Potential Risk of Radiotherapy on Fertility among Male Cancer Survivors

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Abstract

The potential impact of radiotherapy on male fertility depends mainly on the total radiotherapy dose, tumor location, treatment volume, fractionation schedule, pre-treatment fertility status, and post-treatment survival of type-A spermatogonia.

Very low doses of direct testicular radiation could cause damage to the germinal epithelium. Doses above 0.8Gy result in azoospermia and doses below 0.8Gy give rise to oligospermia, with complete recovery (return to pre-irradiation sperm concentration), within 9–18 months following 1Gy or less, 30 months for 2–3Gy and 5 years or more for doses of 4Gy and above.

Leydig cells are more resistant to damage from radiotherapy than the germinal epithelium. Direct testicular irradiation of 20Gy, in 10 fractions, could increase the LH levels, with a decrease in serum testosterone level.

Scattered testicular irradiation is more common. Unlike the majority of normal tissues, radiation doses to the germinal epithelium of the testis given in fractionated courses cause more gonadal damage than single doses. scattered testicular doses of 0.2-0.7, 0.7-1.2, and more than 1.2Gy can cause transient oligospermia, transient azoospermia and prolonged azoospermia respectively. Leydig cell function is usually preserved with scattered doses up to 20Gy in prepubertal boys and 30Gy in sexually mature men.

If the hypothalamic-pituitary axis falls within the radiation fields, the patient is at risk of developing hypopituitarism with subsequent long-term gonadotrophin deficiency in 30-60% of cases receiving high dose radiation (50-70Gy) as in pituitary tumor and nasopharyngeal carcinoma.

Keywords: Radiotherapy; Oncofertility; Testicular

Introduction

Diagnosis of cancer is a life crisis for any person. Its impact varies with the type of cancer, treatment prospects, physical, emotional, and social resources of the patient. Younger persons face an additional potential loss of reproductive function and the opportunity to have children [1].

Infertility is recognized as the inability to conceive after 1 year or more of unprotected intercourse during the fertile phase of the menstrual cycle. The degree and persistence of gonadal damage following radiotherapy depends on the total dose, treated volume, combination regimens, fractionation schedule, fertility status before treatment and survival of type-A spermatogonia after treatment [2].

Testicular Histology and Physiology

The testis consists of the seminiferous (or germinal) epithelium, arranged in tubules, and endocrine components (testosterone-producing Leydig cells) in the interstitial region between the tubules. The seminiferous tubules contain the germ cells, which consist of stem and differentiating spermatogonia, spermatocytes, spermatids and sperms, and the Sertoli cells, which support and regulate germ cell differentiation [3].

In men, germinal stem cells exist in the testicles from the time of birth, but do not develop into the haploid gametes (spermarche) until the boy reaches puberty. In the prepubertal testis, there is a steady turnover of early germ cells that undergo spontaneous degeneration before the haploid stage is reached, which is probably the reason why the prepubertal testis is very vulnerable to cytotoxic therapy. In the mature testicle, the germinal stem cells undergo continual self-renewal and differentiation into mature spermatozoa within approximately 67 days throughout life. Therefore, there are always germ cells in various developmental stages in the testicles [4].

The loss of germ cells has secondary effects on the hypothalamic-pituitary-gonadal axis. Inhibin secretion by the Sertoli cells declines, and, consequently, serum follicle-stimulating hormone (FSH) levels rise, testicular blood flow is reduced, resulting in less testosterone being distributed in

the circulation. Therefore, levels of luteinizing hormone (LH) increase to maintain constant serum testosterone levels [4].

Direct Testicular Radiation

The testis is one of the most radiosensitive tissues with very low doses of radiation causing germinal epithelium or Leydig cell dysfunction. It is directly irradiated in rare situations, such as testicular tumors, testicular relapse of acute lymphoblastic leukemia (ALL) and testicular exposure in whole body irradiation as in cases of bone marrow transplantation (BMT) [5].

Germinal Epithelium Dysfunction

The more immature cells are more radiosensitive with doses as low as 0.1Gy causing morphological and quantitative changes to spermatogonia. Doses of 2–3Gy result in overt damage to spermatocytes. At doses of 4–6Gy, numbers of spermatozoa are significantly decreased implying damage to spermatids. The decline in sperm count following damage to more immature cells takes 60–70 days with doses of up to 3Gy. Doses above 0.8Gy result in azoospermia and doses below 0.8Gy give rise to oligospermia. A much faster fall in sperm concentration occurs following doses of 4Gy and above because of damage to spermatids [6].

Recovery of spermatogenesis takes place from surviving stem cells (type A spermatogonia) and is dependent on the dose of radiation. Complete recovery, as indicated by a return to pre-irradiation sperm concentrations and germinal cell numbers, takes place within 9–18 months following 1Gy or less, 30 months for 2–3Gy and 5 years or more for doses of 4Gy and above [7].

In many cases, men who regain spermatogenesis after radiotherapy have low sperm counts and motility and increased rate of chromosomal abnormalities. These effects appear to be dose-dependent and persist for up to 3 years after radiotherapy, so that contraception for a period of 1–3 years is recommended after testicular irradiation [3].

Leydig Cell Dysfunction

Leydig cells are more resistant to damage from radiotherapy than the germinal epithelium. Impairment of Leydig cell function following radiotherapy result in biochemical abnormalities in the form of raised LH level with low or normal testosterone level. Significant rises in LH have been demonstrated with single dose radiation of above 0.75Gy. However, no change in testosterone level was seen at these doses, and LH values showed a gradual return to normal levels over 30 months [6].

Higher testicular radiation doses result in more marked Leydig cell insufficiency. Giwercman et al. [8] studied 20 men, previously treated with unilateral orchidectomy for testicular cancer, who received direct testicular irradiation at a dose of 20Gy, in 10 fractions, for carcinoma in situ in the remaining testis. A significant increase in mean LH levels was observed within the first 3 months, with a decrease in mean serum testosterone level [8].

Shalet et al. [9] observed similar results in adults treated with high dose (30Gy) testicular irradiation following unilateral orchidectomy. Serum testosterone levels were significantly reduced and LH levels significantly increased compared with a control group who had undergone unilateral orchidectomy without subsequent radiotherapy.

Scattered Testicular Radiation

Testicular damage is commonly caused by scattered radiation directed to adjacent tissues to the testis. The possible risk of testicular exposure to scattered doses is 0.4 – 18.7 % of the administered dose even with the use of protective gonadal shielding [10]. This may occur in external beam radiotherapy (EBRT) for pelvic organs cancer (as colorectal, bladder and prostate cancer), pelvic lymph nodes (LN) as in cases of lymphoma and seminoma, adjacent soft tissue tumors (as soft tissue sarcoma in thigh), adjacent bony cancers (as metastases in pelvic bone), or rarely in brachytherapy for prostate cancer.

Germinal Epithelium Dysfunction

The fractionation regimen potentially affects the radiation-induced testicular dysfunction. Whereas in all other organ systems, fractionation of radiation reduces the damage, radiation doses to the germinal epithelium of the testis given in long fractionated courses cause more gonadal damage than single doses [11].

Testicular doses of less than 0.2Gy had no significant effect on sperm counts, whilst doses between 0.2 and 0.7 Gy caused a transient reduction in sperm concentration, with a return to normal values within 12–24 months. Doses more than 0.7 Gy cause transient azoospermia and doses more than 1.2 Gy cause prolonged azoospermia [6].

Assessment of semen quality parameters in four men treated for prostate cancer with brachytherapy revealed no change in sperm concentration or motility at the 6-month post-treatment, and 3 of the 4 men were able to initiate pregnancies [12]. The scattered radiation dose with brachytherapy is typically less than 0.2 Gy.

Kinsella et al. [13] published data concerning 17 patients who had received low-dose scattered irradiation during treatment of Hodgkin disease (HD) with follow up from 3 to 7 years after completion of radiation therapy. Testicular doses between 0.2 and 0.7 Gy caused a transient dose dependent reduction in sperm concentration, with a return to normal values within 12–24 months.

In a study of 10 patients who received a testicular dose of radiation of 1.2–3 Gy, in 14–26 fractions, during inverted Y-inguinal field irradiation for HD. All patients were azoospermic

following treatment and recovery was not seen in a single patient despite follow-up of over 15 months in four patients and up to 40 months in one [14]. An update of these data revealed no recovery of spermatogenesis in patients receiving doses of 1.4–2.6 Gy after 17–43 months follow up, but a return of fertility in the two patients with testicular radiation doses of 1.2 Gy, suggesting that this may represent a threshold for permanent testicular damage [15].

Leydig Cell Dysfunction

Significant rises in LH with no change in testosterone level have been demonstrated with fractionated dose radiation of above 2Gy. However, fractionated radiation appears to produce tubular damage similar to that seen with single doses. Leydig cell function is usually preserved with doses up to 20Gy in prepubertal boys and 30Gy in sexually mature men [3].

Hypothalamo-Pituitary Radiation

Cranial radiation is used to manage pituitary tumours, skull base and brain tumours, head and neck cancer, and for the prophylaxis of intracranial disease in patients with ALL. If the hypothalamic-pituitary axis falls within the radiation fields, the patient is at risk of developing hypopituitarism. The effect of radiation is determined by the dose and the time that has elapsed since treatment. Classically, growth hormone (GH) is the most sensitive of the anterior pituitary hormones to irradiation, followed by gonadotrophins [16].

Gonadotrophin deficiency occurs infrequently and is usually a long-term complication following a minimum radiation dose of 30Gy. A much higher incidence of gonadotrophin deficiency (30-60% after 10 years) occur after more intensive irradiation (>70Gy) used for nasopharyngeal carcinomas and tumours of the skull base and following conventional irradiation (50 Gy) for pituitary tumours [17].

Radiation-induced anterior pituitary hormone deficiencies are irreversible and progressive. Regular testing is mandatory to ensure early diagnosis and early hormone replacement therapy in adults to preserve sexual function and improve the quality of life [17].

Discussion

In the past, the primary goal of cancer therapy (i.e., survival) tended to overshadow survivorship considerations. However, with recent advances in oncology, survival rates are increasing, and therefore, issues affecting long-term cancer survivors especially fertility preservation become more important and more widely recognized for better quality of life for cancer survivors.

Radiation oncologists have the responsibility to inform patients about the potential risk of radiotherapy on fertility and methods of fertility preservation before the start of cancer treatment. Moreover, in cancer patients who are interested in maintaining their fertility, every possible effort should be taken to avoid potential impact of radiotherapy on gonadal function, and assessment of pre-treatment fertility is important for selection of the optimum method for fertility preservation.

Conclusion

The testis is one of the most radiosensitive tissues. Direct testicular irradiation (such as testicular exposure in whole body irradiation as in cases of BMT), and scattered radiation (directed to surrounding primary or metastatic cancer) may cause damage to both germinal epithelium and Leydig cell function. The degree and persistence of this damage following radiotherapy depends on total dose, irradiated volume, combination regimens, fractionation schedule, fertility status before treatment and survival of type-A spermatogonia after treatment. Furthermore, late gonadotrophin deficiency may occur as a result of hypothalamo-pituitary irradiation.

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