Chapter 3

The Effect of Radiotherapy on the Human Reproductive System

Tom W Kelsey, Chia-Ho Hua, and W Hamish B Wallace

Introduction

Cancer in childhood is rare. The most recent SEER Cancer Statistics Review, released in April 2018 and covering 2011–2015, shows that for ages 0–14 the incidence of all cancer sites was 16.4 per 100,000 children, with mortality 2.1 per 100,000. Five-year relative survival for the same age group was 83.8% for years 2008–2014 [1]. (Rates from the European Cancer Information System are similar but are currently available only to 2012.) As of 2015, 1 in 750 of the adult population of the United States was a long-term survivor of childhood cancer [1, 2]. Cancer is more common after puberty, with incidence rising from 12.9 for ages 5–9 to 23.3 for ages 15–19 in the United States for years 2011–2015 [1], and many of these patients will be cured by combination treatment, with surgery, chemotherapy, and radiotherapy. Long-term survivors are nevertheless at risk of developing a number of late sequelae [3], including impaired fertility, adverse pregnancy outcomes, and health problems in offspring [4–6]. Loss of fertility is one of the most devastating consequences of radiotherapy for these young patients, who, having overcome their disease, have expectations of a normal reproductive life.

Normal Ovarian Development and Follicular Depletion

Current understanding of the human ovarian reserve is that the ovary establishes several hundred thousand nongrowing follicles (NGFs) by followed by a decline in the population by menopause, when approximately 800 remain at an average age of 50–51 [7]. With approximately 450 ovulatory monthly cycles in the normal human reproductive life span, this progressive decline in NGF numbers is attributed to follicle death by apoptosis. The Wallace–Kelsey model of human ovarian reserve from conception to menopause best fits the combined histological evidence that has been described [8, 9] and validated using external data [7] (Figure 3.1). This model allows us to estimate the number of NGFs present in the ovary at any given age, and it suggests that 81% of the variance in NGF populations is due to age alone. Further analysis demonstrates that 95% of the NGF population variation is due to age alone for ages up to 25. The remaining 5% is due to factors other than age, e.g. smoking, body mass index (BMI), parity, and stress. We can speculate that as chronological age increases, factors other than age become more important in determining the rate at which NGFs are lost through apoptosis.

There is speculation that this widely held tenet of mammalian ovarian function may require revision. A report in 2004 suggested the presence of germ stem cells in the adult mouse ovary [10], with two subsequent reports by the same group suggesting the ability of bone marrow–derived cells to give rise to new immature oocytes [11, 12]. More recently, another group has identified the presence of proliferative and culturable female germline stem cells in newborn and adult mouse ovaries [13]. Strikingly, when these cells (transgenically labeled) were injected into a chemotherapy-treated ovary, they became enclosed within follicles and offspring bearing the transgene were produced. These data provide a basis for reevaluating the regenerative capacity of the mammalian ovary and new approaches for overcoming fertility loss.

While the emerging evidence thus appears to provide evidence in support of the existence of germ stem cells within the adult mammalian ovary, there is no robust evidence to date that these cells contribute to follicle formation leading to viable eggs [14]. There is evidence that significant NGF population regeneration can occur in extreme situations in the human ovary [15], but the Wallace–Kelsey model of ovarian follicle decline provides no
supporting evidence of neo-oogenesis in normal human physiological aging.

**Radiation and the Hypothalamic–Pituitary–Ovarian Axis**

The ovaries may be damaged following total body, abdominal, or pelvic irradiation [16], and the extent of the damage is related to the radiation dose, fractionation schedule, and age at the time of treatment [17–19]. The human oocyte is sensitive to radiation, with an estimated LD$_{50}$ of less than 2 Gy [20]. This is the lethal dose to destroy 50% of NGFs present in the ovary. The number of NGFs present at the time of treatment, together with the dose received by the ovaries, will determine the “fertile window” and influence the age of premature ovarian insufficiency (POI). Long-term ovarian failure has been reported in 90% of patients after total body irradiation (TBI) (10.00–15.75 Gy) and in 97% of females treated with total abdominal irradiation (20–30 Gy) during childhood [21–23]. Our understanding of the LD$_{50}$ of the human oocyte has made it possible to estimate the age at which POI may occur (Figure 3.2). Furthermore, we have estimated the sterilizing dose following any given dose of radiotherapy at any given age, based upon the Wallace–Kelsey model for NGF decline (Figure 3.3) [24, 25]. This will help clinicians provide accurate information when counseling women about fertility following treatment for childhood cancer. Gonadotropin deficiency following high-dose cranial irradiation (more than 24 Gy in the treatment of brain tumors) manifests as delayed puberty or absent menses and can be treated by hormone replacement therapy. Interestingly, early puberty is often reported in females with cranial radiation doses of less than 24 Gy [26]. However, we have shown a subtle decline in hypothalamic–pituitary–ovarian function following low-dose cranial radiotherapy (18–24 Gy). This is characterized by decreased luteinizing hormone (LH) secretion throughout the cycle, an attenuated LH surge, and short luteal phases [27], which may compromise reproductive function. Cranial radiotherapy is also associated with increased risk of oligomenorrhea, reduced estradiol, and increased prolactin in survivors [28, 29]. Recent data confirm lower fertility in childhood cancer survivors treated with either hypothalamic/pituitary irradiation more than 22 Gy or ovarian/uterine irradiation more than 5 Gy [30, 31]. Nowadays, the most commonly used fertility preservation measure is...
the surgical transposition of the ovaries outside the irradiation field before the initiation of pelvic radiation in adults with gynecological malignancies [24]. This approach may be considered for patients not planning to receive high-dose systemic chemotherapy. Surgery is effective at protecting the ovaries from direct irradiation damage, but fertility may be affected by scatter radiation, by damage to the ovarian vasculature during surgery, or by torsion of the transposed ovary. To avoid this, ovarian tissue cryopreservation may be considered at the same time as oophoropexy.

**Radiation and the Uterus**

The uterus is at significant risk of damage following abdominal irradiation, pelvic irradiation, or TBI in a dose- and age-dependent manner [32]. Uterine function may be impaired following radiation doses of 14–30 Gy as a consequence of disruption to uterine vasculature and musculature elasticity [23]. Even lower doses of irradiation, as in TBI, have been reported to cause impaired growth and blood flow [33]. The clinical consequences are increased risk of miscarriage and premature delivery [22]. A uterine contribution to an inability to conceive following radiotherapy is not clear but seems likely.

A small number of studies have been reported that attempted to improve uterine function in survivors of cancer with POI. In young adult women previously treated with TBI, physiological sex steroid replacement therapy improves uterine function (blood flow and endometrial thickness) and may potentially allow them to benefit from assisted reproductive technologies [33]. Larsen et al. studied uterine volume in 100 childhood cancer survivors and assessed uterine response to high-dose estrogen replacement therapy in three patients with ovarian failure and reduced uterine volume following abdominal and/or pelvic irradiation [34]. There was no significant difference in uterine volume, endometrial thickness, or uterine artery blood flow following sex steroid treatment, suggesting that higher doses of pelvic radiation cause greater damage than lower doses (as in TBI), and that this damage may be irreversible. While data are sparse for the childhood case, there is good evidence that adult women treated

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**Figure 3.2** Predicted age at POI for known age and known dose to the ovary. A 5-year-old with average NGF population treated with 1 Gy has predicted POI at age 42, losing about 8 years of reproductive life span; the same child treated with 12 Gy has predicted POI at age 12, indicating consideration of the use of fertility preservation techniques. The predictions are modifications of existing predictions [25] adapted to use the Wallace–Kelsey model of NGF population in healthy females [9]
with radiotherapy to the abdomen are at high risk of uterine dysfunction leading to miscarriage, premature delivery, low birth weight, and placental abnormalities [35]. There is no current evidence that the child uterus is inherently better protected from the effects of radiotherapy.

**Testicular Function**

In males, testicular damage can involve the somatic cells of the testis (Sertoli, peritubular myoid, and Leydig cells) or the germ cells. Spermatogonia are generally more radiosensitive and prone to undergo apoptosis than somatic cells [36]. Sertoli cells are responsible for nurturing developing germ cells, and Leydig cells produce testosterone. Recent data have revealed the essential contribution of peritubular myoid cells in mediating the effect of testosterone on spermatogenesis. Gonadal damage in males treated for cancer can result from either systemic chemotherapy or radiotherapy to a field that includes the testes. Cytotoxic treatment targets rapidly dividing cells, and it is therefore not surprising that spermatogenesis is impaired after treatment for cancer. The exact mechanism of this damage is uncertain, but it appears to be linked to depletion of the proliferating germ cell pool and associated stem spermatogonial cells. Although the prepubertal testis does not complete spermatogenesis and produce mature spermatozoa, cytotoxic treatment given to prepubertal boys may impair future fertility. Importantly, the prepubertal testis is susceptible to cytotoxic damage.

**Radiotherapy to the Testis**

In males, radiation doses as low as 0.1–1.2 Gy can impair spermatogenesis, with doses over 4 Gy causing permanent azoospermia. The somatic cells of the testis are more resistant than the germ cells, and Leydig cell dysfunction is not observed until 20 Gy in prepubertal boys and 30 Gy in sexually mature males [37].

Within the pediatric and adolescent age group, testicular damage occurs with direct irradiation to the testes, for example in the management of

![Effective and mean sterilizing doses](image-url)
leukemia [38]. In patients with leukemic infiltration of their testes, radiation doses of 24 Gy are used, and this results in permanent azoospermia [39]. Total body irradiation applied as conditioning treatment before bone marrow transplantation (BMT) also irradiates the testes. However, the effects of this can be difficult to elucidate as it is usually given concurrently with alkylating agents, but doses of 9–10 Gy have produced gonadal dysfunction [40].

There have been many advances in technologies underpinning the delivery of radiotherapy, including intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and proton therapy (PT). There are case reports that suggest, for example, that IMRT can lead to a reduction in acute effects [41], and there is initial evidence that VMAT also reduces acute effects with PT reducing the risk of secondary malignancies in younger patients [42]. However, robust and large-scale clinical trial evidence is lacking in this area, and hence accurate survey and meta-analysis studies are not yet possible. More data are needed before the precise effects of modern radiotherapy to the testis can be reliably estimated.

Summary

While many children and adults diagnosed with cancer can now realistically hope for long-term survival, they must often live with the consequences of their treatment. Infertility is one of the most devastating adverse effects of cancer treatment in this patient group. Radiotherapy can significantly impair future fertility, and treatments for certain cancers can be sterilizing [24]. Although predicting individual fertility following treatment is challenging due to the lack of biomarkers in children that indicate future fertility, we can both calculate sterilizing doses and predict age at POI on the assumption that the patient had close to average untreated fertility potential. Nevertheless, further epidemiological studies and investigation of markers indicating gonadal damage may be of use to our patients.

References


Introduction


