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PENTEC ORGAN SYSTEM REVIEW

Testicular Dysfunction in Male Childhood Cancer Survivors Treated With Radiation Therapy: A PENTEC Comprehensive Review

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Purpose: The male reproductive task force of the Pediatric Normal Tissue Effects in the Clinic (PENTEC) initiative performed a comprehensive review that included a meta-analysis of publications reporting radiation dose-volume effects for risk of impaired fertility and hormonal function after radiation therapy for pediatric malignancies.

Methods and Materials: The PENTEC task force conducted a comprehensive literature search to identify published data evaluating the effect of testicular radiation dose on reproductive complications in male childhood cancer survivors. Thirty-one studies were analyzed, of which 4 had testicular dose data to generate descriptive scatter plots. Two cohorts were identified. Cohort 1 consisted of pediatric and young adult patients with cancer who received scatter radiation therapy to the testes. Cohort 2 consisted of pediatric and young adult patients with cancer who received direct testicular radiation therapy as part of their cancer therapy. Descriptive scatter plots were used to delineate the relationship between the effect of mean testicular dose on sperm count reduction, testosterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) levels.

Results: Descriptive scatter plots demonstrated a 44% to 80% risk of oligospermia when the mean testicular dose was <1 Gy, but this was recovered by >12 months in 75% to 100% of patients. At doses >1 Gy, the rate of oligospermia increased to >90% at 12 months. Testosterone levels were generally not affected when the mean testicular dose was <0.2 Gy but were abnormal in up to 25% of patients receiving between 0.2 and 12 Gy. Doses between 12 and 19 Gy may be associated with abnormal testosterone in 40% of patients, whereas doses >20 Gy to the testes were associated with a steep increase in abnormal testosterone in at least 68% of patients. FSH levels were unaffected by a mean testicular dose <0.2 Gy, whereas at doses >0.5 Gy, the risk was between 40% and 100%. LH levels were affected at doses >0.5 Gy in 33% to 75% of patients between 10 and 24 months after radiation. Although dose modeling could not be performed in cohort 2, the risk of reproductive toxicities was escalated with doses >10 Gy.

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Conclusions: This PENTEC comprehensive review demonstrates important relationships between scatter or direct radiation dose on male reproductive endpoints including semen analysis and levels of FSH, LH, and testosterone.

Introduction

Disease outcomes for childhood cancer survivors have dramatically improved during the past 4 decades, with a 5-year survival rate of >80% for all children diagnosed at <19 years of age.[1] Nevertheless, childhood cancer survivors experience late morbidity and mortality as a consequence of their primary therapy.[2] Among the myriad late effects,[3] reproductive complications remain a significant source of distress among pediatric cancer survivors and significantly affect the quality of their survivorship.[4-6] In fact, impaired male fertility and gonadal dysfunction are the most common late endocrine complications in male childhood cancer survivors[7] and are multifactorial, stemming from all treatment modalities including surgery, radiation therapy (RT), and chemotherapy. In particular, the effect of RT on testicular and gonadal dysfunction is well documented, but to our knowledge, a dose-volume analysis of the association of testicular RT dose with gonadal dysfunction has not been performed. In this review, the Pediatric Normal Tissue Effects in the Clinic (PENTEC) testes task force provides a meta-analysis of studies evaluating the effect of testicular dose on gonadal and reproductive dysfunction and attempts to derive dose-response relationships.

Clinical Significance

Normal adult testis physiology

Male fertility is dependent on spermatogenesis, a complex biological process that results in the production of spermatozoa within the seminiferous tubules of the testes. Sertoli cells, under regulation of follicle stimulating hormone (FSH), provide essential growth factors to ensure a favorable niche for germ cell development. Sertoli cells also secrete inhibin B, which, through negative feedback, influences the production of FSH.[8] Leydig cells, under hormonal regulation by luteinizing hormone (LH), secrete testosterone, which acts as a critical paracrine factor for spermatogenesis.[9]

RT-induced germ cell injury/dysfunction

Irradiation of the testes can damage testicular germ cells, thereby impairing fertility and also sexual maturation and function.[10] The mechanism of radiation injury to the testes resulting in impaired spermatogenesis is complex and depends on the total dose delivered, the fraction size, and the volume of testes irradiated, although the latter is largely irrelevant because the testicles are small and are rarely partially exposed. Decline in sperm counts owing to ionizing irradiation results from depletion of spermatogenesis at all stages, including type A and B spermatogonia, primary and secondary spermatocytes, and finally, spermatozoa.[11]

RT-induced endocrine dysfunction

Leydig cells are more radioresistant than the germ cells, so normal testosterone levels may persist even with severe impairment in spermatogenesis. Low testosterone levels may also have multiple signs and symptoms. Adolescent boys may have incomplete or delayed sexual development. Men may have reduced sexual desire and activity, decrease in spontaneous erections, erectile dysfunction, gynecomastia, low bone mineral density, hot flashes or sweats, reduced muscle bulk and strength, increased body mass index and body fat, decreased energy (which may also be seen in preadolescents), poor concentration and memory, sleep disturbance, and normochromic, normocytic anemia.[12] Children and young adults with cancer may receive testicular irradiation either as an unintended or intended component of their therapy, typically via (1) indirect scatter (thus, incidental) irradiation to the testes owing to treatment of lymphoma, sarcoma, and seminoma with RT fields that include the neighboring pelvis or (2) direct testicular RT for the treatment of acute lymphoblastic leukemia (ALL), testicular carcinoma in situ (TCIS), and rarely, sarcomas.

Indirect effects of RT on testicular function

Although not the subject of this report, it is recognized that cranial radiation can disrupt the hypothalamic-pituitary axis in a dose-dependent fashion and result in deficiencies of FSH and/or LH, with secondary declines in Leydig cell function, hypotestosteronism, and reduced spermatogenesis. A report from the St. Jude Lifetime Cohort Study demonstrated that cranial RT leads to substantial risk of hypothalamic and pituitary dysfunction, with growth hormone, LH, and FSH the most commonly affected pathways.[13] Vatner et al evaluated 189 patients who were treated for brain tumors with proton RT and demonstrated that although doses ≤20 GyRBE (relative biological effectiveness) did not induce gonadotropin deficiency, a dose ≥40 GyRBE was associated with a 14% risk of gonadotropin deficiency at 4 years after treatment.[14] The hypothalamus may be more sensitive to injury than the pituitary gland, but this remains controversial.[15]

Chemotherapy effects on testicular function

A critical modifying factor is alkylating chemotherapy (eg, cyclophosphamide equivalent dose of 4-5 g/m^2),[16,17] which can significantly impair spermatogenesis and make it difficult to determine a dose-response relationship for RT-associated testicular dysfunction. Although standard doses of chemotherapy rarely affect Leydig cell function, alkylating agents at cyclophosphamide equivalent doses >4000 mg/m^2 can increase Leydig cell failure.[18] Other chemotherapeutic regimens such as mechlorethamine, vincristine, procarbazine, and prednisolone (MOPP), which was historically used for Hodgkin lymphoma, are associated with infertility or azoospermia in 80% to 100% of patients.[19] It remains unclear if the effects of alkylating chemotherapy have an additive or synergistic effect with testicular RT on reproductive endpoints.

Endpoints and Toxicity Scoring

Semen analysis is the gold standard assessment for infertility and includes sperm count (normal, oligospermia, or azoospermia) and morphology (normal, abnormal). Normal postpuberty semen concentration is typically considered between 15 million and 39 million sperm/mL by the World Health Organization,[20] but in some older studies included in this review, less than 20 million sperm/mL was considered abnormal. Azoospermia is the absence of spermatozoa, whereas oligospermia is a reduction in sperm count. Sperm motility, vitality, and morphology should also be evaluated but could not be used in this report because these data were not available in most of the studies.

Leydig cell function is reflected in the testosterone level (normal, relative decline but normal, and abnormal) or the need for testosterone supplementation. Testosterone measurements typically reach their maximum in the morning, and therefore, morning total testosterone is most ideal to measure. The clinical manifestation of testosterone deficiency varies with age and includes delayed onset of puberty in prepubescent males and reduced sexual function and gynecomastia in postpubertal males.[21]

An indirect consequence of impaired testosterone production is elevations in inhibin B, FSH, and LH levels owing to the feedback loop along the hypothalamic-pituitary-gonadal axis. Although inhibin B and FSH can be useful adjuncts to sperm analysis, caution is necessary if they are used independently for surveillance, given the lack of specificity seen in several studies.[22] As previously discussed, although semen analysis remains the gold standard predictor of male fertility, young cancer survivors are typically hesitant or unable to provide a sample. Testicular size or volume has been shown to correlate with spermatogenesis in several studies.[23-25] Testicular damage may lead to reduced testicular volume; testicular size can be measured by an orchidometer, ruler, or ultrasound. Although testicular ultrasound is the gold standard, it is seldom used in studies. Wilhelmsson et al evaluated testicular volume in 74 male survivors after hematopoietic stem cell transplant and demonstrated that an adult testicular volume ≥15 mL was able to identify 80% of nonazoospermic childhood cancer survivors with 91% specificity.[26] Endpoints used in this study were semen analysis, Leydig cell function (testosterone), and LH and FSH levels. Other endpoints such as testicular size and sperm morphology, although useful, were not available in most studies.

Anatomy and Developmental Dynamics

Testicular development is complex and begins with the formation of the genital ridge at approximately the third week of embryogenesis. The development of the mesonephric or Wolffian ducts contributes to the formation of multiple male genital structures, including the seminal vesicles, epididymis, and vas deferens.[27] Primordial germ cells migrate from the yolk sac to the genital ridge by the sixth week of gestation, and several complex genetic alterations, including the sex-determining region of the Y chromosome and activation of the *SOX9* gene, result in testicular development with Sertoli cell and Leydig cell migration and differentiation. Ultimately, testicular descent occurs through 2 distinct stages, known as transabdominal and inguinoscrotal. During testicular development, testosterone levels first peak by 12 to 14 weeks of gestation, shortly after birth, and then during the onset of puberty.[28,29] The onset of puberty triggers spermatogenesis owing to an increase in testosterone levels and results in the formation of mature spermatozoa.

Defining Volumes: Pediatric Imaging Issues

The testes can be delineated on a computed tomography simulation scan, and accurate dose-volume histogram data can be obtained. However, in most studies included in this review, computed tomography–based treatment planning was not performed, and testicular dose was therefore estimated by other methods, including (in some studies) via fundamental physics principles related to internal scatter, thermoluminescent dosimeter measurements,[30] and water phantom measurements.[31]

Review of Dose-Response Data and Risk Factors

Methodology

We performed a systematic review of studies evaluating the relationship between testicular RT dose and the risk of androgen deficiency, impaired spermatogenesis, and infertility in male childhood cancer survivors. Eligible studies

were identified as those that specifically reported radiation dose to the testis in pediatric and adolescent or young adult patients and its effect on spermatogenesis and/or androgen production. On July 2, 2014, a search of PubMed for peer-reviewed articles was performed (Appendix E1) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Some reports of clear relevance that surfaced after the formal search were also analyzed at the discretion of task force members. Figure 1 demonstrates the selection criteria with a PRISMA flow diagram. Two authors reviewed all titles and abstracts and excluded 3502 studies that were not relevant to our study. From the remaining 280 articles, another 204 articles were excluded, which left 76 articles for which the full text was reviewed. An additional 60 articles were excluded after review of full text owing to insufficient radiation information provided. An additional 15 studies were identified by the PENTEC steering committee. Therefore, 31 studies were included in the qualitative synthesis, and 4 studies had enough RT dose data for descriptive study plots. Other studies were excluded from the quantitative synthesis owing to a high level of uncertainty (>10%) regarding how mean testicular dose was determined in those articles. Of the 31 studies, 12 included exclusively pediatric data and 19 included either adult patients or a mix of adolescent and adult patients. Given the dearth of series describing only pediatric testicular data, we included adolescent or young adult (AYA) and adult patients who also received testicular radiation. Of the 31 studies, 7 included only pediatric data (participants ≤15 years old), 10 included pediatric and AYA data (participants 15-39 years old), and 14 included AYA and adult data (participants >39 years old).

Patient cohorts

From our qualitative and quantitative synthesis of articles selected, we identified 2 cohorts of patients from multiple

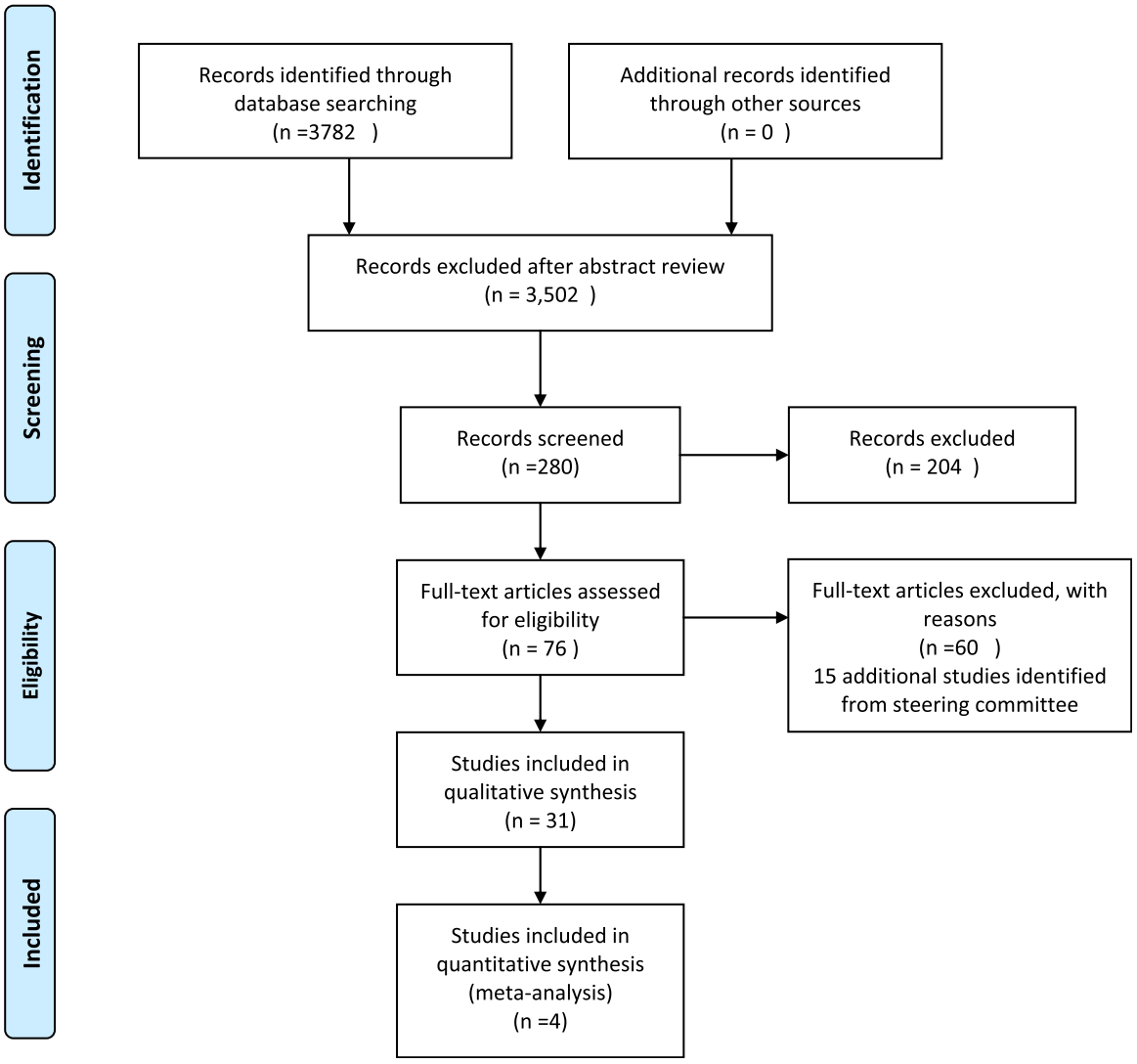

Fig. 1. Selection criteria for studies evaluating testicular radiation therapy and effect on male reproductive complications using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

retrospective studies who received a similar pattern of testicular radiation, classified as indirect or incidental testicular exposure (cohort 1) or direct or intentional testicular exposure (cohort 2).

Indirect or incidental testicular exposure consisted of pediatric and young adult patients with cancer who received scattered (incidental) testis exposure during pelvic-region RT for Hodgkin or non-Hodgkin lymphoma or for seminoma or nonseminoma. Patients in some of these studies were treated with a testicular shield of 1 or both testicles,[32-39] some studies did not use shielding,[40-42] and in some studies, testicular shielding was not specified.[43-45] In the study by Martin et al,[38] 3 of 11 patients had testicular shielding. Chemotherapy regimens varied between studies but typically included mechlorethamine, oncovin, procarbazine, and prednisone (MOPP); Adriamycin, bleomycin, vinblastine, and doxorubicin; or lomustine, vincristine, amethopterine, and procarbazine (COMP).

Direct or intentional testicular exposure consisted of pediatric and young adult patients with cancer who received direct testis RT dose as part of their primary cancer therapy, typically for ALL or TCIS. A minority of patients with rhabdomyosarcoma and neuroblastoma (testicular metastases) also received testicular RT and were included in this cohort. These patients typically received >5 Gy. Although all patients in this cohort received testicular RT, in 4 of the studies, cranial or craniospinal irradiation was also delivered. Chemotherapy regimens significantly varied between studies.

Table 1 demonstrates the patient demographics, treatment, and endpoint characteristics of the patient cohorts included in the qualitative synthesis.

Statistical methods

Given the limited and heterogeneous data available, any form of statistical analysis and modeling was not possible. Instead, descriptive scatter plots were used to show the available data and to summarize the various toxicities as a function of mean testicular dose with range also displayed.

Effect of scatter radiation on sperm count

Nine studies reported on the effect of scattered dose to the testes (Table 1).[33,34,36,37,40,41,43,45,46] Of the 9 studies, we were able to estimate the mean testicular dose in 4. We plotted the risk of sperm count reduction (oligospermia) as a function of dose (Fig. 2A) as observed in the studies by Centola et al,[34] Hahn et al,[37] Hansen et al,[42] and Kinsella et al.[41]

Centola et al[34] reported on 8 patients with seminoma with a mean age of 33 years (range, 24-40 years) who were treated with para-aortic and ipsilateral pelvic fields and no chemotherapy. The testes received a mean dose of 0.44 Gy (range, 0.21-0.78 Gy), and after treatment, 7 of the patients had a reduction in sperm count, although no patients were azoospermic. At 6 months, 4 of the 5 patients evaluable at this time point had oligospermia, and at 12 months, all patients had recovered sperm counts.

Hahn et al[37] evaluated spermatogenic activity in 18 patients treated for seminoma (n = 14), Hodgkin disease (n = 3), or lymphosarcoma (n = 1) with 32 Gy in 16 fractions to para-aortic and ipsilateral pelvic fields. The mean testes dose was 0.78 Gy (range, 0.32-1.78 Gy). Ten of 14 patients (71%) developed azoospermia after RT, but 12 of the 14 patients with seminoma recovered sperm counts by 80 weeks after treatment (18 months). Seven of the 14 patients (50%) recovered to their baseline count between 45 and 105 weeks.

Hansen et al[42] evaluated testicular function after unilateral orchiectomy in 51 patients with testicular germ cell tumors (27 with seminoma and 24 with nonseminoma) treated with radiation to the para-aortic and ipsilateral iliac and pelvic lymph nodes to a median gonadal dose of 1.70 Gy (range, 1.20-4.80 Gy). Twenty of the 51 patients (39%) received adjuvant chemotherapy, including vincristine and bleomycin (19 patients with nonseminoma) and vinblastine and bleomycin (1 patient). Of note, after orchiectomy and before RT, 51% of patients had total sperm counts below the reference level. After 18 months of follow-up, 38 of 45 patients showed azoospermia, and an additional 5 patients showed oligospermia. Recovery did occur gradually; after 12 months, approximately 20% of patients had spermatozoa in the semen, which increased to 61% after 5 years.

Kinsella et al[41] evaluated testicular function according to dose in 17 patients who received RT to 36 to 40 Gy with either mantle field only (did not contribute to testicular dose), subtotal nodal irradiation with sequential mantle and para-aortic fields, infradiaphragmatic subtotal nodal irradiation with sequential pelvic field and para-aortic field irradiation, and total nodal irradiation. The mean testicular dose was 0.27 Gy. Of the 17 patients, 10 provided serial semen specimens, and only 8 had normal pretreatment levels. Of those 8 patients, 3 demonstrated a transient decline in sperm counts up to 18 months from treatment.

In some studies,[33,36,43] the testicular dose was unable to be validated for modeling purposes owing to inadequate methodology about field design or lack of dose reporting. Gandini et al[36] evaluated sperm counts at 3, 6, 9, 12, and 24 months in 95 patients treated for seminoma at a mean age of 30 years (range, 20-43 years) who underwent RT to the lumbar-aortic nodes to a mean dose of 26 Gy. They demonstrated that 26% of patients were azoospermic at 6 months, but there was significant recovery, with only 6% to 10% of patients azoospermic after 1 year. Similar findings were demonstrated by Eberhard et al,[46] who evaluated sperm counts in 112 men younger than age 50 with testicular germ cell cancer, 31 of whom received RT to the para-aortic and ipsilateral iliac nodes to a dose of 25.2 Gy in 14 fractions, with an estimated scatter dose to the testes that ranged from 0.04 to 0.43 Gy. Only 10 of the 31 patients were evaluable for sperm analysis. Of those, 2 patients (20%) were found to be azoospermic at 6 months, and only

Table 1 Study and patient cohorts included in the qualitative synthesis

Study	Patients, no.	Median age at treatment, y	Disease	Field of RT	Testis dose, Gy	Chemotherapy	Endpoints	Median follow-up time (y); median follow-up time (y); endpoints	Conclusions
Centola et al,[34] 1994	8	33 (mean; range, 24-40)	Seminoma	Hockey-stick with clam shell shield of remaining testes	Scattered (0.21-0.78)	None	Sperm count, motility, morphology, HOS	8.3; sperm count follow-up: 1	Transient decrease in sperm count after testicular doses of 28-90 cGy, with recovery of normal sperm count or ability to father offspring by maximum of 30 mo after RT
Kinsella et al,[41] 1989	17	22 (range, 15-35)	HD	40 Gy to involved sites and 36 Gy to uninvolved sites	Scattered (0.06-0.70)	No chemotherapy (n = 16), MOPP at relapse 6 mo after RT (n = 1)	FSH, LH, T	5.0; FSH: 5.0, LH: 5.0, T: 5.0	Scatter RT >20 cGy can result in transient injury to the seminiferous tubules manifested by FSH elevations for 6-24 mo after RT (<20 cGy, FSH remained normal); no evidence of Leydig cell injury using LH and T up to 70 cGy; RT for early-stage HD therefore has little or no risk of irreversible testicular injury
Gandini et al,[36] 2006	95	29.8 (mean; range, 20-43)	Seminoma	Lumbar-aortic nodes	Scattered	No chemotherapy	Sperm count	Not reported	Recovery of spermatogenesis after RT or chemotherapy was not associated with pretherapy sperm parameters; pretreatment cryopreservation is therefore needed
Brydoy et al,[43] 2012	1191	31 (range, 15-58)	Seminoma and nonseminoma	Dog-leg, L fields, para-aortic field (n = 39)	Scattered	CVB, BEP, EP, CEB, BOP/VIP, carboplatin, other	Sperm count, FSH, inhibin B	11.0; inhibin: 11.0; sperm count: 9.0	RT had no late effects on spermatogenesis, whereas chemotherapy did; routine evaluation of s-inhibin B was not recommended in the initial fertility evaluation
Pedrick et al,[33] 1986	18	27 (range, 17-45)	HD	Total lymphoid irradiation	Scattered (0.28-1.35 Gy)	None	Sperm count	Sperm count: 2.0	There is time-dependent recovery of spermatogenesis after testicular irradiation
Hahn et al,[37] 1982	14	30.5 (range, 24-35)	Seminoma	Dog-leg	Scattered (0.32-1.78 Gy)	None	Sperm count	Not reported	Aspermia occurred in 10 of 14 patients after >65 cGy testicular RT; at lower doses, aspermia may not have occurred or was of short duration; recovery of sperm occurred in 12 patients in 30-80 wk after start of RT; the data suggest that the time of recovery may be dose dependent between 19 and 148 cGy; during the recovery period, patients with oligospermia may be fertile and should be counseled appropriately
Eberhard et al,[46] 2004	112	24	Seminoma and nonseminoma	25.2 Gy in 14 fractions; para-aortic and ipsilateral iliac lymph nodes	Scattered (0.04-0.43 Gy)	BEP, BEP/CVB, EP	Sperm count	Not reported	Sperm concentrations were reduced after RT or >2 cycles of chemotherapy and recovered to pretreatment levels 2-5 y after treatment
Ben Arush et al,[45] 2000	20	9.2 (range, 5.8-13.3)	HD or NHD	Inverted Y, median dose 23.2 Gy (range, 15.5-40 Gy)	Scattered	MOPP/ABVD, MOPP, or COMP	Sperm count, FSH, LH, T, E2, PRL	Mean, 9 y	RT and chemotherapy combinations including nitrogen mustard or cyclophosphamide had higher rates of oligospermia and azoospermia; MOPP/ABVD did not have better sperm count outcomes compared with MOPP alone; prepubertal state did not protect the gonad from reduced sperm counts

(*Continued*)

Table 1 (*Continued*)

Study	Patients, no.	Median age at treatment, y	Disease	Field of RT	Testis dose, Gy	Chemotherapy	Endpoints	Median follow-up time (y); median follow-up time (y); endpoints	Conclusions
Ortin et al,[40] 1990	8	14 (range, 9-15)	HD	Mantle and inverted Y (range, 15-44 Gy) alone (n = 1) or with pelvic (range, 31.2-44.8 Gy; n = 7)	Scattered	None	Sperm count, FSH, LH, T, fertility	10	Prepubescent and postpubescent tests are affected by 6 cycles of MOPP with or without pelvic RT; recovery of spermatogenesis is likely after pelvic RT alone but unusual after 6 cycles of MOPP; basal FSH may provide an estimate of possible impaired spermatogenesis, but semen analysis is a more accurate assessment of male gonadal function
	12	14 (range, 8-15)	HD	Mantle and inverted Y (range, 15-44 Gy) alone (n = 7) or with pelvic (range, 20-44 Gy; n = 5)	Scattered	MOPP	Sperm count, T, FSH, LH, fertility	8.5	
Brauner et al,[47] 1988	21	8.3 (range, 4.2-12.7)	ALL (prophylactic, n = 6; testicular disease, n = 15)	Testicular	24 in 2 fractions	One or more of the following: prednisone, 6-mercaptopurine, vincristine, MTX, asparaginase, daunorubicin, cyclophosphamide, cytarabine	T, LH	3.3; LH: 3.3, T: 3.3	The youngest children at testicular RT were more vulnerable; spontaneous virilization occurred in 3 older children after RT
Castillo et al,[48] 1990	15	6.8 (range, 1.3-12)	ALL (prophylactic, n = 12; relapse, n = 3)	Testicular + 24 Gy cranial	Prophylaxis: 12 (n = 12); relapse: 15 (n = 1), 24 (n = 2)	Modified CALGB 6801	Tanner stage, testicular volume, bone age, sperm count, FSH, LH, T	10	All boys treated with 12-15 Gy had normal Leydig cell function, although higher levels of gonadotropins suggested subclinical Leydig cell damage; boys treated with 24 Gy had Leydig cell failure; all survivors able to produce a semen specimen were azoospermic
Jahnukainen et al,[25] 2011	18	5 (range, 1-15) for study population (N = 51)*	ALL	Testicular ± cranial, spinal	10 (n = 1), 24 (n = 17)	Prednisolone, vincristine, doxorubicin, asparaginase, MTX, 6-mercaptopurine ± cyclophosphamide	Testicular size, sperm count and concentration, semen volume, abstinence, seminal plasma (pH, Zn, fructose, glucose), FSH, LH, T, free T, inhibin B, E2, PRL	20 for study population*	Cyclophosphamide of ≤10 g/m^2 and prophylactic cranial RT did not affect fertility or semen quality but could impair long-term Leydig cell function
Green et al,[49] 2010	3497	Unknown (<21 y at RT)	CCSS	Testicular	0.001-3.99 (n = 3137), 4.00-4.99 (n = 62), 5.00-5.99 (n = 45), 6.00-14.99 (n = 116), 15.00-23.99 (n = 137)	Alkylating agents (various regimens)	Fertility (≤7.5 Gy vs >7.5 Gy)	-	The HR of siring a pregnancy was decreased by >7.5 Gy testicular RT, higher cumulative alkylating agent dose, or treatment with cyclophosphamide or procarbazine; compared with siblings, survivors not exposed to alkylating agents, hypothalamic or pituitary RT, or testicular RT had an HR for siring a pregnancy of 0.91 (95% CI, 0.73-1.14; $P = .41$)
Blatt et al,[50] 1985	7	12.7 (range, 6-19)	Testicular relapse of ALL	Testicular + 18-24 Gy cranial (n = 6) or 18 Gy CSI (n = 1)	24	Vincristine, prednisone, 6-mercaptopurine, MTX, asparaginase	Pubic hair, testis size, T, FSH, LH	5	24-Gy testicular RT is associated with risk for Leydig cell dysfunction

(*Continued*)

Table 1 (*Continued*)

Study	Patients, no.	Median age at treatment, y	Disease	Field of RT	Testis dose, Gy	Chemotherapy	Endpoints	Median follow-up time (y); median follow-up time (y); endpoints	Conclusions
Leiper et al,[51] 1986	13	8.9 (range, 5.5-11.9)	ALL (prophylactic, n = 1; relapse, n = 12)	Testicular + 24 Gy cranial (n = 9) or 24 Gy CSI (n = 4)	Prophylactic: 15 (n = 1); relapse: 24 (n = 11), 36 over 2 courses (n = 1)	6-mercaptopurina, MTX, vincristine, cytosine arabinoside, prednisolone, ± cyclophosphamide ± doxorubicin, ± thioguanine and CCNU	Bone age, height velocity, puberty stage, FSH, LH, T	4.9	Testicular RT before puberty has a high risk of permanent Leydig cell damage, requiring testosterone supplementation
Sklar et al,[52] 1990	11	5.4 (range, 0.7-16.5) for study population (N = 60)*	ALL	24 Gy CSI + 12 Gy abdominal including testicular (n = 11)	12	CCG-101 or CCG-143	Testicular volume, pubertal development, FSH, LH, T	5.0 for study population*	The risk of primary germ cell dysfunction was 55% with CSI plus 12-Gy abdominal RT, 17% with CSI, or 0% with cranial RT alone (P = .002); Leydig cell function appeared resistant to direct RT as high as 12 Gy
Siimes et al,[53] 1990 and 1995	18	9.7 (0.1-15.8) for ALL, unknown for solid tumors	ALL in 13 of 15 patients with testicular RT; various diagnoses in other patients	Testicular (n = 15) or TBI (n = 3)	Testicular: 6-12 (median, 10); TBI: 10-12 in 1-6 fractions	At least 1 of the following: vincristine, cyclophosphamide, 6-mercaptopurine, MTX, anthracyclines, asparaginase, arabinose	Testicular volume, FSH, LH	Mean, 10.3 for study population*	ALL survivors have inferior testicular function compared with solid-tumor survivors; testicular RT results in generally severe but variable testicular damage
Sedlmayer et al,[54] 2001	9	32.8 (range, 27-42)	TCIS	Testicular (anterior electron beam)	13 in 10 fractions	Cisplatin, etoposide, and bleomycin (n = 2)	FSH, LH, T	3.0	13 Gy in 10 fractions of 1.3 Gy may enhance the therapeutic ratio in favor of Leydig cell function
Shalet et al,[55] 1989	5	Unknown (range, 1-5)	Rhabdomyosarcoma (n = 3), orchioblastoma (n = 1), anal neuroblastoma (n = 1)	Testicular	27.5-30 in 20-28 fractions	Dactinomycin (n = 3)	FSH, LH, T	14	Testicular RT given to boys aged 1-4 y had significantly higher Leydig cell damage compared with testicular RT given to adult men
Bang et al,[56] 2009	51	32 (range unknown)	TCIS	Testicular	16 (n = 37), 20 (n = 14)	None (n = 40), chemotherapy (unknown agents, n = 11)	LH, T, SHBG	3.1 (16 Gy), 10.0 (20 Gy), 2.3 (16 Gy with chemotherapy), 10.8 (20 Gy with chemotherapy)	Compared with 20 Gy, 16 Gy of testicular RT better preserved T levels; more men treated with 20 Gy needed androgen therapy
Dieckmann et al,[57] 1993	4	32 (range, 27-33)	TCIS	Testicular	18 (n = 1), 20 (n = 4)	Cisplatinum-based for relapse (n = 1)	FSH, LH, T	Not reported	18-20 Gy testicular RT in adult men can preserve Leydig and stromal cells
Giwercman et al,[58] 1991	18	31 (range, 26-46)	TCIS	Testicular	20 in 10 fractions	None	FSH, LH, T, DHT, SHBG, 4AD, DHAS	2.5	20-Gy testicular RT in adult men resulted in partially impaired Leydig cell function
Hansen et al,[42] 1990	51	30 (range, 21-40)	Seminoma (n = 27), nonseminoma (n = 24)	Anterior and posterior opposing L-shaped fields	Scattered	None (n = 31); vincristine/ bleomycin (n = 19), cisplatin, dactinomycin, bleomycin (n = 1)	Sperm count, FSH	6.4	Azoospermia is dose dependent and affected by radiation scatter; recovery depended on the dose delivered to the testes, and adjuvant chemotherapy prolonged the recovery period
Martin et al,[38] 1985	11	Range, 19-47	Seminoma (n = 8), rectal cancer (n = 1), teratoma (n = 1), lymphoma (n = 1)	Unknown	Scattered	C-MOPP (n = 1)	Sperm count, motility, hamster egg penetration	2.0	Sperm concentration can be impaired before RT; there is an inverse correlation between testicular radiation dose and sperm concentration
Huddart et al,[44] 2005	239	CRT group: 32 (15-68);		Majority received dog-leg RT of 30 Gy	Direct	Platinum based	Fertility, T, FSH, LH, T	10.2 y (0-20.3 y)	Gonadal dysfunction was more common in adult men with testicular cancer

(*Continued*)

Table 1 (*Continued*)

Study	Patients, no.	Median age at treatment, y	Disease	Field of RT	Testis dose, Gy	Chemotherapy	Endpoints	Median follow-up time (y); median follow-up time (y); endpoints	Conclusions
		RT group: 35 (19-82)	Seminoma (n = 292), nonseminoma (n = 388)						managed with orchidectomy alone, and chemotherapy can result in additional impairment; gonadal dysfunction reduced QOL (assessed by the EORTC QLY-C30 questionnaire); screening for gonadal dysfunction during follow-up of survivors was recommended
Brennemann et al,[32] 1998	20	29.8	Seminoma	36 Gy infradiaphragmatic RT with remaining testis protected by Pb shielding resulting in gonadal dose of 0.21 Gy	Scattered	None	Sperm density, FSH, LH, T	Not reported	Pretreatment FSH predicted for posttreatment Sertoli cell function (spermatogenesis); Leydig cell dysfunction was evident in patients after cisplatin-based chemotherapy but not after RT
	18	31.4	Nonseminoma	None	Not applicable	Cisplatin, bleomycin, and either (1) vinblastine ± ifosfamide or (2) etoposide	Sperm density, FSH, LH, T	Not reported	
Shamberger et al,[59] 1981	26	40 (16-63)	Sarcoma	Abdomen/pelvis/thigh (proximal RT) or neck, chest, lower extremity below knee (distal RT)	Scattered	Doxorubicin, cyclophosphamide, methotrexate	Sperm count, FSH, LH, T	2.0	Testicular function is impaired by adjuvant chemotherapy with doxorubicin, cyclophosphamide, and high-dose methotrexate, but is reversible; if combined with RT to the thigh or abdomen, this injury may be permanent
Nader et al,[60] 1983	12	17-45	Seminoma (n = 10), nonseminoma (n = 2)	Varied but typically included abdomen, paraaortic and inguinal, or pelvic	Scattered	None	FSH, LH, T	12.0	Scatter radiation affects testicular function even after 15-20 y of follow-up
Freund et al,[61] 1987	8	31 (24.5-42)	Seminoma	Stage I: paraaortic and ipsilateral external and common iliac nodes; stage IIL included retroperitoneal nodes	Scattered	Dactinomycin (n = 1)	Sperm count, morphology, FSH, LH, T	1.4	Testicular function is impaired after scatter radiation, but recovery of testicular function occurs and is time dependent
Shapiro et al,[62] 1985	27	49 (14-67)	Sarcoma	Obliqued fields	Scattered	None	Sperm count, FSH, LH	Not reported	Scatter radiation increases serum LH and FSH concentrations but does not seem to significantly affect total testosterone levels
Chemaitilly et al,[18] 2019	1516	30.8	Multiple histologies including leukemia (n = 520), lymphoma (n = 337), and bone and soft-tissue sarcomas (n = 223)	Whole abdomen, inverted Y, pelvis, prostate, bladder, testes, iliac, femoral, inguinal, total lymphoid, total body	Scattered and direct	Cyclophosphamide (n = 902)	LH, T	22	Leydig cell failure was more likely at older age and with testicular RT and exposure to alkylating agents and was associated with adverse physical and psychosexual outcomes; Leydig cell dysfunction had similar risk factors but was not associated with adverse health outcomes

Abbreviations: 4AD = 4-androstenedione; ABVD = Adriamycin, bleomycin, vinblastine, and doxorubicin; ALL = acute lymphoblastic leukemia; BEP = bleomycin, etoposide, and platinum; BOP = bleomycin, vincristine, and cisplatin; CCG = Children's Cancer Study Group; CCNU = lomustine; CCSS = Childhood Cancer Survivor Study; CEB = cisplatin, etoposide, bleomycin; C-MOPP = cyclophosphamide, vincristine, prednisone, procarbzine; COMP = cyclophosphamide, vincristine, methotrexate, prednisone; CVP = cyclophosphamide, vincristine, prednisone; CALGB = Cancer and Leukemia Group B; CRT = chemoradiation therapy; CSI = cranial or craniospinal irradiation; DHAS = dehydroepiandrosterone; DHT = dihydrotestosterone; E2 = estradiol; EORTC = European Organisation for Research and Treatment of Cancer; EP = Etoposide and Cisplain; FSH = follicle-stimulating hormone; HOS = hypoosmotic swelling test; HD = Hodgkin's Disease; HR = hazard ratio; LH = luteinizing hormone; MOPP= mechloroethamine, vincristine, procarbazine, prednisone; MTX = methotrexate; NHD = Non-Hodgkin's Disease; PRL = prolactin; QOL = quality of life; RT = radiation therapy; SHGB = sex hormone-binding globulin; T = testosterone; TCIS = testicular carcinoma in situ; TBI = total body irradiation; VIP = cisplatin, etoposide, ifosfamide.

* Data provided for entire study population, of which a subset of patients treated with RT is reported in this table.

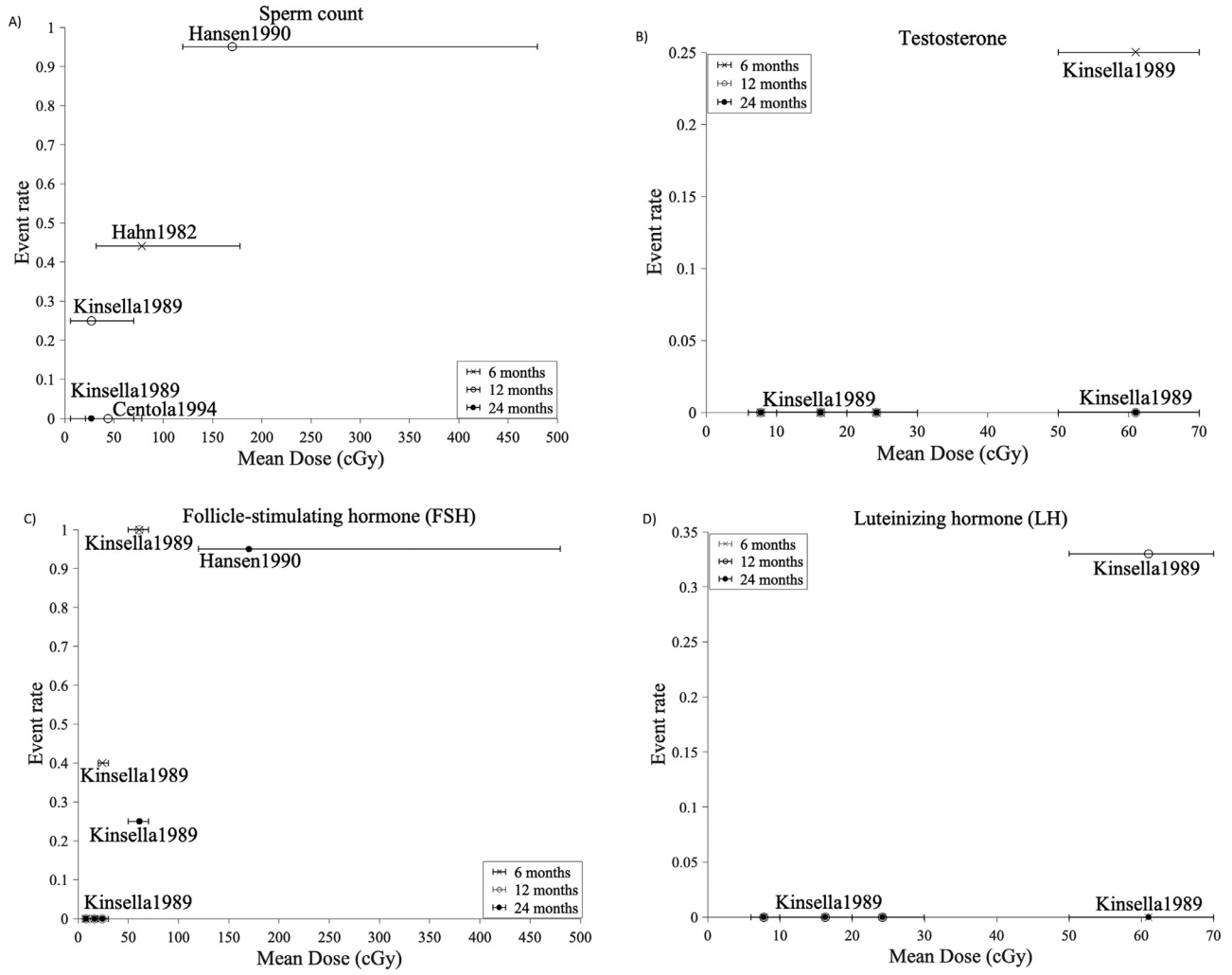

Fig. 2. Effect of mean testicular dose on (A) oligospermia, (B) abnormal testosterone, (C) abnormal follicle stimulating hormone, and (D) abnormal luteinizing hormone. Where there are multiple dots for the same author, these are plotted at the various doses for which they reported an effect. Each dot represents 1 or more patients at that dose level. Data are binned by time of events or follow-up at 6, 12, and 24 months, which are shown by different symbols. When outcomes were the same at more than 1 follow-up time point, more than 1 symbol is used. The lines and whiskers represent the dose range used in the study and the mean value, respectively.

1 patient was found to be azoospermic by 12 months (10%). Martin et al[38] evaluated sperm count and function before and after RT in 11 patients (8 with seminoma, 1 with lymphoma, 1 with rectal adenocarcinoma, and 1 with teratoma) aged between 19 and 47 years who received testicular doses between 0.04 and 5 Gy. The patients with seminoma were treated to 30 Gy to the pelvic or para-aortic fields; the patient with rectal adenocarcinoma was treated with 45 Gy to the pelvis, and the patient with lymphoma received 61.6 Gy to the lumbosacral spine. Of note, 7 of the 11 patients were found to have oligospermia before RT, which excluded them from the dose-response analysis. Of the 4 patients who were not azoospermic, 100% were azoospermic at 12 months after RT, and 2 of 4 (50%) were azoospermic at 2 years. In one of the largest studies on scatter dose, Brydoy et al[43] reported sperm counts in 1191 testicular cancer survivors who received either surgery only, radiation, chemotherapy with a cumulative cisplatin dose ≤850 mg, or chemotherapy with a cumulative cisplatin dose >850 mg with or without retroperitoneal lymph node dissection or RT. RT (n = 39) was typically given to patients with seminoma by dog-leg or L fields or by para-aortic fields. Although radiation dose in the early years was 36 to 40 Gy, this was gradually reduced to 25 to 27 Gy. The rates of azoospermia were approximately 5% after surgery alone, 10% after surgery and RT, 20% after cisplatin ≤850 mg with or without RT, and 40% after cisplatin >850 mg with or without RT. One older study by Pedrick et al[33] evaluated sperm counts in patients treated with RT for Hodgkin disease and seminoma, respectively, and demonstrated similar rates of azoospermia noted in the previously mentioned studies.

In summary, these data suggest that scatter radiation alone (with estimated doses in the range of 0.2-2 Gy) may cause temporary azoospermia and that there is substantial recovery during the following 2 years. However, other modifying factors such as chemotherapy may impair recovery, as seen in some of the studies previously mentioned.

Effects of Scatter Radiation on Hormone Levels

We plotted the risk of abnormal levels of FSH, LH, and testosterone versus estimated mean testicular dose at a time point up to 24 months (Fig. 2B-D). Kinsella et al[41] evaluated the effect of testicular scatter radiation in patients with stage I-IIIA Hodgkin disease who received a dose between 0.06 and 0.70 Gy. Patients who received a dose ≤0.2 Gy to the testes did not have any significant elevation in FSH relative to the normal range. However, in patients who received 0.2 to 0.3 Gy, 40% had FSH elevations relative to the normal range at 6 months. For patients who received a dose of 0.50 to 0.70 Gy, all patients had elevations in FSH relative to the normal range at 6 months, and by 24 months, only 1 of the 4 patients (25%) had returned to his baseline level of FSH. For testosterone levels, only 2 of the 17 patients had a decrease in serum testosterone levels from baseline; 1 received 0.16 Gy and the other received 0.62 Gy.

Huddart et al[44] evaluated gonadal and sexual dysfunction in germ cell tumor survivors who received orchiectomy either alone or with chemotherapy, RT, or both and evaluated changes in hormone levels. Patients who received RT underwent dog-leg RT to 30 Gy for stage I seminoma. The study showed that 45% of patients in the RT group had an elevation in FSH, compared with 11% with an elevation in LH. Of importance is that when chemotherapy was given with RT, the rate of FSH and LH elevation increased to 71% and 21%, respectively. Brennemann et al[32] evaluated serum FSH, LH, and testosterone levels in 20 patients with seminoma who underwent infradiaphragmatic RT of the retroperitoneal and ipsilateral iliac nodes to 36 Gy and in whom the remaining testis received an estimated dose of 0.21 Gy. Of the 12 patients who had normal FSH before RT, all 12 had elevations in FSH at 6 months, and 10 of the 12 (83%) had persistent elevation of FSH at 24 months. In terms of testosterone levels, all levels were normal at 6 to 24 months after RT. Hansen et al evaluated spermatogenesis after RT in 27 patients with seminomas and 24 patients with nonseminoma who had received a mean testicular dose of 1.7 Gy (range, 1.2-4.8 Gy). At 5 years, only 14% of patients had normal serum FSH levels.

Shamberger et al[59] evaluated testicular function in 26 men with sarcoma who received adjuvant chemotherapy (doxorubicin, cyclophosphamide, and high-dose methotrexate) with or without RT. Eleven patients (mean age, 35 years) who received chemotherapy and distal RT (<0.3 Gy to the testes) were evaluated for FSH, LH, and testosterone levels at a mean of 23 months after therapy. In this cohort, 3 of the 11 men (27%) were azoospermic. Although the mean FSH and LH levels were increased 3-fold and 1.7-fold, respectively, compared with controls, the mean testosterone concentration was similar to the reference level for men. Nader et al[60] evaluated FSH, LH, and testosterone levels in 12 men with testicular tumors treated by unilateral orchiectomy followed by abdominal and/or pelvic irradiation between 5 and 20 years after therapy. Dose to the contralateral testes was between 0.1 and 35 Gy (n = 12), with most patients receiving between 1 and 3.5 Gy (n = 9). The LH and FSH levels were abnormal in 75% of patients, but the testosterone level was abnormal in only 1 patient (8%), who received 2 Gy to the remaining testis. Freund et al[61] evaluated testicular function in 8 patients (aged 24-40 years) with low-stage seminoma who were treated with RT after unilateral orchidectomy and in whom the testicular dose ranged from 0.15 to 1.6 Gy. Sperm parameters and serum hormone levels were obtained 10 to 24 months after RT. Elevated LH levels (>50 ng/mL) were observed in 4 of 6 patients (66%), although very elevated levels (>100 ng/mL) were found in patients who received 0.7 and 0.9 Gy and at 10 and 16 months after radiation. Elevated FSH levels were also observed in 4 of 6 patients (66%). Testosterone levels were abnormally low in 2 of 8 patients (25%) at time points of 20 and 22 months after RT. Izard et al[63] performed a review of abnormal testosterone levels plotted against dose and demonstrated an increase in abnormal testosterone levels with higher RT doses. At doses >20 Gy, the percentage of patients with an abnormal testosterone level increased to more than 40%. Shapiro et al[62] evaluated hormonal changes in testicular function in 27 patients with soft-tissue sarcoma (ages 14-67 years) who received between 0.01 and 25 Gy (22 of the patients received <3 Gy) to the testes and showed no significant change from baseline testosterone values after 2 years of radiation.

Effect of Direct RT to the Testes

Thirteen studies were identified that evaluated the effect of direct testicular radiation on several endpoints related to spermatogenesis, including hormonal levels (FSH, LH, testosterone), sperm count, testicular volume, and fertility.[25,47–58] Most studies evaluated some of these endpoints but not all of them. Seven studies evaluated the effect of testicular RT in ALL in either the prophylactic or relapse setting. The testicular doses in these studies ranged from 12 to 24 Gy. Castillo et al[48] evaluated 15 boys with ALL who received a testicular radiation dose of 12 Gy (n = 12), 15 Gy (n = 1), or 24 Gy (n = 2). This study showed that all patients who received testicular radiation between ages 5 and 12 years and could give a semen analysis had azoospermia. In addition, although patients who received an RT dose of 12 Gy had normal testicular size, those who received >12 Gy had testicular volumes that were below the expected normal range. Jahnukainen et al[25] assessed testicular function in adult survivors of childhood ALL at a median follow-up of 20 years, and 18 of those patients received testicular radiation to either 10 Gy (n = 2)

or 24 Gy (n = 16). No patients who received a dose of 24 Gy had spermatozoa in their semen specimen. In addition, testicular volume was significantly reduced in survivors treated with >20 g/m^2 of cyclophosphamide or testicular radiation, and importantly, none of them fathered a child. Similar findings were reported by Siimes et al,[53] who evaluated testicular function in 109 males surviving either leukemia or solid tumors, of whom 18 received testicular RT (median dose 10 Gy) and 35 received cranial RT. The study found significant reduction in testicular volume and an increase in the serum FSH and LH level compared with patients who received no central nervous system or no testicular RT. Sklar et al[52] evaluated testicular function in 60 survivors of ALL who received chemotherapy and 18 or 24 Gy of cranial RT, with or without additional RT. In those who also received 12 Gy craniospinal plus abdominal RT (group 1), 50% had elevated FSH levels, compared with 17% and 0% in those receiving only additional cranial or craniospinal RT (ie, without abdominal RT [group 2]) or cranial RT alone (group 3), respectively. In contrast, Leydig cell function, reflected by LH and testosterone values, and pubertal development were unaffected in most patients, regardless of the extent of the extracranial RT. One of the 11 patients (9%) who received a testes dose of 12 Gy in the craniospinal plus abdominal RT group had elevation in LH level. Testosterone was reduced in 2 of 50 patients in this cohort (4%)—1 patient in group 1 (9%) and another in group 3 (4%). The dose effects from RT on LH levels in this study differ from other studies showing that even small doses can affect LH values. The study was limited owing to the difficulty of differentiating between the contribution of the cranial and noncranial RT effect and the small number of patients who received a direct testes dose of 12 Gy. Leiper et al[51] evaluated 13 boys with ALL who received direct testicular RT (11 received 24 Gy) and cranial irradiation (24 Gy) as treatment for either relapse or prophylaxis. They demonstrated that 6 boys (46%) were able to achieve Tanner stage III-V puberty, whereas 5 boys showed no evidence of pubertal development. This was thought to be due to the age of irradiation, with patients who were older at the time of RT more likely to have evidence of pubertal development. In addition, all patients showed raised levels of FSH, and 11 of the 13 showed elevations in LH levels.

The remaining studies evaluating the effect of direct RT on gonadal dysfunction were conducted in patients with TCIS or solid tumors. Bang et al[56] evaluated 51 men who were treated with RT for TCIS who received either 16 or 20 Gy of RT and demonstrated worse Leydig cell dysfunction in patients who received 20 Gy, reflected as an annual decrease in testosterone levels of 2.6%. Giwercman et al[58] evaluated 20 men who received 20 Gy in 10 fractions for TCIS of the remaining testis that was not removed and demonstrated similar findings to those of Bang et al, with a decrease in baseline serum testosterone values and an increase in serum LH and FSH levels.

One of the most consequential studies on Leydig cell dysfunction after RT was reported from the St. Jude Lifetime Cohort study, which evaluated the effect of risk factors such as testicular dose in men ≥18 years old and with at least 5 years of follow-up after cancer diagnosis. Testicular doses were estimated based on the prescribed dose for direct treatment, and indirect exposures were estimated using treatment records and phantom measurements. Patients were stratified into 4 RT groups including 0 Gy, >0 to 11.9 Gy, 12 to 19.9 Gy, and ≥20 Gy. On multivariable logistic regression analysis, 14% of patients had Leydig cell failure at doses >0 to 11.9 Gy, 41% at doses 12 to 19.9 Gy, and 68.4% at doses ≥20 Gy.[18]

In summary, the data suggest that at doses <0.2 Gy, there is no risk of FSH hormonal dysfunction, but from 0.2 to 0.8 Gy, there is an increase in the risk of FSH elevation, ranging from 40% to 100%. For LH, at doses >0.5 Gy, the LH level was increased in 33% to 75% of patients between 10 and 24 months after radiation. In some studies, LH values normalized after 24 months,[41] whereas in others, the effects were more permanent.[18,44] Testosterone levels were generally found to be normal in patients receiving ≤0.2 Gy and abnormal in up to 14% to 25% of patients who received between 0.2 and 12 Gy. Doses between 12 and 19 Gy may be associated with abnormal testosterone levels in 40% of patients, whereas doses greater than 20 Gy are associated with abnormal results in 68% of patients.

This PENTEC systematic review demonstrates important relationships between RT scatter or direct dose and reproductive endpoints including semen analysis; FSH, LH, and testosterone levels; and testicular size. Doses <10 Gy may cause temporary oligospermia or azoospermia, which in most patients recovers months to years later, whereas doses >10 Gy may cause permanent azoospermia and doses >24 to 30 Gy will definitely cause azoospermia, likely with no chance of recovery. The risk is also modified and influenced by chemotherapeutic agents that affect reproductive functions. Unfortunately, a lack of consistent RT data on testicular dose and uniform reporting of outcomes made it impossible to develop normal-tissue complication probability models.

Limitations

1. Data quality was poor because essentially all of the literature available for review was retrospective. In addition, testicular doses were largely estimated (eg, based on fundamental physics principles), and few studies used actual patient-specific measurements (eg, thermoluminescent dosimeter measurements) or meaningful quality control measures (eg, independent central review); thus, the doses reported could have uncertainties of a factor of 2 (Table E1).
2. Adult cohorts were included for analysis of low-dose radiation exposure of the testes owing to limited sample sizes in pediatric studies.
3. Few studies were available that exclusively ascertained the effect of radiation dose to the testes on outcomes without chemotherapeutic agents that may also affect testicular function.

4. There were interstudy differences that made the pooling and comparing of data between studies potentially problematic. For example, there were often major differences in patient populations, radiation technique, systemic therapies, endpoints assessed, and assessment methods. Even within a given endpoint (eg, testosterone), testosterone levels may not have been obtained in the morning, some studies reported "total" versus "free" testosterone, and few reports considered the effect of body mass index, which can alter testosterone levels. Similarly, for the endpoint of spermatogenesis, most studies did not delineate whether semen analysis was collected as recommended (eg, after a minimum of 2 days and a maximum of 7 days of sexual abstinence and assessed on 2 separate occasions). Testosterone concentrations are affected by age, acute illness, nutritional deficiency, obesity, diabetes, opioids, glucocorticoids, sleep disorders, and obstructive sleep apnea. These issues are not generally addressed in studies of childhood cancer survivors.
5. Studies included in the current analysis most often measured hormonal levels, sperm counts, spermatogenesis, and testicular volume but not fertility as an endpoint after testicular radiation. Long-term childhood cancer survivors are often concerned about future potential for infertility. The Childhood Cancer Survivor Study measured fertility outcomes using self-administered questionnaires without capturing the personal choice not to attempt a pregnancy, unrecognized pregnancies, and men uninformed of pregnancies by their partners. The increased risk of erectile dysfunction secondary to testicular radiation was not analyzed in the present study.
6. We were limited in our ability to determine the effect of testicular dosimetry, beyond mean dose, on testicular function owing to inconsistencies in how RT dose was reported. Therefore, a complete dose-response relationship or normal tissue complication probability modeling could not be performed.

Toxicity Scoring Recommendations

There exists a profound paucity of prospective data regarding the radiation dose-response relationships of reproductive complications in male childhood cancer survivors. Prospective multi-institutional and registry studies are needed to do the following:

1. Standardize endpoints, assessments, and follow-up schedules across institutions.
2. Validate current models using longitudinal assessments in the same patient.
3. Investigate potential predictors of standardized endpoints, including (1) patient-related factors such as age, race, socioeconomic status (including access to fertility therapies), sperm counts, spermatogenesis, hormone levels, and desire for pregnancy; (2) disease factors; and (3) treatment factors such as testicular dose measured by in vivo dosimetry; radiation technique, including use of photon versus proton beams; field arrangement; shielding; irradiated volume; direct versus scattered irradiation; biologically effective dose; fractionation; and effect of concurrent and sequential surgical and systemic therapies including stem cell transplant.
4. Assess the effect of psychological factors and counseling on recovery from reproductive complications of RT.

Validated predictive models for male reproductive complications would enable future clinical trials with individualized, risk-adapted therapy to help reduce the risk of these complications and guide counseling at an interdisciplinary survivorship clinic.

Data Reporting Standards Specific to the Testes

Systematic reviews of mostly retrospective and some prospective data are limited owing to inadequate data on dose and fractionation received, estimation of testicular dose, nonuniform reporting of hormone levels (FSH, LH, and testosterone), and heterogeneous patient populations. Therefore, we propose reporting the following information in future studies to improve data quality:

1. Patient sex, age at diagnosis, and race
2. Clinical indication for RT (cancer diagnosis)
3. Age at which RT was received
4. RT prescription dose and dose per fractionation
5. RT technique and modality (2-dimensional vs 3-dimensional vs intensity modulated RT vs volumetric modulated arc therapy, electrons, or protons)
6. Dosimetric data for testicular dose: mean dose and D0.1cc testicular dose
7. Definitions of oligospermia and azoospermia that are consistent within studies and use the World Health Organization criteria
8. Chemotherapy or immunotherapy and the total chemotherapy dose or alkylating dose
9. Whether surgery such as orchiectomy was performed
10. Levels of FSH, LH, and testosterone before treatment and every 6 months after treatment for up to 24 months
11. Description of underlying genetic abnormalities (Klinefelter syndrome, etc)
12. Description of fertility outcome, including if a child was conceived and at what time point the event happened

Future Investigations

Future studies are needed to better accomplish the following:

1. Standardization of follow-up and endpoint evaluations to have consistent measurements of testicular RT and to

understand the effects on reproductive complications such as infertility
2. Analysis of effects of different radiation treatment techniques such as proton RT, intensity modulated RT, and 3-dimensional conformal RT on testicular dose and reproductive complications
3. Standardization of male reproductive survivorship guidelines to anticipate reproductive complications and identify opportunities for interventions
4. Examination of how combined-modality treatment (both surgery and chemotherapy) affects reproduction
5. Establishment of contouring guidelines for male reproductive organs to ensure consistent dose reporting to the testes
6. Evaluation of the association between quality of life and reproductive outcomes in pediatric cancer survivors

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