replacement therapy in order to achieve normal puberty development.

With modern chemotherapy programs, testicular relapse in acute lymphoblastic leukemia (ALL), especially T-cell subtype, is rare. In case of testicular relapse, local RT is standard management (National Comprehensive Cancer Network, 2018b). Despite the expectation of RT-related infertility, RT up to 24–26 Gy (2 Gy/fraction) to both testes is recommended, due to the high risk of bilateral testicular relapse.

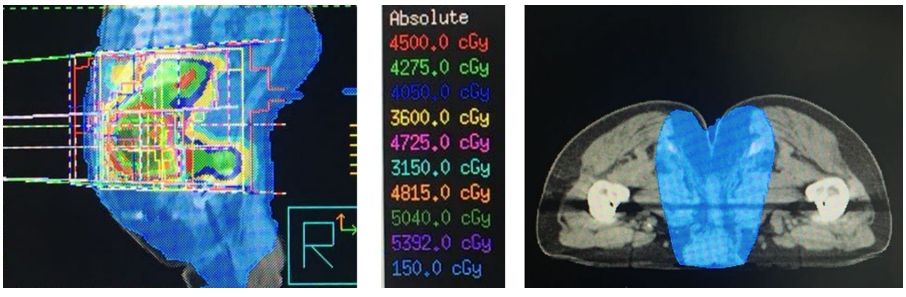
RT is routinely used as an adjuvant to radical surgery in deep and high-grade soft tissue sarcoma (National Comprehensive Cancer Network, 2018c). The doses required in these diseases are such that direct irradiation of the scrotum may produce azoospermia as well as endocrine dysfunction.

Concerning bone marrow transplantation, conditioning regimens commonly involve total body irradiation (TBI) (De Felice *et al.*, 2016b). Most patients receiving TBI conditioning have gonadal failure. Recovery of gonadal function is rare and occurs in less than 20% of male patients. The majority of these patients developed normal secondary sexual characteristics, with normal testosterone levels, but elevated levels of luteinizing hormone (LH), indicating mild Leydig cell dysfunction.

Testis scattered irradiation. Generally, testis is outside the target volume but can be exposed to scattered radiation depending on clinical primary tumor location and regional nodal involvement. Irradiation to the pelvic lymph node areas, as in the treatment of pelvic tumors (including prostate cancer, rectal cancer, anal canal carcinoma, bladder cancer, testicular tumors, or lymphoma), results in a scattered dose to the testis of 1.5–3 Gy. For instance, transient oligozoospermia can be evident in patients treated with a long course of neoadjuvant RT, especially in those lesions located <5 cm from anal verge (De Felice *et al.*, 2016c). An example of dose distribution is presented in Fig. 2. The exact correlation between damage and recovery of spermatogenesis has not been assessed. From the published data, to reduce the risk of permanent sterility, it seems reasonable to suggest limiting the dose to scrotum to 1 Gy, if possible, according to tumor extent. In fact, an update analysis revealed no recovery of spermatogenesis in patients receiving doses of 1.4–2.6 Gy after a median follow-up of 35 months (range 17–47) but a return of fertility in the two patients with testicular radiation doses of 1.2 Gy, indicating that this may represent a threshold for permanent testicular damage (Centola *et al.*, 1994).

Patients with stage I seminoma can be adequately managed with adjuvant para-aortic irradiation (total dose 20 Gy) and stage

Figure 2 Dose distribution in low rectal cancer treatment.



IIA/B with adjuvant para-aortic and iliac dogleg irradiation (total dose 30 Gy) (National Comprehensive Cancer Network, 2018a). While para-aortic irradiation should not affect gonadal function and sperm banking is therefore unnecessary, dogleg irradiation could cause lowering of sperm counts or even infertility (De Felice *et al.*, 2016d). In Hodgkin lymphoma, the classic subdiaphragmatic field includes the retroperitoneal and pelvic lymph nodes and spleen (National Comprehensive Cancer Network, 2018d). Thus, gonadal toxicity may be an issue, especially if no special precautions are taken to shield the testes. In these cases —with appropriate testicular shielding—azoospermia is usually transient, with recovery of sperm counts to fertile levels.

Hypothalamic–pituitary axis dysfunction. As in female, irradiation to the hypothalamic–pituitary axis may produce deficiencies in gonadotrophin production (De Felice *et al.*, 2018b). Hypothalamic–pituitary axis dysfunction represents a well-known potential secondary effect of cranial irradiation (De Felice *et al.*, 2018b). Its impact on the development of endocrinopathies depends on the RT-induced damage to the hypothalamus and/or the pituitary gland. By secreting gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), the hypothalamic–pituitary axis is responsible for fine regulation of male fertility. Onset of hormone insufficiency is variable and usually may manifest at doses up to 40 Gy. For instance, in pituitary gland cancer, conventional doses of 45 at 1.8 Gy daily fractions carry a hypopituitarism risk range of 10% to 30% and an estimated 50% risk of deficiency of at least one pituitary hormone within 5 years after RT.

Prophylactic cranial RT is used to prevent central nervous system relapse of acute leukemia. Historically, a total dose of 24 Gy has the lowest central nervous system relapse rate but relatively high risk of neurocognitive disabilities and hypothalamic/pituitary dysfunction. In current practice, the prescription radiation dose for prophylactic cranial RT is 18 Gy (2 Gy/fraction). Prophylactic cranial RT is limited to high-risk patients—ALL: age >10 years, and/or T-cell phenotype, especially those with white blood cell count at diagnosis >100 000, and/or cranial nerve palsy; acute myeloid leukemias (AML): monocytic variants or elevated white blood cell count at diagnosis (National Comprehensive Cancer Network, 2018b,e).

DISCUSSION

To our knowledge, there are no published randomized trials aimed to analyze radiation exposure effects on testicular function and its impact on patients' QoL. Despite the well-recognized RT-related risk of infertility, few epidemiologic studies have been performed to better characterize this association or to identify risk factors. Spermatogonia are more sensitive to ionizing radiation than Leydig cells. Therefore, male cancer survivors are more likely to experience infertility than problems with pubertal development or sexual function. Patients should also be informed against having children for at least 3 years after irradiation, to allow elimination of spermatozoa with genetic anomalies. Surely, treatment goals include complete eradication of tumor with optimal function preservation, minimizing RT-related toxicities. With the increasing incidence of cancer survivors, the value of spermatogenesis impairment needs to be assessed. Independently of primary tumor location, data acquisition before treatment, such as sperm count, remains decisive. Patients should be informed about fertility-preserving measures before RT.

CONCLUSION

Adequate medical knowledge and understanding of gonadal function include understanding multiple mechanisms required for regulatory processes of male fertility. Knowledge of radiation therapy mechanisms for its gonadotoxic effects plays an essential role for clinical management, especially for the appropriate patient information. A multidisciplinary team evaluation, including at least surgical oncologists, radiation oncologists, medical oncologists, and reproductive endocrinologist, should be the standard to counsel patients more accurately on both clinical outcomes and risk of possible gonadal toxic consequences.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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