Long-Term Effects of Childhood Cancer Therapy on Growth and Fertility

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Introduction

Survival rates for most childhood malignancies have improved remarkably over the past decade with an overall survival rate for England and Wales for children less than 15 years of age quoted as 75 % (1993 and 1997) [1]. This improvement has been attributed to advances in treatment, better supportive care, and centralizing treatment in specialized centers with entry of patients into clinical trials [2, 3]. Approximately 1 in every 640 individuals in the US between the ages of 20 and 39 years is a survivor of childhood cancer [4]. Long-term survival rates vary with cancer type, demographic characteristics such as age, gender and race, tumor characteristics such as location and extent of disease, morphology, and genetic alterations.

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Attempts to improve survival in poor prognosis groups have led to therapeutic protocols that use more intensive therapy increasing the probability of treatment complications and long-term adverse outcomes in survivors.

With the improvement in survival rates, focus has shifted to minimizing the late effects associated with intense cancer therapy. For example, in the treatment of Wilms' tumor and Hodgkin's lymphoma, survival rates have been maintained despite a reduction in the overall intensity of treatment used for most patients. Reports concerning the frequency and severity of late effects of treatment vary widely and accurate estimates of the incidence and severity are difficult to define. Previous cohort studies have estimated that between 33 and 75 % of adult survivors experience problems [5, 6].

The Childhood Cancer Survivor Study (CCSS) – a large cohort study in the US – found that more than 40 % of survivors of childhood cancer report long-term adverse effects in specific areas of health. Patients treated for soft-tissue sarcomas were identified as among those with the highest risk of such problems [7]. The cohort demonstrated a 10.8-fold excess in overall mortality. Recurrence of the original cancer was the leading cause of death among 5-year survivors, accounting for 67 % of deaths [8]. Nevertheless, the overall proportion of survivors affected is currently relatively small [9].

A recent study looking at the barriers to follow-up care of survivors in the US and the UK found that the majority of survivors are not receiving recommended health care. Key barriers identified included a general lack of awareness of late effects by survivors, a lack of capacity for survivor care within cancer institutions, primary care physicians being unfamiliar with the health care needs of survivors, and a general lack of communication between survivors, cancer centers, and primary care physicians. Strategies to overcome these barriers are being investigated [10].

The late effects of cancer therapy may be subdivided into:

1. Impairment of endocrine function
2. Abnormal growth
3. Sub-fertility

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4. Cardiac and renal complications
5. Pulmonary fibrosis and restrictive lung disease
6. Secondary malignancies
7. Neurological impairment
8. Cognitive decline and psychological effects
9. Reduced quality of life
10. Early death

The risk of late effects are directly related to the treatment received rather than the underlying pathological diagnosis. Their anticipation and detection are essential as they may be amenable to prevention and treatment [11]. The following chapter focuses on impaired endocrine function, abnormal gonadal sub-fertility, and secondary malignancy.

Endocrine Late Effects

Endocrine disturbances have been documented in 20–50 % of childhood cancer survivors resulting from the underlying condition, the nature, and cumulative dosage of cytotoxic chemotherapy, and the dose and schedule of irradiation [12].

Patients with central nervous system tumors are at increased risk with the prevalence of an endocrinopathy documented in more than 70 %. This is often as a result of radiation injury to the hypothalamus, thyroid, or gonads [13].

Endocrine abnormalities often impose a negative impact on growth, body image, sexual function, and quality of life.

The range of endocrine complications includes gonadal damage, thyroid disorders, and dysfunction of the hypothalamic-pituitary axis. Neuroendocrine abnormalities may occur following external radiation for a number of tumors when the hypothalamic-pituitary axis falls within the fields of radiation. Deficiency of one or more anterior pituitary hormones, most commonly growth hormone, has been demonstrated after therapeutic cranial irradiation for primary brain tumors, prophylactic cranial irradiation for acute lymphoblastic lymphoma (ALL), and total body irradiation (TBI) as conditional treatment before bone marrow transplant (BMT).

Direct Radiation Damage to the Hypothalamic Pituitary Axis (HPA)

Following cranial radiotherapy patients are at risk of: growth hormone deficiency, an attenuated pubertal growth spurt, early or delayed puberty, and multiple pituitary hormone deficiencies.

The impact of radiation is dependent on the total dose, fraction size, number of fractions, and the duration of therapy (see Chap. 8). Lower radiation doses are associated with isolated growth hormone deficiency while higher doses may cause panhypopituitarism. A tissue's radiosensitivity is directly proportional to its mitotic activity and inversely proportional to its cellular differentiation. Radiation effects on slowly proliferating tissues such as the brain only become obvious with time.

The pathophysiology of radiation-induced damage has not been completely elucidated. Direct neuronal injury has been proposed to be the main mechanism rather than reduced cerebral blood flow.

The hypothalamus has been shown to be more radiosensitive than the pituitary and is damaged by lower doses of cranial radiation. This is suggested by suppression of insulin-mediated and spontaneous growth hormone secretion following cranial irradiation but preservation of the growth hormone response to hypothalamic-releasing factors [14–16]. Doses of less than 50 Gray (Gy) affect the hypothalamus with subsequent growth hormone deficiency. Higher doses used in the treatment of nasopharyngeal carcinomas and tumors of the base of the skull may cause direct anterior pituitary damage leading to early and multiple pituitary hormone deficits [17–20]. The pituitary hormones are generally lost in the following order: growth hormone, leutenizing hormone/follicle stimulating hormone, ACTH, and thyroid stimulating hormone [21].

Hypothalamic-pituitary dysfunction secondary to radiation is also time dependent [22, 23]. The progressive nature of the hormonal deficits following radiation damage to the hypothalamic-pituitary axis can be attributed to the delayed effects of radiotherapy on the axis or the development of secondary pituitary atrophy following a lack of hypothalamic releasing factors [15, 24, 25].

An additional risk factor is the age of the child at the time of radiotherapy. Younger children have been shown to be more sensitive than older children and adults to radiation-induced damage of the hypothalamic-pituitary axis [26].

Growth Hormone Deficiency

Growth hormone deficiency is usually the first and frequently the only manifestation of neuroendocrine dysfunction following cranial irradiation. It is classically characterized by diminished spontaneous (physiological) growth hormone secretion in the presence of preserved peak responses to provocative tests although the latter will also become abnormal [27].

Growth hormone is usually secreted in an intermittent pulsatile pattern with the majority of secretory bursts during sleep. Spontaneous growth hormone secretion is determined by the number of pulses, pulse amplitude, and the total 24-h integrated GH concentration derived from sampling every 20 min over a 24-h period. The reported frequency of radiation-induced growth hormone deficiency reported will be influenced by the physiological or pharmacological test used. Most prospective studies have used provocative testing and so the true extent of growth hormone deficiency may be underestimated.

The severity and onset of GH deficiency are dose dependent and the incidence increases with time elapsed after irradiation. Virtually all children treated with cranial irradiation doses in excess of 30 Gy will be growth hormone deficient 2 years after treatment. Low-dose cranial irradiation (18–24 Gy) used as CNS-directed therapy in ALL may lead to isolated growth hormone deficiency [28–32]. Isolated growth hormone deficiency has also been documented following total body irradiation with doses as low as 10 Gy [31, 33].

Short stature after cancer treatment has been well documented, particularly following cranial and craniospinal irradiation [34].

The effect of final height is more profound with treatment at a younger age [35].

Outcome in adult height and sitting height is poor in children surviving medulloblastoma due to craniospinal irradiation (CSRT) and chemotherapy. A study at the Children's Hospital of Philadelphia evaluated adult height and sitting height in 51 medulloblastoma patients stratified into four groups: G1, GH-deficient (GHD) patients treated with 23–39 Gy craniospinal radiation but not treated with GH [recombinant human (rh)GH]; G2, patients treated with rhGH; G3, patients who were not GHD; and G4, patients treated with 18 Gy CSRT and rhGH [36].

Sitting height. The sitting heights were available for 35 patients (two in group G1, 26 in group G2, two in group G3, and five in group G4), and the results are shown in Fig. 35.1. Compared with the general population, the sitting heights were impaired in all of the children (total group mean SDS, −2.96; $P<0.0001$). In groups G2 and G4, the mean sitting height SDS were -3.3 ± 1.43 and -1.62 ± 1.16, respectively. Similar to the comparison of standing adult height outcome, the sitting height of group G4 was significantly taller than that of group G2 ($P=0.021$). Therefore, higher dosing of rhGH and reduced CSRT doses improved sitting height, although sitting height SDS was still short in comparison to the normal population. Although limited to two patients, the sitting height SDS for group G3 (non-GHD patients) was −2.0. The adult stature in the entire group G3 was shorter than midparental height and not different from group G2, whose spinal growth was impaired despite rhGH treatment. These observations suggest that despite GH sufficiency in group G3, the loss of stature in comparison to midparental height is due to CSRT injury to spinal growth.

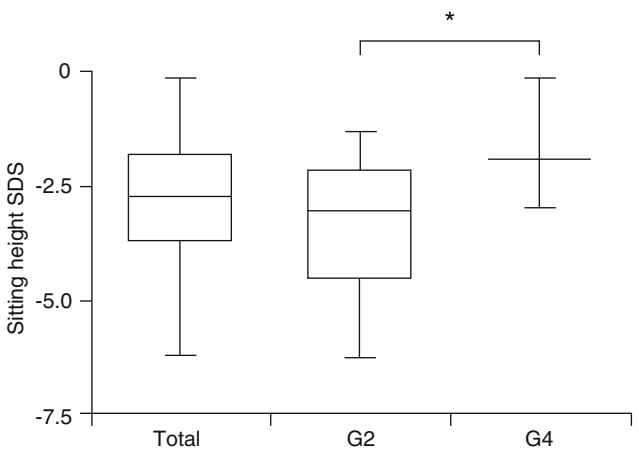

Fig. 35.1 Sitting height outcome. Sitting height SDS in total patients (n=35), in group G2 (n=26), and in group G4 (n=5). The *box and whiskers plot* represents +2 SD and −2 SD (*error bars*), the 25 and 75 % (*box*), and the mean (*horizontal bar*). *, P=0.021

Early diagnosis and treatment is important as response to growth hormone is poorer than in idiopathic growth hormone deficiency especially in children who have received spinal radiotherapy [37].

Growth hormone deficiency is also believed to cause a reduced lean body mass and increased fat mass, metabolic abnormalities including an adverse lipid profile and glucose intolerance, reduction in bone mineral density and impaired quality of life [38–41]. Insulin resistance, impaired glucose tolerance or even type 2 diabetes mellitus have been recently reported in children who have received total body irradiation.

It is well accepted to treat documented growth hormone deficiency in childhood with replacement doses of recombinant human growth hormone. Diagnosis of GH insufficiency can sometimes be problematic at times, however, especially in the early postirradiation period [25]. Measurements of peak growth hormone secretion will miss deficits confined to qualitative, subtle differences in pulsality (neurosecretory dysfunction) [42] and those in whom there is an inability to augment pubertal growth hormone adequately [43, 44]. Measurements of insulin-like growth factors and their binding proteins are unreliable indicators of growth hormone secretion in this situation [45]. A high index of suspicion for growth hormone deficiency is therefore needed following irradiation.

Growth in children is a sensitive marker of growth hormone status. The presence of significant growth deviation over a 1-year period (growth velocity below the 25th percentile) or a drop in height of greater than or equal to one standard deviation is highly suggestive of clinically significant growth hormone deficiency. However, obesity can result in preservation of a normal height velocity with a worsening height prognosis, as can precocious puberty, another common consequence of cranial irradiation in young girls.

Growth monitoring is an essential part of followup of children who have received cranial irradiation as part of treatment. Sitting and standing heights should be measured every 3–6 months. The sitting height is obtained by using a sitting height stadiometer and is particularly important in those who received spinal irradiation. The impact of spinal irradiation on spinal growth is such that greater auxological emphasis must be placed on the leg length changes rather

than the total height. Spinal irradiation will particularly impair late pubertal growth.

With biochemical or clinical evidence of growth hormone deficiency (height velocity <5 cm/year) treatment is usually commenced with recombinant growth hormone as a daily subcutaneous injection. Due to the evolving nature of growth hormone insufficiency it is important that treatment begin as soon as possible.

Growth hormone is potentially mitogenic and concerns have been raised about its use in cancer survivors. However, long-term studies of patients treated with physiological replacement doses of recombinant growth hormone have failed to demonstrate any increased risk of tumor recurrence or increased frequency of second tumors although continued surveillance is needed [46–48].

However, most centers do not advocate introducing therapy within the first 2 years after cancer treatment as this is the time of highest relapse.

Abnormalities of Gonadotrophin Secretion

Gonadotrophin deficiency. Disruption of gonadotrophin secretion generally occurs at radiation doses above 40 Gy [49, 50]. Deficiencies of both follicle-stimulating hormone (FSH) and leutenizing hormone (LH) have been documented. The clinical picture shows considerable variability from subclinical abnormalities detectable only by gonadotrophin releasing hormone (GnRH) testing to a significant reduction in circulating sex hormones levels and delayed puberty. Gonadotrophin deficiency is generally a reflection of hypothalamic dysfunction [51]. It is therefore possible to restore gonadal function and fertility by use of exogenous GnRH replacement therapy. Because of differential sensitivities of testicular and ovarian cell types to cytotoxic chemotherapy or radiotherapy, spontaneous progression through puberty is no guarantee of subsequent fertility.

Precocious puberty. The effect of cerebral irradiation on the hypothalamic-pituitary-gonadal axis (HPGA) is dose dependent. Whereas higher doses cause a deficiency, lower doses can cause premature activation leading to early or precocious puberty. The mechanism for early puberty following irradiation is believed to be secondary to disinhibition of cortical influences on the hypothalamus.

The definition of precocious puberty is the onset of puberty before the age of 8 years in girls and 9 years in boys. This can be distinguished from early puberty, which means onset between 8 and 10 years in girls and 9 and 11 years in boys.

Low-dose cranial irradiation (18–24 Gy) used in central nervous system prophylaxis for ALL has been associated with a higher incidence of early or precocious puberty, an effect seen mainly in girls. No increased frequency of precocious puberty over the normal population has been documented in male ALL survivors [52, 53]. This may reflect sex differences in the control of the onset of puberty (Fig. 35.2).

Ogilvy-Stuart et al. demonstrated that in 46 GHD children previously irradiated for brain tumors (25–47.5 Gy) the onset of puberty occurred at an early age in both sexes and there was a significant linear association between age at irradiation and age at onset of puberty, i.e., the younger the age at irradiation the earlier the onset of puberty [54].

The consequence of early puberty is that of a premature pubertal growth spurt followed by early epiphyseal fusion and a reduction in final adult height.

Children with precocious puberty are also usually growth hormone deficient. Both problems contribute to a poorer prognosis with respect to final height potential by reducing peak height velocity [55], and the time over which childhood growth can take place.

Height loss after radiation has also been shown to be disproportionate with a significant portion being a loss of sitting height [56]. Direct radiation to the spine further disrupts spinal growth with only a partial response to growth hormone therapy, which mainly stimulates long bone growth. Thus, the younger the child at the time of irradiation, the greater the risk of subsequent skeletal disproportion [57].

Close monitoring of these patients is essential after treatment with respect to growth and puberty. Six-monthly clinical assessment of pubertal status is needed as well as auxology measurements. Growth hormone and gonadotrophin secretion and bone age should be done as indicated.

Suppressing pubertal progression and delaying skeletal fusion with GnRH analogues and treatment with growth hormone gives the best prognosis in terms of height potential although the final height achieved is still lower than target [58, 59].

Hypothyroidism. The risk of hypothyroidism following treatment for childhood cancer is related to radiation field, dose, and adjuvant chemotherapy. Chemotherapy alone has not been shown to cause hypothyroidism [60]. Thyroid

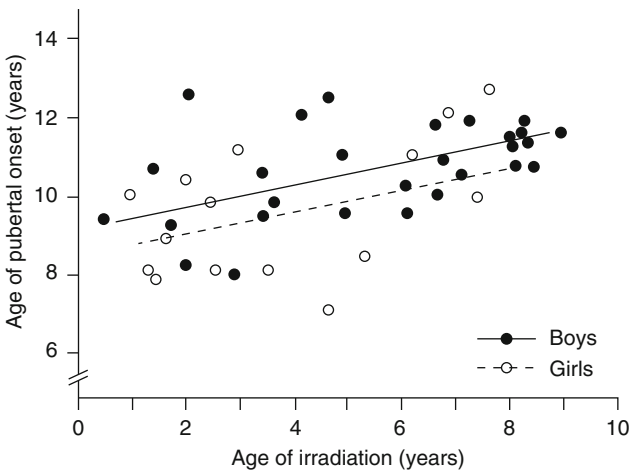

Fig. 35.2 Age at onset of puberty compared with age at irradiation in children treated for brain tumors [54]

dysfunction may occur due to central thyroid stimulating hormone (TSH) deficiency following cranial irradiation, primary end organ damage due to direct irradiation to the gland or a combination of both, for example following craniospinal irradiation or TBI.

TSH deficiency. The hypothalamic pituitary axis and production of TSH appears least vulnerable to radiation damage. The risk of TSH deficiency from cranial irradiation is dose [61] and time related [62] as for other pituitary hormone deficiencies. However, the risk is low. In a survey of 71 children who had been treated with cranial irradiation, 6 % showed evidence of TSH deficiency at a median of 12 years follow up [62]. The risk of TSH deficiency occurs at doses >50 Gy.

End organ damage. The thyroid gland is sensitive to direct irradiation. Hypothyroidism, thyroid nodules, and hyperthyroidism have all been described. Primary hypothyroidism is the most common consequence of direct radiation injury and occurs frequently at doses that exceed 26 Gy. In a population of 1787 adults and children who received neck irradiation for Hodgkin's disease the risk for developing hypothyroidism was 47 % at 27 years [63] and approximately half the patients with thyroid dysfunction were diagnosed in the first 5 years. The presence of thyroid nodules after radiation is very common. The percentage reported with thyroid cancer varies from 14 to 40 %, the risk increasing with time since treatment, and those treated at a young age most at risk [64, 65].

Combined central and primary hypothyroidism. The commonest cause for thyroid dysfunction now seen by the pediatric endocrinologist is due to a combined effect of primary and central dysfunction due to cranial and direct irradiation. The patients most at risk are those who have received craniospinal irradiation for brain tumors. In one study [66] of 119 patients who had been treated as children with craniospinal irradiation, raised TSH levels were seen in 22 % who had received craniospinal irradiation alone and 69 % who had received craniospinal irradiation and chemotherapy. The overall prevalence of primary dysfunction was 28 % compared to 3 % for central dysfunction. In a more recent study evaluating thyroid function in children treated with craniospinal irradiation (36 vs. 23 Gy) with or without chemotherapy, those treated with the lower dose of radiotherapy who also received chemotherapy, and those treated at a younger age, had the highest incidence of hypothyroidism (100 % for those aged <5 years) [67]. There is a risk of primary hypothyroidism after TBI, which may be compounded by a central decline in TSH production. After fractionated TBI the risk is reduced – only 16 % in one study had features of thyroid dysfunction at long-term follow-up [68].

Evaluation of thyroid dysfunction. Biochemical diagnosis of thyroid dysfunction is based on basal thyroid function tests – TSH and free thyroxine (FT4) level. Detection of primary hypothyroidism is relatively easy with rising TSH levels and declining FT4 levels. If there is evidence of increasing TSH levels with persisting normal FT4 levels (compensated primary hypothyroidism), treatment should be started prior to overt hypothyroidism as persistently elevated TSH levels are thought to increase the risk of thyroid cancer.

The diagnosis of central or combined hypothyroidism can be notoriously difficult. Treatment should be considered for individuals at risk who have a low normal or subnormal FT4 level, especially if declining over time, with low, normal, or mildly raised TSH levels, with or without symptoms [69].

Fertility

Direct damage to the gonads may occur due to radiotherapy involving the spine or pelvis or by systemic chemotherapy. This may lead to subfertility or infertility in both males and females.

The Effects of Chemotherapy

The extent of cytotoxic damage to the gonads is dependent on the agent used, the age and sex of the patient, and the dose received. Toxic chemotherapeutic agents include alkylating agents such as the nitrogen mustard compounds (cyclophosphamide, ifosfamide, and melphalan); nitrosoureas (carmustine, CCNU), busulphan, thiotepa, and cisplatin; procarbazine, and etoposide. Alkylating agents act as inhibitors of DNA synthesis and damage those cells with rapid mitotic activity such as the germinal cells of the testicular tubules leading to severe germinal aplasia and oligosper- mia/azoospermia in adulthood [70].

The germinal epithelium is more sensitive to the detrimental effects of chemotherapy than the somatic cells. This means that following gonadotoxic chemotherapy, male patients may become oligospermic or azoospermic but testosterone production by the Leydig cells is unaffected so secondary sexual characteristics develop normally [71, 72]. However, with higher doses of chemotherapy, Leydig cell dysfunction also occurs [73].

Treatment of Hodgkin's lymphoma has traditionally been associated with a high rate of azoospermia due to the use of procarbazine and alkylating agents such as chlorambucil and cyclophosphamide. Newer hybrid regimens have been designed with the above agents being alternated with anthracycline agents resulting in significantly less gonadotoxicity [74].

Ovarian dysfunction has also been documented after chemotherapy with a significant number seen following treatment of Hodgkin's lymphoma [62–65]. Causative agents include procarbazine and the alkylating agents. These effects are age and dose related [75–79].

The Effects of Radiotherapy

The degree of radiation damage depends on the field of treatment, total dose, and fractionation schedule [80–83]. In males, doses as low as 0.1–1.2 Gy can cause Sertoli cell damage with impaired spermatogenesis and with doses greater than 4 Gy leading to permanent infertility [80–82]. Germ cells are more susceptible to radiation damage than somatic cells. Leydig cells responsible for testosterone production in males, are relatively radio-resistant, and are damaged at doses of around 20 Gy in prepubertal boys and up to 30 Gy in sexually mature males [84, 85].

In females, total body, abdominal, or pelvic irradiation may lead to ovarian and uterine damage, the extent being dependent on the radiation dose, fractionation schedule, and age at time of treatment.

The human ovary contains a fixed pool of primordial oocytes maximal at 5 months of gestation, which declines with increasing age in a biexponential manner, eventually leading to menopause at an average of 50–51 years. At this age, approximately 1000 oocytes remain. The number of primordial oocytes present at the time of treatment, together with the dose of radiotherapy received by the ovaries, determines the fertile "window" and the age at which premature ovarian failure occurs [86].

The radiosensitivity of the human oocyte has recently been estimated to be less than 2 Gy [87]. The Faddy-Gosden equation

$$dy / d\text{ay}\, x = -y\left[0.0595 + 3,716 / \left(11,780 + y\right)\right]$$

where x denotes age, $y(x)$ is population at age x, with initial value $y(0) = 701{,}200$; the initial value denotes population at birth provides a mathematical model for calculating the rate of natural follicular decline in women.

A recent study has looked at predicting the age of ovarian failure after radiation based on data obtained from young women who developed ovarian failure after total body irradiation.

It is not possible to diagnose ovarian failure clinically, biochemically, or radiologically before the onset of puberty. The above mathematical model may be useful in predicting the onset of ovarian failure in women receiving radiotherapy [86] (Table 35.1).

Acute ovarian failure, defined as the loss of ovarian function within 5 years of diagnosis, is known to develop in a subset of survivors of pediatric and adolescent cancers. A cohort study with female participants >18 years from the CCSS was conducted looking at incidence and risk factors. Acute ovarian failure developed in small subset (6.3 % of cases) especially in those treated with at least 1000-cGy radiation to the ovaries [88].

Abdominal and pelvic irradiation are used in the treatment of a variety of malignancies such as Wilms' tumor, pelvic rhabdomyosarcoma, and Ewing's sarcoma of the pelvis or spine with dose and volume dependent upon the diagnosis and tumor size. The prevalence of ovarian failure following whole abdominal radiotherapy has been unacceptably high with the majority of patients failing to complete pubertal development without hormone replacement therapy. The introduction of flank irradiation in 1972 has resulted in significantly less pubertal failure but the onset of a premature menopause may occur with time. Irradiation involving the uterus in childhood is associated with an increased incidence of nulliparity. Even if a pregnancy is achieved there is a high incidence of early miscarriage or intrauterine growth retardation with small-for-gestational-age offspring due to problems with uterine blood flow and distensibility [89–91].

Permanent menopause may be induced in women over 40 years of age following gonadal radiotherapy treatment with 6 Gy, while significantly higher doses are required to completely destroy the oocyte pool and induce ovarian failure in younger women and children [92]. This reflects the smaller follicle reserve in older patients and hence increased susceptibility to smaller doses of irradiation.

Determination of the impact of chemotherapy and radiotherapy on gonadal function currently involves regular clinical assessment of pubertal status, biochemical assessment of gonadotrophins and sex steroids, menstrual history in females, and semen analysis in males. It has not been possible to detect early gonadal damage in a prepubertal child due to a lack of a sensitive marker of gonadal function.

Inhibin B is a potential marker of gonadotoxicity in this age group. It is secreted primarily from Sertoli cells in males and developing small antral follicles in females. It plays a key role in spermatogenesis and folliculogenesis in adult males and females, respectively. Gonadotoxic chemotherapy has been shown to be associated with a reduction in inhibin B levels [83]. A pilot study assessing inhibin B in relation to sensitive measurements of gonadotrophins as markers of the early gonadotoxic effects of chemotherapy in prepubertal children treated for cancer found that in prepubertal girls with cancer, chemotherapy is associated with suppression of inhibin B. Sustained suppression following treatment may indicate permanent ovarian damage. In prepubertal boys, chemotherapy had little immediate effect on Sertoli cell production of inhibin B. Inhibin B, together with sensitive measurements of FSH, may be a potential marker of the gonadotoxic effects of chemotherapy in prepubertal children with cancer [84].

Fertility Protection and Preservation

Infertility is functionally defined as the inability to conceive after 1 year of intercourse without contraception. Rates of permanent infertility and compromised fertility after cancer therapy vary and depend on many factors. The effects of chemotherapy and radiation therapy depend on the drug or

Table 35.1 Predicted age at ovarian failure with 95 % confidence limits for ages at treatment from 0 to 30 years and for doses 3, 6, 9, and 12 Gy

	3 Gy			6 Gy			9 Gy			12 Gy		
Age	Low	Mean	High	Low	Mean	High	Low	Mean	High	Low	Mean	High
0	31.2	35.1	39.0	18.7	22.6	26.5	9.8	13.7	17.6	4.0	7.9	11.8
1	31.3	35.2	39.1	19.0	22.9	26.8	10.4	14.3	18.2	4.8	8.7	12.6
2	31.5	35.4	39.3	19.3	23.2	27.1	10.9	14.8	18.7	5.5	9.4	13.3
3	31.6	35.5	39.4	19.7	23.6	27.5	11.5	15.4	19.3	6.2	10.1	14.0
4	31.7	35.6	39.5	20.1	24.0	27.9	12.1	16.0	19.9	6.9	10.8	14.7
5	31.9	35.8	39.7	20.5	24.4	28.3	12.7	16.6	20.5	7.7	11.6	15.5
6	32.1	36.0	39.9	20.9	24.8	28.7	13.3	17.2	21.1	8.4	12.3	16.2
7	32.2	36.1	40.0	21.3	25.2	29.1	13.9	17.8	21.7	9.1	13.0	16.9
8	32.4	36.3	40.2	21.7	25.6	29.5	14.6	18.5	22.4	9.9	13.8	17.7
9	32.6	36.5	40.4	22.1	26.0	29.9	15.2	19.1	23.0	10.6	14.5	18.4
10	32.8	36.7	40.6	22.6	26.5	30.4	15.8	19.7	23.6	11.4	15.3	19.2
11	33.0	36.9	40.8	23.0	26.9	30.8	16.5	20.4	24.3	12.1	16.0	19.9
12	33.2	37.1	41.0	23.5	27.4	31.3	17.1	21.0	24.9	12.9	16.8	20.7
13	33.4	37.3	41.2	23.9	27.8	31.7	17.8	21.7	25.6	13.6	17.5	21.4
14	33.6	37.5	41.4	24.4	28.3	32.2	18.5	22.4	26.3	14.4	18.3	22.2
15	33.9	37.8	41.7	24.9	28.8	32.7	19.1	23.0	26.9	15.1	19.0	22.9
16	34.1	38.0	41.9	25.4	29.3	33.2	19.8	23.7	27.6	15.9	19.8	23.7
17	34.3	38.2	42.1	25.9	29.8	33.7	20.5	24.4	28.3	17.0	20.5	24.4
18	34.6	38.5	42.4	26.4	30.3	34.2	21.2	25.1	29.0	18.0	21.3	25.2
19	34.9	38.8	42.7	27.0	30.9	34.8	21.8	25.7	29.6	19.0	22.0	25.9
20	35.1	39.0	42.9	27.5	31.4	35.3	22.5	26.4	30.3	20.0	22.8	26.7
21	35.4	39.3	43.2	28.0	31.9	35.8	23.2	27.1	31.0	21.0	23.5	27.4
22	35.7	39.6	43.5	28.6	32.5	36.4	23.9	27.8	31.7	22.0	24.3	28.2
23	36.0	39.9	43.8	29.1	33.0	36.9	24.6	28.5	32.4	23.0	25.0	28.9
24	36.3	40.2	44.1	29.7	33.6	37.5	25.3	29.2	33.1	24.0	25.7	29.6
25	36.7	40.6	44.5	30.3	34.2	38.1	25.9	29.8	33.7	25.0	26.5	30.4
26	37.0	40.9	44.8	30.8	34.7	38.6	26.6	30.5	34.4	26.0	27.2	31.1
27	37.3	41.2	45.1	31.4	35.3	39.2	27.3	31.2	35.1	27.0	27.9	31.8
28	37.7	41.6	45.5	32.0	35.9	39.8	28.0	31.9	35.8	28.0	28.7	32.6
29	38.0	41.9	45.8	32.5	36.4	40.3	29.0	32.6	36.5	29.0	29.4	33.3
30	38.3	42.2	46.1	33.1	37.0	40.9	30.0	33.2	37.1	30.0	30.1	34.0

location of the radiation field, dose, dose intensity, method of administration, disease, age, gender, and pretreatment fertility of the patient. Male infertility can result from the disease itself as seen in patients with testicular cancer and Hodgkins lymphoma or more frequently from damage or depletion of germinal stem cells (Table 35.2). Measurable effects of chemotherapy or radiotherapy include compromised sperm number, motility, morphology, and DNA integrity. In females, fertility is affected by any treatment that decreases the number of primordial follicles, affects hormonal balance, or interferes with the functioning of the ovaries, fallopian tubes, uterus, or cervix.

Male and female fertility may be transiently or permanently affected by cancer treatment or only manifest in women later through premature ovarian failure. Female fertility may be compromised despite maintenance or resumption of cyclic menses. Even if women are initially fertile after cancer treatment, the duration of their fertility may be shortened with a premature menopause.

There is a paucity of data regarding rates of male and female infertility following most current cancer treatments and oncologists have difficulty providing precise guidance to patients about their risks for infertility.

A review of current literature by the American Society of Clinical Oncologists assessed cancer patients' interest in fertility preservation, quality of evidence supporting current and forthcoming options for preservation of fertility in men and women, and the role of the oncologist in advising patients.

Available evidence suggests that fertility preservation is very important to many people diagnosed with cancer. Infertility from cancer treatment may be associated with psychosocial distress. Even though cancer survivors can become parents through routes such as adoption and third party reproduction (using gamete donation or a gestational carrier) most prefer to have a biological offspring even if they have concerns about birth defects that could result if the parent

Table 35.2 Best assessment of risk of subfertility following current treatment for childhood cancer by disease

Low risk of subfertility (<20 % risk)	
1.	Acute lymphoblastic leukemia
2.	Wilms' tumor
3.	Soft tissue sarcoma stage 1
4.	Germ cell tumors (with gonadal preservation and no radiotherapy)
5.	Retinoblastoma
6.	Brain tumor
	Surgery only Cranial irradiation <24 Gy
Medium risk of subfertility	
1.	Acute myeloblastic leukemia
2.	Hepatoblastoma
3.	Osteosarcoma
4.	Ewing's sarcoma
5.	Soft tissue sarcoma
6.	Neuroblastoma
7.	Hodgkin's disease – "hybrid therapy"
8.	Brain tumor
	Craniospinal radiotherapy Cranial irradiation >24 Gy
High risk of subfertility (>80 % risk)	
1.	Total body irradiation
2.	Localized radiotherapy; pelvic/testicular
3.	Chemotherapy conditioning for bone marrow transplant
4.	Hodgkin's disease – alkylating agent-based therapy
5.	Soft tissue sarcoma – metastatic
Low risk <20 %, High risk >80 %	

had cancer treatment before conception or anxiety about their own longevity or their child's lifetime cancer risk [93–96].

Parents may also be interested in fertility preservation on behalf of their children with cancer. Impaired future fertility is difficult for children to understand but potentially traumatic for them as adults. The use of established methods of fertility – semen cryopreservation and embryo freezing – in postpubertal minor children requires parental consent. However, the modalities available to prepubertal children to preserve fertility are limited by their sexual immaturity and are essentially experimental.

Advances in assisted reproductive technologies have focused attention on the possibility of preserving gonadal tissue for future use [97–99]. Such technique does raise a number of important legal and ethical issues. Concerns include protection of children's reproductive rights and obtaining valid informed consent both for storage and for future use of cryopreserved material. Given the absence of proven therapeutic benefit and potential risk associated with these procedures, together with the uncertainty of predicting infertility from new chemotherapeutic and reproductive strategies, it is questionable whether such treatment is justified or ethical in children without scientific trials. The technique of autotransplantation in patients following cancer treatment raises the theoretical possibility of reintroduction of malignant cells.

Current recommendations from the American Society of Clinical Oncology suggest that the two methods of fertility preservation with the highest likelihood of success are sperm cryopreservation for postpubertal males and embryo freezing for females. Conservative surgical approaches and transposition of ovaries or gonads or gonadal shielding before radiotherapy may also preserve fertility in selected cases. Other available fertility preservation methods should be considered experimental and be performed in centers with the necessary expertise after due ethical process [100].

Although data are limited, there appears to be no detectable increased risk of disease recurrence associated with most fertility preservation methods and pregnancy even in hormonally sensitive tumors [101, 102].

Aside from hereditary genetic syndromes, there is no evidence that a history of cancer, cancer therapy, or fertility interventions increase the risk of cancer or congenital abnormalities in progeny. Available studies, including large registry studies, have shown no increased risk of genetic abnormalities, birth defects, or cancers in children of cancer survivors [72, 103–107].

Conclusion

Endocrine disturbances are common in childhood cancer survivors with an increased prevalence in patients with central nervous system tumors.

Growth hormone deficiency is the commonest endocrine abnormality following cranial radiotherapy occurring between 2 and 5 years from treatment depending on the dose. Multiple pituitary hormone deficiencies also occur at higher doses. Serial monitoring of height, sitting height, weight, and pubertal staging with calculation and interpretation of height velocity and body mass index are essential to enable anticipation and prompt management of growth and puberty problems.

Fertility in both males and females can be affected by cancer treatment given prepubertally. The two methods of fertility preservation with the highest likelihood of success are sperm cryopreservation for postpubertal males and embryo freezing for females. Oncologists should discuss with families how cancer treatment can affect fertility prior to the commencement of therapy and fertility preservation offered where appropriate and available.

A major challenge for the future remains to maintain a high cure rate for childhood cancers while further reducing endocrine and other late effects associated with therapy.

Second Tumors

Charles Keys Robert Carachi

The survival of childhood cancers has improved greatly in the last 30 years. With better diagnostic and therapeutic regimens most children who are now diagnosed with cancer will have a survival rate at 5 years of approximately 70 % [108]. This improved survival is achieved at the expense of the long-term effects of having a childhood malignancy and their irradiation and chemotherapeutic treatments. These late effects include reduced fertility, cardiovascular morbidity, adverse endocrine function, and psychological effects. The development of a second malignant neoplasm (SMN) is also a well-recognized late outcome.

As more children survive into adulthood the extent of SMNs is becoming more apparent. However, such malignancies are difficult to study for several reasons. They take a long time to develop, which requires long follow-up and retrospective data collection. Furthermore, small cohorts of patients make results difficult to interpret. However, large cancer groups have published data from large cohorts of children with cancer and have identified prevalence rates and general patterns of associated tumors. Also certain risk factors have been found such as genetic susceptibilities, effects of treatment regimens, lifestyle, and environmental factors.

Incidence and Associations

Overall in the US, SMNs in survivors of cancer account for 6–10 % of all cancers [108]. A European cohort study showed an overall incidence of 3 % of developing an SMN after a childhood cancer [109]. More recently a cohort study of over 16,000 patients identified an overall risk of developing an SMN by 25 years as 4.2 % [110] (Table 35.3).

Various patterns of associations between primary and SNMs have been noted.

The association between retinoblastoma and developing an SMN, especially sarcomas, has long been known [112]. The proposed mechanism is a combination of genetic susceptibility and radiotherapy exposure. One study showed a 30-year cumulative incidence of SMN of 35 % in patients who received radiotherapy and 5.8 % in those who did not [113].

Wilms' tumor patients are also known to develop SMNs. One study showed an incidence of 0.4 % [114]. These SNMs tend to be bone and soft tissue sarcomas, and are often in the field of previous irradiation. Acute myeloid leukemia, lymphoma, and brain tumors have also been reported (Figs. 35.3a, b).

Sarcomas have been the subject of many studies occurring either as the primary tumor, which then develop an SMN, or as the SMN following a different primary tumor. Following the treatment of soft tissue sarcomas several SMNs have been recognized including a second sarcoma, brain tumors, leukemias, neuroblastomas, and lymphomas [115].

The risk of SMN following a Ewing sarcoma has been the subject of debate. One recent study reported a relative risk of 12.7 % of developing an SMN at 20 years [116]. A second sarcoma following irradiation accounted for most of these.

Brain tumors are the most common solid tumor of childhood, and SMNs following them are well recognized [117]. The incidence is variable and there can be a wide variety of neoplasms including non-Hodgkins lymphoma, basal cell carcinoma, malignant melanoma, and Kaposi sarcoma.

SMN following lymphoma is also becoming more prevalent. Most patients with Hodgkin's lymphoma can now be cured, making this more common. The risk of lung cancer is significantly increased in patients with previous Hodgkin's disease [118]. Other SMNs include leukemia and cancers of the esophagus, stomach, colon, and breast [119]. Patients with non-Hodgkin's lymphoma have also been shown to have an increased risk of all malignancies, especially leukemia and lung cancer [120]. Hodgkin's disease has also been reported as an SMN following leukemia, but in general this is very rare for reasons that are still unknown [121].

Thyroid neoplasms following radiotherapy for childhood malignancy is a well-established late outcome. Primary malignancies include lymphomas, leukemias, Wilms' tumor, and neuroblastomas. These thyroid neoplasms can be either benign or malignant [65].

Risk Factors/Etiology

The risk of developing an SMN is a balance of genetic predisposition, exposure to previous therapy, lifestyle, and environmental factors.

Table 35.3 First and second tumors associated with risk factors

First tumor	Second tumor	Risk factors
Retinoblastoma	Bone and soft tissue sarcoma, pineal, melanoma	Genetic disease, radiation
Wilms' tumor	Bone and soft tissue sarcoma, leukemia, brain	Radiation
Neuroblastoma	Thyroid, bone and soft tissue sarcoma	Radiation
Sarcomas	Other sarcomas of bone and soft tissues	Radiation; neurofibromatosis
Lymphoma	Leukemia, other lymphoma, sarcoma	Alkylating agents, epipodophyllotoxins; radiation

Adapted from Meadows [111]

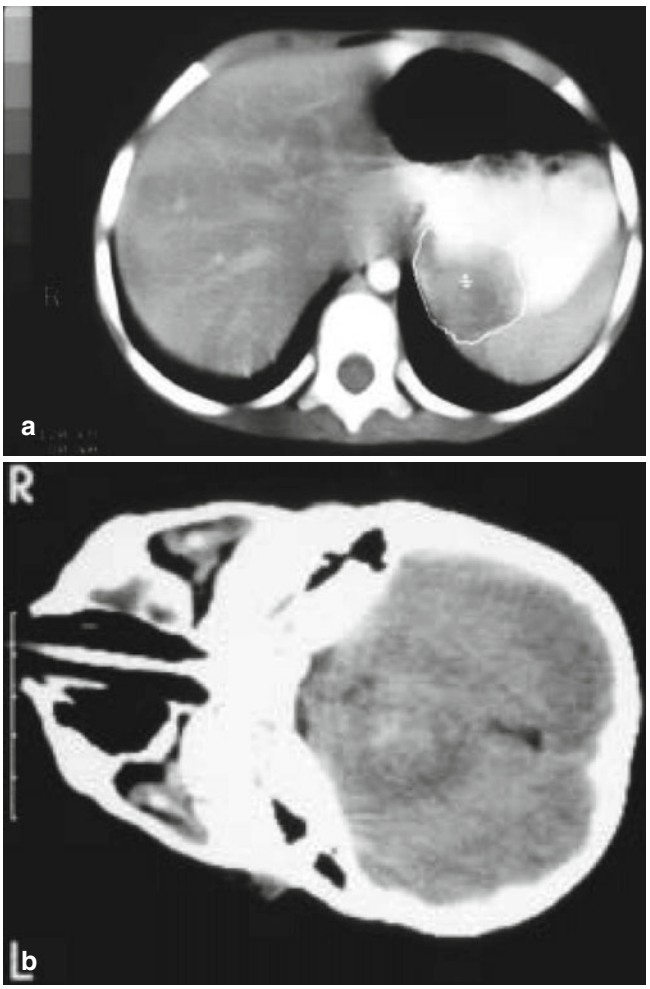

Fig. 35.3 (**a**) This is a CT scan of a 2-year-old boy who presented with a large abdominal mass. He had a large Wilms' tumor on the left side invading the liver. He subsequently was found to have chromosome breakage syndrome when he became unwell following chemo- and radiotherapy. (**b**) Two years later after his treatment was completed, he developed signs of raised intracranial pressure. This CT scan of the brain shows a separate brain tumor. He succumbed shortly after treatment was instituted. His brother also died after treatment for a rhabdomyosarcoma of the head and had a second tumor, a ganglioneuroblastoma of the abdomen discovered at post mortem

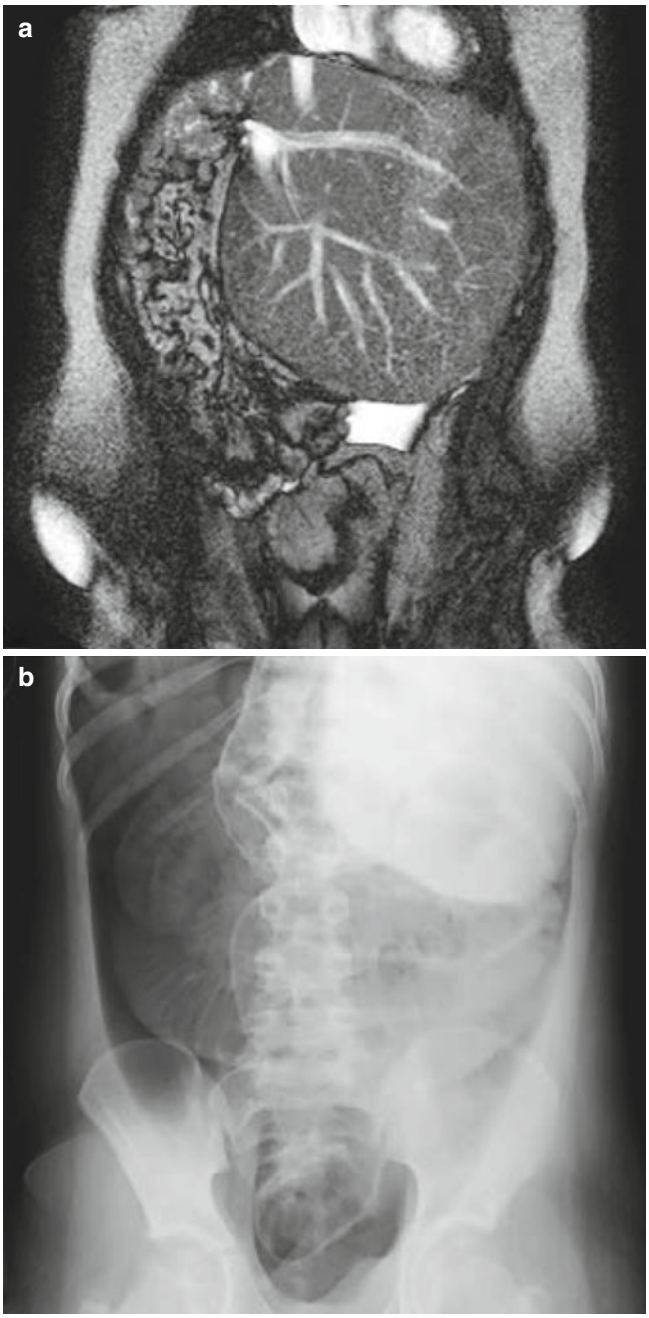

Fig. 35.4 (**a**) This is a scan of a child with a familial rightsided hepatoblastoma that has been successfully resected and following treatment was cured. Genetic studies on the family revealed he had the APC gene mutation. On follow-up 3 years later he developed rectal bleeding. This scan shows compensatory growth of the residual normal left lobe of liver. (**b**) This x-ray demonstrates a complication of a pneumoperitoneum after an attempted biopsy of polyps in the colon. Multiple polyps were encountered. The patient had a total colectomy, and is well

Much has been written about the genetic susceptibility of SMN in children. The risk of developing an SMN is increased in two common pediatric conditions; neurofibromatosis type I, and the genetic form of retinoblastoma [111]. Neurofibromatosis type I is carried by a mutation on chromosome 17 and accounts for 0.5 % of childhood cancers. This gene is associated with an increased risk of developing an SMN.

The genetic form of retinoblastoma involves a constitutional alteration of chromosome 13. These patients have been reported to have a 50 % risk of developing an SMN by 50 years of age [122]. Li-Fraumeni syndrome is a known indicator of cancer manifesting as sarcomas and subsequent risk of SMNs. A germline p53 gene mutation is accountable for this [123].

Other inherited cancer syndromes include multiple endocrine neoplasias and familial adenomatous polyposis. Beckwith-Wiederman syndrome is associated with primary Wilms' tumor and SMN hepatoblastoma (Fig. 35.4a, b). Recent evidence has shown increased RET gene expression in patients who develop thyroid SMN following radiotherapy [124].

Exposure to radiotherapy has long been linked to an increased risk of developing a subsequent neoplasm. Factors that may influence this include age of the child, field of radiation, and dose of irradiation, in addition to the type of primary neoplasm. In general the younger the age at which radiotherapy is received, the greater the risk. Low doses of radiation are associated with thyroid neoplasms [65] and higher doses with sarcomas, although no definite dose threshold has been found [125]. The development of breast tumors following radiation is not thought to be dose related but may be due to a specific susceptibility [126].

Chemotherapy agents are also known to be associated with the development of SMNs. Alkylating agents and epipodophyllotoxins are the most well known and are associated with secondary leukemia [111].

Evidence suggests that the risk of SMN development is further increased with combined radiotherapy and chemotherapy [127, 128].

Summary

As patients with childhood tumors achieve longer survival more SMNs are being seen. These can occur in some well-established patterns that may follow genetic predisposition. They may result as a late effect of exposure to irradiation and some chemotherapeutic agents.

All patients with childhood malignancies require long-term follow-up. Long-term prospective surveillance of all children with malignancies will afford improved understanding of incidence and possible etiology of these SMNs. This may provide the opportunity to prevent and treat these malignancies.

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