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PENTEC ORGAN SYSTEM REVIEW

Effects of Radiation Therapy on the Female Reproductive Tract in Childhood Cancer Survivors: A PENTEC Comprehensive Review

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Purpose: The PENTEC (Pediatric Normal Tissue Effects in the Clinic) task force aimed to quantify effects of radiation therapy (RT) dose to the female reproductive organs after treatment for childhood cancer.

Methods and Materials: Relevant studies published 1970 to 2017 were identified systematically through PubMed, Medline, and Cochrane databases with additional articles before 2021 identified by the group. Two large studies reported sufficient data to allow modeling of acute ovarian failure (AOF; loss of function ≤5 year from diagnosis) and premature ovarian insufficiency (POI; loss of function at attained age <40 years) based on maximum dose to least affected ovary. Although normal tissue complication probability modeling was not feasible for the uterus due to limited data, the relationship between ultrasound-measured uterine volume and estimated amount of RT was plotted. Limited data regarding vaginal toxicity were available.

Results: The risk of AOF increases with RT dose to least affected ovary, alkylating agent cumulative dose (cyclophosphamide equivalent dose [CED] in g/m^2), age at RT, and stem cell transplantation: Two Gy to the least affected ovary resulted in AOF risk of 1% to 5% (CED = 0, risk increasing with age), 4% to 7% (CED = 10 g/m^2, risk increasing with age), and 6% to 13% (CED = 30 g/m^2, risk increasing with age). For patients aged 1 and 20 years at time of RT, AOF risk was ≥50% at doses of 24 Gy and 20 Gy with no alkylating chemotherapy, 22.5 Gy and 17 Gy with intermediate alkylator dose (10 g/m^2), and 17 Gy and 13 Gy with high alkylator dose (30 g/m^2). Risk of POI increases with survivor (attained) age (rather than age at time of RT), radiation dose to least affected ovary, and alkylator dose. Data review suggested that higher radiation doses to the uterus are

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associated with uterine toxicity, with uterine size considerably restricted after 12 Gy. Vaginal radiation in children is associated with high toxicity risk, although dose-volume data are not available for quantification.

Conclusions: Risk of AOF increases with age at RT, CED exposure, and RT dose; risk of POI likewise increases with RT dose, CED exposure, and survivor age. Both AOF and POI are expected to affect fertility and estrogen production. Data suggest that RT uterine dose >12 Gy may be associated with uterine size restriction. Adult literature suggests that maintaining vaginal dose <5 Gy may limit toxicity. Treatment of life-threatening malignancy remains a priority over reproductive preservation; however, when possible, radiation and surgical techniques should be considered to minimize dose to least affected ovary, uterus, and vagina. Survivors should receive endocrine and gynecologic support; those desiring pregnancy should be counseled early to maximize reproductive options.

Introduction

Radiation therapy (RT) is critical in the management of many pediatric malignancies involving the abdomen or pelvis and for patients requiring total body irradiation (TBI) but can lead to significant female reproductive late effects. Either direct or scattered radiation exposure of the reproductive structures (eg, ovaries, uterus, vagina) can predispose survivors to complications that may affect health and well-being for the remainder of life. Exposure of ovaries to even low radiation doses can lead to endocrine dysfunction as well as difficulty or inability to conceive a child, and exposure of uterus and vagina may also contribute to fertility difficulties as well as compromised sexual health. Specific relationships between radiation exposure, outcomes, and effect on survivorship health are not well understood. This comprehensive review from PENTEC (Pediatric Normal Tissue Effects in the Clinic) aims to describe the risk of ovarian, uterine, and vaginal toxicity from radiation to female reproductive organs in childhood.

Clinical Significance

RT remains an integral part of curative treatment for many pediatric tumors, with typical prescribed doses ranging from 10 Gy to 55 Gy for solid and central nervous system tumors. Fields that involve the abdomen or pelvis may result in radiation exposure to one or both ovaries, uterus, and vagina; for example, patients with Wilms tumor with diffuse spillage or preoperative rupture require fields that encompass the entire abdomen/peritoneal cavity, and exposure of female reproductive organs is unavoidable. Even the more focal unilateral "flank" fields often used to treat Wilms tumor limited to the kidney or lymph nodes may result in ovarian exposure in a young child (Fig. 1). Rhabdomyosarcoma often occurs in young children and may involve vagina, uterus, or bladder, and Ewing sarcoma may develop in pelvic soft tissues, bones, or both. Craniospinal or lumbosacral spinal irradiation may result in incidental dose to the ovaries and uterus due to exit dose from divergent posterior beams directed at the low spine. Certainly, TBI, when prescription dose typically ranges from 2 to 12 Gy, results in exposure of all reproductive structures. Although options to minimize or avoid RT are considered in each of these situations, RT is often required as part of lifesaving therapy.

Unavoidable exposure of both ovaries to radiation can affect both hormone production and fertility. Because the ovaries are paired structures, ovarian function will generally be determined by the dose to the least affected ovary, or the ovary receiving the lowest radiation dose. For this reason, avoidance of exposure to one ovary can reduce or eliminate potential negative effects of RT; minimizing the dose to the more affected ovary, when possible, may provide additional benefits. Due to limitations in potential to visualize and contour the ovaries, as well as a paucity of dose-volume data in terms ovarian tissue exposure (both issues discussed in detail below) the dose to the least affected ovary will refer to maximum point dose to that structure within this article.

Ovarian exposure to radiation can lead to loss of estrogen production. Several terms are used to describe this event within the literature (Table 1). The 2 terms selected by the PENTEC group for modeling in this manuscript are as follows:

1. Acute ovarian failure (AOF), which refers to the loss of estrogen production within 5 years of delivery of radiation, and
2. Premature ovarian insufficiency (POI), which refers to loss of estrogen production and oocyte viability during a longer period any time before 40 years of age.

When radiation has been delivered to a prepubescent child and AOF develops, manifestations may be observed at the time of expected puberty, whereas radiation leading to AOF in a postpubertal adolescent or young adult may result in cessation of menstrual cycles.[1] In both pre- and postpubertal scenarios of AOF, estrogen production is not present and oocytes are not viable for reproduction. Lack of estrogen can affect development as well as bone density and cardiac health. Patients who do not experience AOF may remain at risk for POI.[2,3] Like AOF, POI affects both hormone production and fertility, although the effect occurs later in life. For these reasons, patients with ovaries who receive abdominopelvic radiation in childhood should receive follow-up care from a comprehensive endocrinology team in order to address hormonal supplementation needs and maximize reproductive options.

Radiation exposure to the uterus may affect its vasculature, muscle development, and elasticity; similarly, radiation to the vagina can result in vaginal stenosis/fibrosis, dryness, and soft tissue changes. Effect of childhood radiation on vaginal and uterine health has not been studied in a

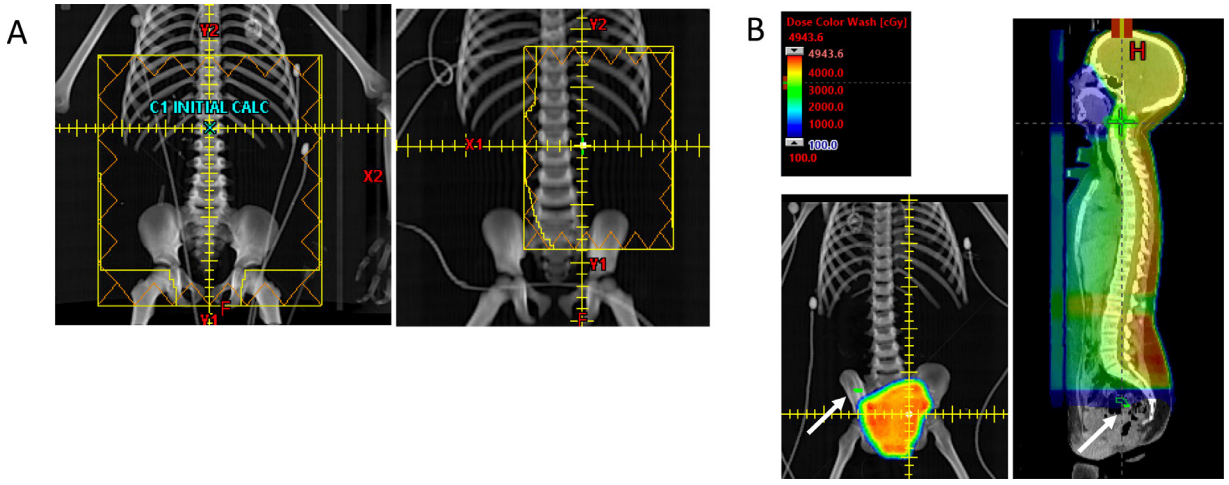

Fig. 1. Radiation fields used for treatment of common pediatric malignancies. (A) whole abdomen (left) and flank fields (right) for Wilms tumor; the whole abdomen field includes the true and false pelvis and encompasses both ovaries. The more limited flank field includes part of false and true pelvis, and crosses midline, with potential to expose one or both ovaries. (B) Ovarian exposure from treatment of a pelvic rhabdomyosarcoma (left) and medulloblastoma (right). In the rhabdomyosarcoma case, the right ovary has been transposed and contoured in green and indicated with white arrow. Total dose is <1 Gy. The left ovary is within the treatment field. In the medulloblastoma case, the ovaries are inferior to the primary beam (green contour, indicated with white arrow); however, are still expected to receive 1 to 2 Gy based on dosimetry.

systematic way. Gynecologic care from a team experienced in cancer survivorship can maximize needed supportive care for optimal sexual and reproductive health.

Endpoints and Toxicity

To characterize female reproductive toxicity after RT in detail, we reviewed published data separately for ovaries, uterus, and vagina. Few publications exist on quantitative aspects of irradiation of uterus and vagina. A more significant quantity of literature exists examining ovarian function after radiation therapy for childhood cancer, although endpoints and patient populations vary considerably across published studies (Tables 2 and E1). We selected AOF and POI, defined previously, as endpoints that would best allow accurate survivorship and family counseling as well as understanding of fertility and endocrine risk. Based on information and data presented in reviewed publications, these endpoints were ultimately used for PENTEC analysis.

Table 1 Endpoints and terminology used within the literature to describe loss of ovarian function

Term (abbreviation)	Definitions in reviewed publications
Acute ovarian failure	Permanent loss of ovarian function within 5 y of cancer diagnosis or no menarche after cancer treatment by the age of 18 y Alternatively, Permanent loss of ovarian function within 5 y of cancer diagnosis
Nonsurgical premature menopause	Has not experienced spontaneous menses for at least 6 mo and other causes, for example, pregnancy, use of agents such as injectable progesterone and gonadotropin-releasing hormone analogs had been excluded
Ovarian failure or premature ovarian failure	Any of the following, depending on study specifics: menopause at younger age than typical normal menopause, abnormal ovarian hormone levels, delayed pubertal development, menstrual irregularities in postpubertal patients, treatment with hormone replacement therapy
Ovarian insufficiency	At younger age than typical normal menopause, any of the following, depending on study specifics: Abnormal ovarian hormone levels, delayed pubertal development, menstrual irregularities in postpubertal patients, treatment with hormone replacement therapy
Premature ovarian insufficiency	At younger age than typical normal menopause, any of the following, depending on study specifics: Abnormal ovarian hormone levels, delayed pubertal development, menstrual irregularities in postpubertal patients, treatment with hormone replacement therapy

Table 2 Summary of selected publications examining ovarian function in female childhood cancer survivors

Study (first author, year)	Cohort: no. cases in study (n) /description of treatment groups (Gp)	Diagnosis or reason to treat	Age (y) range at txt and study	Source of dose information	Radiation type, dose and dose range	Systemic agents	Endpoint assessment methods	Endpoint	Study conclusion
Ahmed et al, 1983[11]	Gp 1 (3): 1-2 y chemo Group 2 (4): no long-term chemo	Medulloblastoma, postop CSI	Gp 1: Txt: 2.5-7.1 Study: prepubertal Gp 2: Txt: 1.3-10 Study: postpubertal	Prescription	30 Gy CSI +15 Gy posterior fossa	Gp 1: alkylating agents Gp 2: None	Clinical examination Serum hormone concentrations	Ovarian function	Ovarian function impaired in Gp 1
Thibaud et al, 1998[12]	Gp 1 (8) Gp 2 (9) Gp 3 (7) Gp 4 (5)	Bone marrow transplant	At txt: Gp 1: 9.5-17.5 Gp 2:7.5-13 Gp 3.2-12 Gp 4: 5.2-13.1 Study: median 3 y posttransplant	Prescription	Gp 1: 0 Gp 2: TBI 2 Gy × 6 Gp 3: 10 Gy × 1 Gp 4: TAI 5-6 Gy × 1	Systemic agent regimens described in reference	Clinical examination: breast development, estradiol, FSH and LH levels	Ovarian function (normal or failure[†])	Ovarian failures in each group; fewest (62.5%) in Gp 1
Blask et al, 1999[13]	Gp 1 (5) Whole abdomen (WA) Gp 2 (12) hemiabdomen (HA) Gp 3 (6) chemo only Gp 4 (50) controls without cancer	Wilms tumor	WA: 2 prepuberty (Pre), 3 post HA: 2 Pre; 10 post Chemo only: 5 Pre; 1 post Controls: 25 Pre; 25 post	Prescription, treatment films	WA: 10.5-30 Gy HA: 10.5-41 Gy	Regimens described in reference	Ultrasound, Gonadotropin levels	Ovarian function (normal or failure) Clinical progression thru puberty Ovary and uterus sizes	Primary ovarian failure if treated with WA postpuberty Normal gonadotropin levels if treated with HA postpuberty
Bath et al, 1999[14]	Gp A (8) Gp B (12) Gp C (5)	Gp A: ALL or AML Gp B: ALL Gp C: Normal controls	Gp A: Txt median: 11.5 (5.9-15.1) Study median: 16.4 (14.1-21.5) Gp B: txt median: 6.7 (3.8-13.5) Study median: 21.8 (15.8-32.8) Gp C: study median: 25.2 (24.1-27.1)	Prescription, treatment records	Gp A: TBI 14.4 Gy/8 fx Gp B: cranial RT Gp C: no radiation	Regimens described in reference	Ultrasonography, gonadotropin and hormone levels	Ovarian function (normal or failure[†]) Clinical progression through puberty Ovary and uterus sizes	Gp A: 75% had absent ovarian function, small uterine volume Gp B: normal progression through puberty

(*Continued*)

Table 2 (*Continued*)

Study (first author, year)	Cohort: no. cases in study (n) /description of treatment groups (Gp)	Diagnosis or reason to treat	Age (y) range at txt and study	Source of dose information	Radiation type, dose and dose range	Systemic agents	Endpoint assessment methods	Endpoint	Study conclusion
Chiarelli et al, 1999[15]	719 female childhood cancer survivors, Ontario Cancer Registry, diagnosed before age 20 from 1964-1988	Various: 225 with abdominopelvic (ABP) RT 71 with no RT but AA chemo	Txt: before age 20 Study: median age 28 (18-49)	Dose and location from treatment records	3 ABP dose bins: Low <20 Gy Medium: 20-35 Gy High >35 Gy 3 AA score bins: Low <50% Medium: 50-75% High >75%	Regimens and described in reference.	Phone questionnaire: 11/93 and 12/94 Censored at age of reported menopause	Incidence and age of nonsurgical menopause	AA, ABP dose, older age at diagnosis increase menopause risk ratios
Schuck et al, 2005[16]	55 pts younger than 30 y at pelvic RT (1/79-12/98) Gp 1: Direct irradiation of both ovaries (10/16 evaluable patients) Gp 2: Both ovaries potentially in treatment fields (8/14 evaluable) Gp 3: At least one ovary not in treatment fields (19/24 evaluable)	Hodgkin disease, sarcomas, Nephroblastoma, Other cancers requiring pelvic RT	Txt: Median (range) age 15 (1-30) Study: Minimum 2 y follow-up	Evaluation of RT plan and sim films; Some ovaries visible with clips; Contralateral ovary assumed spared for hemipelvis RT.	Pelvic Rx doses Gp 1: 15-60 Gy Gp 2: 38-56 Gy Gp 3: 12-54 Gy	No details given	Clinical evaluation Use of hormone replacement therapy Hormone status	OI[‡] as indicated by ovarian hormone levels and/or secondary amenorrhea, menopausal symptoms, sex hormone replacement therapy	OI: Gp 1: 90% Gp 2: 87.5% Gp 3: 47.4% Gp 3 patients with OI older at treatment (18 vs 6 y)

(*Continued*)

Table 2 (*Continued*)

Study (first author, year)	Cohort: no. cases in study (n) /description of treatment groups (Gp)	Diagnosis or reason to treat	Age (y) range at txt and study	Source of dose information	Radiation type, dose and dose range	Systemic agents	Endpoint assessment methods	Endpoint	Study conclusion
Chemaitilly et al, 2006[1]	CCSS: 3390 female survivors older than 18 at time of study	Various cancers (Table 1)	Mean (±SD) Txt with AOF[§]: 9.8 (±6) Study with AOF 32.9 (±6.8) Txt without AOF 8.3 (± 6) Study with AOF 29.6 (± 7.4)	Minimum ovary dose (Min2) per Dosimetrist evaluation of treatment records; primary and scatter doses from planned fields summed using methods of Critchley et al[21]	Min2 dose in 5 bins No RT 1-99 cGy 100-999 cGy 1000-1999 cGy ≥2000 cGy	7 chemo groups focused on AA[‖]	Questionnaires; review of medical records	AOF[§]	215 with AOF. Significant risk factors (multivariate logistic regression model): age at diagnosis, Min2 ovary dose, AA exposure AOF more likely for patients older at treatment
Sklar et al, 2006[3]	CCSS: 2819 female survivors older than 18 at study 1065 female sibling controls with normal menarche	Various cancers (Table 1)	Mean (range) With NSPM[¶] Txt: 12.9 (0-20) Study: 36.8 (21-48) Without NSPM Txt: 8.2 (0-20) Study 29.3 (18-50)	Dosimetrist evaluation of treatment records to calculate dose to ovaries and pituitary. Primary and scatter doses from planned fields summed using methods of Critchley et al[12]	Dose to least affected ovary[#] in 4 bins No RT: 1081 pts 0.1-99 cGy: 1140 pts 100-999 cGy: 258 pts ≥1000 cGy: 74 pts	7 chemo groups focused on AA[‖]	Questionnaires; Medical records reviewed by Dosimetrist coauthor who individually estimated ovary doses.	NSPM[¶] before age 40 without AOF[‖]	65 survivors with NSPM, (survivor vs sibling rate 8% vs 0.8%) Significant NSPM risk factors by Multiple Poisson regression model for NSPM: ovary dose, attained age, AA score, Hodgkin lymphoma (HL) Without HL, RR increases from 1 (no RT) to 109.6 for RT ≥1000 cGy. With HL, RR with no RT is 9.18

(*Continued*)

Table 2 (*Continued*)

Study (first author, year)	Cohort: no. cases in study (n) /description of treatment groups (Gp)	Diagnosis or reason to treat	Age (y) range at txt and study	Source of dose information	Radiation type, dose and dose range	Systemic agents	Endpoint assessment methods	Endpoint	Study conclusion
Beneventi et al, 2014[17]	Single institution: 135 female survivors treated in childhood, with RT and/or CT and/or SCT. Treated 1984-2011, evaluated 1/10-12/12	Cancer: 102 pts Nonmalignant diseases: 33 pts 106 SCT patients: 37 pts had TBI conditioning (30 premenarche)	Median (IQR) age at treatment 10: IQR 6-16 Median age (IQR) at study 19: IQR 16-21	Dosimetric evaluation stated as "treatment protocol employed for the original disease"	TBI: 2 Gy × 6 fractions 37 pts who got SCT Other RT: 12 pts; doses and sites not described	From treatment records	Gynecologic evaluation: ultrasound, interview, blood samples	Ovarian volume Uterine volume Menstrual activity AMH** and inhibin concentrations	TBI or AA conditioning for SCT associated with reduced AMH and Inhibin B levels. Lower uterine volumes in patients treated premenarche
Chemaitilly et al, 2017[18] ††	921 survivors of childhood cancers in SJLIFE cohort, ≥10 y postdiagnosis, 200 with RT	Various cancers	Txt: Mean (SD) age: 8.1 (5.6) Study: Median (range) age: 31.7 (19-60.6) 24 y Median study time postdiagnosis	Doses were reconstructed from each patient's records using age-appropriate anatomic computer phantoms. Lower ovary dose used in analysis. Ovary positions average from scans of 10 patients with visible ovaries	3 dose bins for lower mean ovary dose: 0 cGy 1-999 cGy ≥1000 cGy	Exposure to AA quantified by CED‡‡ CED bins, mg/m^2: 0 <8000 8000-11,999 12,000-19,999 ≥20,000	Medical history and questionnaires; Clinical evaluation; blood tests (serum levels of FSH, LH, estradiol)	POI§§ patients without POI censored at age 40 y	100 with POI. Risk factors by multivariable Cox regression model: BMI, lower mean ovary dose, CED.

(*Continued*)

Table 2 (*Continued*)

Study (first author, year)	Cohort: no. cases in study (n) /description of treatment groups (Gp)	Diagnosis or reason to treat	Age (y) range at txt and study	Source of dose information	Radiation type, dose and dose range	Systemic agents	Endpoint assessment methods	Endpoint	Study conclusion
Clark et al, 2020[19] ‖ ‖	CCSS: 5886 treated 1/70-12/99 SJLIFE: 875 SJLIFE treated after 1962	Various cancers	Median (range): Txt: CCSS: 7.3 (3.2-13.7) Study: CCSS >5 y survivors, age ≥18 at most recent evaluation SJLIFE: treatment: 6.7 y (3.4-13.2) At study: SJLife: >10-ysurvivors	CCSS doses reconstructed by MDALEG from patient's records using age-appropriate anatomic computer phantoms Lower dose ovary used in model. SJLIFE dosimetry not stated but other SJLIFE studies use patient's fields and age-appropriate computer phantoms	Various (0 to >20 Gy)	From treatment records. AA doses summarized by CED[§§]	Questionnaires; Blood tests (hormone levels) Endocrinologist evaluation; For CCSS patients, individual ovary doses reconstructed from treatment records on age-appropriate computer phantoms. For SJLIFE cohort, dosimetry is not described	AOF[¶¶]	CCSS: 353 AOF (6% of cohort) SJLIFE: 50 AOF (5.7% of cohort) Predictors of AOF include age at cancer diagnosis, HSCT, CED, lower of the 2 ovary mean doses Logistic regression model coefficients published with link to an AOF calculator[##]

Abbreviations: AA = alkylating agent; ALL = acute lymphocytic leukemia; AMH = anti-mullerian hormone; AML = acute myeloid leukemia; AOF = acute ovarian failure; CED = cyclophosphamide equivalent dose; CSI =craniospinal irradiation; CT = chemotherapy; FSH = follicle stimulating hormone; Gp = groups; HSCT = hematopoietic stem cell transplant; MDALEG = MD Anderson Late Effects Group; NSPM = nonsurgical premature menopause; OI = ovarian insufficiency; POI = premature ovarian insufficiency; RT = radiation therapy; RR = risk ratio; SCT = stem cell transplant; TAI = thoraco-abdominal radiation therapy; TBI = total body irradiation; Txt = text.

*Nitrosourea, vincristine, and nitrosourea.

† Ovarian failure assessed by lack of breast development or normal menstruation and abnormal basal plasma concentration of estradiol, gonadotropins, and other ovary-related hormones.

‡ Ovarian insufficiency, also referred to in paper as "ovarian failure": abnormal ovarian hormone levels, delayed pubertal development, menstrual irregularities in postpubertal patients, use of hormone replacement therapy.

§ Never menstruating or ceased having menses within 5 years after their cancer diagnosis.

‖ AAs of particular interest were procarbazine and cyclophosphamide.

¶ Menopause defined as "has not experienced a spontaneous menses for at least 6 months and other causes eg, pregnancy, use of agents such as injectable progesterone and gonadotropin-releasing hormone analogs had been excluded." Patients with AOF were excluded.

Dose-volume nature of ovary dose is not clear from the article, but it is for the lower of the 2 ovarian doses (dose to least affected ovary).

** AMH and inhibin are secreted by cells in ovarian follicles implying that lower concentrations indicate lower follicle number.

†† Used in PENTEC Premature Ovarian Insufficiency model.

‡‡ Units mg/m^2 = weighted average of cyclophosphamide treatments.[34]

§§ Persistent amenorrhea with evidence of a primary ovarian origin before the age of 40 years. Patients with AOF are included.

‖ ‖ Model used for Figure 4.

¶¶ Permanent loss of ovarian function within 5 years of cancer diagnosis or no menarche after cancer treatment by the age of 18 years. Note this definition is slightly different from that of §.

Link to online calculator: https://ccss.stjude.org/aofcalc.

In most publications, accurate dosimetric data were not available and radiation dose-volume relationships were not analyzed (a scenario resulting from difficulty characterizing/contouring ovaries in young children and the lack of 3-dimensional radiation planning in many older studies). Chemotherapy represented a significant confounder in most studies and was accounted for in varying ways. These factors have made clear understanding of ovarian dose-volume-toxicity relationships extremely challenging. As outlined previously, radiation-related ovarian toxicity may develop up to 4 decades after RT; thus, the lack of accurate, long-term follow-up data affects all published work in this area.

Uterine toxicities may include small uterine volume, impaired arterial blood flow, uterine fibrosis, and endometrial dysfunction, which have been associated with increased risk of early pregnancy loss, preterm birth, and delivery of low-birthweight infants.[4] Literature that would allow true mathematical modeling of RT-associated risk of such toxicity is not available, and thus we performed a comprehensive literature review in order to use a descriptive approach of the effect of RT on uterine size and arterial blood flow.

Vaginal late toxicities may include fibrosis, stenosis, vaginal dryness, mucosal thinning, and retained menstrual products resulting from closure of the vaginal canal. Few published studies exist examining vaginal toxicity in pediatric cancer survivors, and so a brief discussion will be provided based on these studies and the authors' experience and expertise.

Anatomy and Developmental Dynamics

All structures within the female reproductive tract (vagina, cervix, uterus, fallopian tubes, and ovaries) are present at the time of birth, without dramatic anatomic change from infancy until puberty.[5] Ovaries are the female gonads, located within the pelvis, and attached to the uterus via the ovarian ligament. Ovarian follicles are oocytes and their supporting cells, and a female infant will have 1 to 2 million oocytes within her ovaries; this is her lifetime supply. At the initiation of puberty, levels of luteinizing hormone and follicle stimulating hormone secretion from the anterior pituitary gland increase, stimulating increased estrogen secretion by ovaries. Increased estrogen leads to breast development, axillary and pubic hair growth, increase in height, and menarche. At this time, ovulation begins, with oocyte release, and concomitant follicle loss, approximately every 28 days. The number of oocytes (and follicles) continues to decline with increasing age. Estrogen, produced by ovarian follicles, continues to support many normal physiological functions until menopause, when the menstrual cycle ceases due to loss of ovarian follicles. As menopause approaches, larger numbers of follicles may mature with each cycle, leading to depletion of all follicles and declines in estrogen level.

The uterus is a muscular cavity where a fertilized oocyte may implant and grow and is composed of endometrium, myometrium (thick layer of smooth muscle), and perimetrium.[5] During menstrual cycles, estrogen secreted by ovarian follicles leads to thickening of the endometrium, which is shed during menstruation if oocyte fertilization does not occur. If fertilization does occur, the endometrium will continue to thicken to support the growing embryo, requiring significant blood supply from spiral uterine arteries, and the uterus will stretch massively in order to accommodate the growing fetus and placenta. The vagina is a muscular tunnel that connects the uterus to the exterior. It allows for sexual intercourse, oocyte fertilization, passage of menstrual contents, and vaginal delivery of an infant.

Defining Volumes: Pediatric Imaging Issues

Ovarian tissue is difficult to impossible to identify on computed tomography (CT) based imaging in young children and remains difficult even in older children and adults. Ovaries are very small in prepubertal children (mean, 0.6-1.05 cm^3),[6,7] enlarging during puberty to a mean 5.8 cm^3.[7] Ovarian position is also variable. Although ovaries are most commonly located within the true pelvis (area delineated by the anterior-superior iliac spines, inner side walls of ilium, and symphysis pubis), they may also be located in the false pelvis (superior or lateral to true pelvis); this scenario occurs most frequently in very young children.[8] As a result of this variability, surrogate bony or other landmarks do not allow for accurate volume delineation.[9] Bladder and rectal filling status may affect ovarian position and cause positional variability. Avoidance of constipation during the RT course through medical bowel regimen may reduce positional variability related to rectal filling; along the same lines, treating with a consistently empty or full bladder may reduce the effect of dynamic bladder size. Effects of full versus empty bladder should be evaluated, when possible, with regard to positional reproducibility and radiation dose to pelvic organs.[10] In addition, presence of tumor may at times result in ovaries being pushed into nonphysiological positions, and this may change with tumor response to therapy. Ovarian tissue may be identified on magnetic resonance imaging (MRI) with information transferred to CT planning images via image registration. Identification of ovaries on axial imaging is outside of the scope of expertise of most radiation oncologists and generally requires side-by-side image review with a pediatric radiologist; even with expert review, ovaries are occasionally not identifiable on MRI or CT in premenarchal children. Ovaries are most reliably identified by placement of at least one surgical clip, which may be accomplished at the time of ovarian relocation or cryopreservation, or at the time of cancer surgery. For treatment planning dosimetric evaluation, ovaries should be contoured individually, when visualized, with a planning organ-at-risk volume added through at least a 5 mm isotropic expansion.

A contrast-soaked cotton swab or other marker may be placed within the vagina at the time of simulation in order to delineate the vaginal canal and surrounding tissues (eg, vaginal walls and uterus; Fig. 2). The uterus may be small in

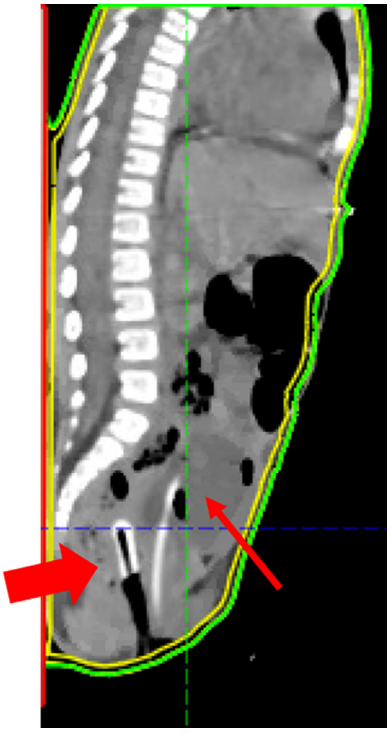

Fig. 2. Computed tomography simulation image demonstrating empty rectum, vaginal marker (thick arrow), and bladder filling using Foley catheter placement under general anesthesia (thin arrow). These interventions may assist with volume definition and reduction in internal organ motion. Full bladder may, in certain cases, maximize distance between radiation field and vagina, uterus, and bilateral or contralateral ovaries.

a young child and is identified as the soft tissue occupying the space between urethra/bladder and rectum; the uterus is also visible on MRI. As described previously, stabilization of rectal and bladder volumes can minimize interfraction motion of these pelvic organs.

Review of Dose-Volume Response Data and Risk Factors

Identification of eligible studies

Relevant studies published from 1970 to 2017 were identified through search of the PubMed, Medline, and Cochrane databases with additional articles prior to 2021 identified by the group. Search terms included "radiotherapy AND female AND cancer AND (oocyte OR premature menopause OR gonadotoxicity)." Initial search revealed 2392 records, of which 856 were relevant on initial review, and 42 on detailed review. After literature review, publications that reported the number of survivors with and without events for specific reproductive organ doses were identified. Various endpoints were reported in these publications (Tables 2 and 3) but very few articles reported information on specific ovarian dose or volume. The most applicable articles relating dose to ovarian outcomes are summarized in Table 2,[1,3,11-19]; their dosimetry grades and scores are in Table E1. We identified fewer studies for the uterus, most of which reported ultrasound measurements of uterine volume depending on treatment. These are summarized in Table 3.[13,14,17,20-25] Because of the proximity of ovaries and uterus, 3 articles reported radiation effects for both organs. We found only 3 studies[26-28] on dosimetric aspects of vaginal complications in pediatric patients.

Ovaries: Insights into the decline in ovarian reserve

Unique aspects of the ovary lead to the somewhat paradoxical observation that the ovary becomes more sensitive to radiation-related damage as a person ages, a phenomenon first described in the 1980s by Wallace et al.[29,30] This stands in contrast to other tissues (including uterus and vagina), that are more sensitive in a young child than an adolescent or adult, and likely occurs because a female person has the highest number of oocytes and ovarian follicles at birth (providing more reserve) and in early childhood, as revealed by histologic studies[31] (Fig. 3). In a normal female, the number of ovarian follicles declines with age from >1 million at birth to approximately 1000 at normal menopause (on average 50 years), as shown in Figure 3. Average follicle numbers, their approximate decline, and standard deviations, have been determined from histologic studies of samples from persons who have not undergone radiation. A mechanistic view of dependence of radiation-induced POI based on the histologic data are given by the widely cited Wallace model.[29,30] In this and related publications from Wallace et al, follicle radiosensitivity is given by a linear model with lethal dose = 2 Gy (dose of radiation to destroy 50% of the primordial follicles), which was determined from a small group of children and adolescents who received TBI.[30] The Wallace model assumes that a dose of radiation (D) reduces a patient's number of follicles from age-normal, N(age) to N(age)e^(−D × ln2/2), effectively resetting the patient's ovarian reserve to that of an older person. The rate of normal follicular decline in the older person with the equivalent biologic age is assumed to continue from that point and the patient experiences menopause when the number of follicles is characteristic of menopause. Wallace et al[32] defined the "effective sterilizing dose" as the dose at which the patient's oocyte population will fall to <1000, rendering the patient's reproductive status equivalent to that matching the histologic samples from an average 58-year-old woman. For example, the predicted effective sterilizing dose for a 5-year-old is approximately 19.5 Gy and for a 15-year-old, approximately 17.5 Gy. This is an idealized model scenario, and, clinically, patients experiencing an effective sterilizing radiation dose, as defined by Wallace, would be observed as a subset of patients falling within the 5-year time window of AOF. Although the Wallace model is fascinating, and its

Table 3 Summary of literature review on uterine function in childhood cancer survivors

Study (first author, pub year)	Source and no. of patients (n), by treatment group (Gp)	Age (y) range at txt and study	Uterus dose	Dosimetry evaluation	Assessment method	Study findings
Blask et al, 1999[13]	Gp 1 (5) Whole abdomen (WA) Gp 2 (12) hemiabdomen (HA) Gp 3 (6) chemo only Gp 4 (50) controls without cancer	Average patient age at study 14.4 y WA: 2 prepuberty [Pre], 3 post HA: 2 Pre; 10 post Chemo only: 5 Pre; 1 post Controls: 25 Pre; 25 post-imaged for noncancer conditions	5 WA RT- 3 postpuberty, >20 Gy Rx 12 HA 14 Gy, others 10.5-41 Gy	Prescription, treatment films	Transabdominal ultrasound and clinical evaluation	No significant dependence of sonographic abnormality on abdominal dose ($P = .683$) reported
Bath et al, 1999[14]	Group A (5): TBI for ALL or AML (standard chemo for disease) Group B (12): cranial RT + chemo for ALL; Group C (5): normal controls	Gp A: At txt: median 11.5 (5.9-15.1); At study: 16.4 (14.1-21.5) Gp B: At txt: 6.7 (3.8-13.5); At study: 21.8 (15.8-32.8) Gp C: at study: 25.2 (24.1-27.1)	Group A: 14.4 Gy/8 fx Groups B out-of-field uterine dose Group C: none	Group A: TBI prescription Group B: not described Group C: N/A	Clinical assessment followed and ultrasonography to measure uterine volume,* artery pulsatility, endometrial thickness; Serum assays of gonadotropin and other hormone levels	Group A: Significantly low uterine volume and absent artery pulsatility; 4 weeks of physiological sex steroid replacement therapy increased uterine volume, though it remained below normal (Groups B and C). Linear relation between volume and age at treatment noted No significant differences among groups in endometrial thickness and pulsatility index
Holm et al, 1999[20]	12 female survivors who had TBI conditioning for allogeneic BMT before 12/31/90. All had chemotherapy; none had spinal RT	Median age (range) at BMT: 12.7 y (6.1-17.6 y) At study: 21.5 y (11.6-25.6y). At study, all postpubertal; 11/12 had menarche	4 pts: midline dose 8.5-10 Gy in 1 fx 8 pts: midline dose 10.9-11.7 Gy in 3 fx	TBI prescription	Transabdominal ultrasound; uterine and ovarian volumes* and uterine arterial blood flow	Uterine volume significantly reduced compared with 166 normal subjects. Impaired blood flow. Normal uterine volume not reached despite sex steroid replacement therapy

(*Continued*)

Table 3 (*Continued*)

Study (first author, pub year)	Source and no. of patients (n), by treatment group (Gp)	Age (y) range at txt and study	Uterus dose	Dosimetry evaluation	Assessment method	Study findings
Critchley 1992[21] and 2002[22,†]	Gp 1 (10): Women with premature ovarian failure (POF) who received WA RT as children Gp 2 (22): controls with POF but no RT	Median age (range) at treatment 2.5 y (0.1-11 y); at study 24 y (15-31) Median age of control group 31 y (23-37 y)	WA RT 20-30 Gy, median dose 27.5 Gy (20-30)	Prescription dose	Ultrasonography: uterine length, uterine artery pulsatility index (Doppler ultrasound), endometrial thickness. Scans conducted while subjects were receiving sex steroid replacement therapy	Uterine length in WA survivors significantly less than in cohort without RT. No artery Doppler signals from 5 RT pts, signal from one artery in 3 RT pts vs normal signals from all controls. Endometrial thickness did not increase normally in 3/10 with RT but increased in all 18 patients without RT
Larsen et al, 2004[23]	100 survivors of pediatric cancers Diagnosed 1/70-12/96 Off treatment for at least 1 y at study All had chemotherapy; 56 had RT	Median age (range) at diagnosis 5.4 y (0.1-15.3); at study 25.7 y (18.5-44.4); all were postpubertal at study	4 dose groups: Gp 1 (44): No RT Gp 2 (21): RT above diaphragm Gp 3 (19): RT below diaphragm with possible uterine exposure Gp 4: Definite dose to uterus: TBI (10) (11.3 Gy [8.5-12.5]) or whole abdomen or pelvis (6) (median, 30.6 Gy [25.9-54.1])	Prescription, treatment records, films	Ultrasonography: Uterine volume,* endometrial thickness, uterine artery blood flow (Doppler ultrasound) All measurements were for nulliparous patients	Uterine volume was significantly lower in Gp 4: In Group 4, younger age at treatment significantly correlated with lower uterine volumes at study. No significant differences in endometrial thickness between groups No chemotherapy effects on uterine volume were seen. Pregnancies occurred in all 4 groups
Beneventi et al, 2014[17]	135 survivors of childhood cancers treated 1984-2011	At treatment: 92 were premenarche at treatment, 43 postmenarche At study: 89% were 14 y or older	106 had stem-cell transplant (SCT), 37 with TBI conditioning (2 Gy × 6 fx, bid) 12 patients had other radiation therapy	Prescription for TBI Other RT not described	Ultrasonography (120 pts); uterine volume* and artery pulsatility index (Doppler ultrasonagraphy); blood tests to determine AMH and inhibin-B concentrations as indicators of ovarian function	TBI was associated with significant reduction in uterine size. Premenarche at TBI (n = 28): 7.45 mL (IQR 4.27-17.55) Postmenarche at TBI (n = 6): 20.27 mL [IQR 16.45-22.26]

(*Continued*)

Table 3 (*Continued*)

Study (first author, pub year)	Source and no. of patients (n), by treatment group (Gp)	Age (y) range at txt and study	Uterus dose	Dosimetry evaluation	Assessment method	Study findings
Inagaki et al, 2013[24]	5 females; BMT for SAA or RCC	At treatment: median (range) 9 (6-10) At study: All >12 y	TBI 3 Gy × 1 fx and high-dose cyclophosphamide	TBI prescription	No specific uterine measurements; clinical evaluation only	All had normal menses beginning spontaneously at aged 10-12
van de Loo et al, 2019[25]	Dutch Childhood Oncology Group Long-term effects after childhood cancer as part of a retrospective cohort study DCOG LATER_VEVO Gp1 (55) CCSs[5] had RT likely to involve part/all of uterus as part of treatment, 53 had chemotherapy Gp 2 (110) had no RT, 93 had chemotherapy Gp 3 (110): general population controls	Gp1: 44/55 treated with RT were nulligravidous at study Gp 2: 88/110 without RT were nulligravidous at study Gp3: 88/110 controls were nulligravidous at study	All CCSs were younger than 18 y at treatment and had survived at least 5 y before study; Treatment dates 1963-2002 All >18 y at evaluation. All participants had transvaginal ultrasound scan, blood sample, answered questionnaire, had clinical assessment For CCSs with RT: Rx doses: 33% <15 Gy; 40% between 15 and 30 Gy; 15% >30 Gy	Prescription and field films. Detailed dosimetry unavailable to investigators. Prescription bins: Low (≤15 Gy) Medium (15-30 Gy) High (>30 Gy)	3D ultrasonogaphy with vendor software for volumetrics and pulsatility index for uterine artery blood flow Nulligravidous and gravidous women were evaluated separately because uterine volume increases after pregnancy Pregnancy outcomes were also reported	Significantly smaller uterine volume found for all CCSs, whether treated with RT or not, compared with general population controls. Difference between RT-exposed and non-RT-exposed CCSs uterine volumes was not significant. No difference in uterine artery pulsatility between all 3 groups. Significantly higher rate of pregnancy complications in CCSs who had RT

Abbreviations: 3D = 3-dimensional; ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; BMT = bone marrow transplant; CCSs = childhood cancer survivors; RCC = refractory cytopenia of childhood; RT = radiotherapy; SAA = severe aplastic anemia; TBI = total body irradiation; Txt = text.

* Uterus and ovarian volumes are approximated by ellipsoid with measured major axes in the sup-inf, rt-lt, ant post directions.

† For a review that include results of Critchley et al.[21]

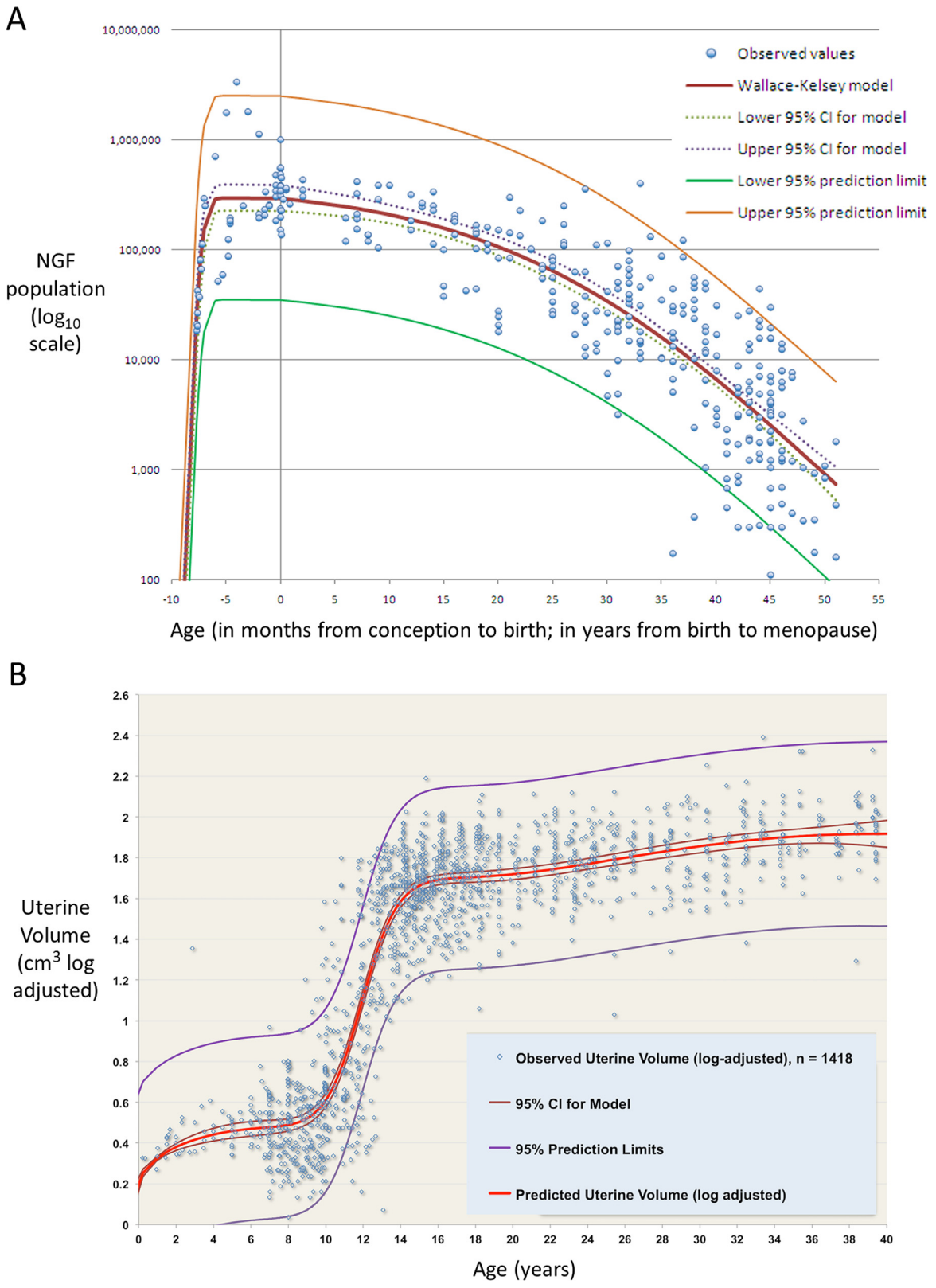

Fig. 3. Normal patterns of change in ovary and uterus. (A) The natural decline in nongrowing follicles with age from conception to 51 years. Circles are 325 data points taken from 8 histologic studies. Solid curves are the double Gaussian model fit to the data with 95% prediction limits by Wallace and Kelsey. Dashed curves are the 95% confidence interval for the model. The Wallace-Kelsey model indicates approximately 1000 follicles remaining at 50 years of age for females born with the median number of follicles (reproduced from Fig. 1 in Wallace and Kelsey, 2010,[31] with permission). (B) Log-adjusted data and normative model demonstrating predicted uterine volume according to age (reproduced from Fig. 2 in Kelsey et al, 2016,[37] with permission). *Abbreviations*: NGF = nongrowing follicles.

qualitative components are sensible, the PENTEC group elected to work from larger clinical studies that include chemotherapy and a greater range of clinical scenarios.

Mathematical models of acute ovarian failure and premature ovarian insufficiency

One large study[19] provided a published model of AOF and another[18] reported sufficient data to allow conversion by the PENTEC team of a published Cox model to a logistic regression model of POI. From these, the risks of AOF and POI as functions of RT dose to the least affected ovary, and the alkylating agent cumulative dose (cyclophosphamide equivalent dose [CED] in g/m^2), were calculated. The details of these 2 models are described as follows.

AOF model

Based on patient self-reported ovarian function and information abstracted from medical and radiation therapy records in the Childhood Cancer Survivorship study and the St. Jude Lifetime (SJLIFE) cohort, Clark et al[19] published several predictive models of AOF using logistic regression, random forest, and support vector machines. They defined AOF as occurring "when an individual permanently stops menstruating within 5 years of their cancer diagnosis, does not progress through puberty, or does not achieve menarche by 18 years of age following cancer treatment." The Childhood Cancer Survivorship cohort's ovarian dosimetry was reconstructed by the MD Anderson Late Effects Group from each patient's records using age-appropriate anatomic computer phantoms and estimating left and right ovary positions, although uncertainty in the exact ovarian position is a recognized inherent limitation. The model building cohort contains 5886 childhood cancer survivors with a median age of 7.3 years at cancer diagnosis and a median follow-up of 23.9 years; 2712 patients had ovarian radiation exposure. The validation cohort includes 875 survivors identified from the SJLIFE study. The logistic regression model, also available as an online calculator of patient-specific probability of AOF,[33] was recommended by the primary authors because of its transparency and interpretability compared with their other models because its performance was similar. Using the logistic regression model coefficients given within the published article (Table E2 from primary publication),[19] one can calculate the probability of AOF as

$$p = 1/[1 + e\text{^}(-(-4.174 + 0.0433 \times \text{Age} + 1.00693 \times \text{HSCT} + 0.105 \times \text{AgeD} \times \text{HSCT} + 0.0351 \times \text{CED} + 0.169 \times D_{ovary}))] \quad (1)$$

where P is the probability of AOF, AgeD is the age (years) at cancer diagnosis, HSCT is hematopoietic stem cell transplant (1 = yes, 0 = no), CED is the value (g/m^2) of cumulative cyclophosphamide equivalent dose of alkylating chemotherapy agents, and D_{ovary} is the mean dose to least affected of the patient's 2 ovaries (Gy, capped at 30 Gy).[34]

We used the published Clark model to generate graphs illustrating the relative effects on AOF of patient age at diagnosis, ovary dose, and alkylating agent chemotherapy for patients who did not receive stem cell transplant because loss of ovarian function is nearly universal after myeloablative chemotherapy.[35] Figure 4 shows the probability of AOF after least affected ovarian doses of 0 to 30 Gy for 3 scenarios of alkylating agent

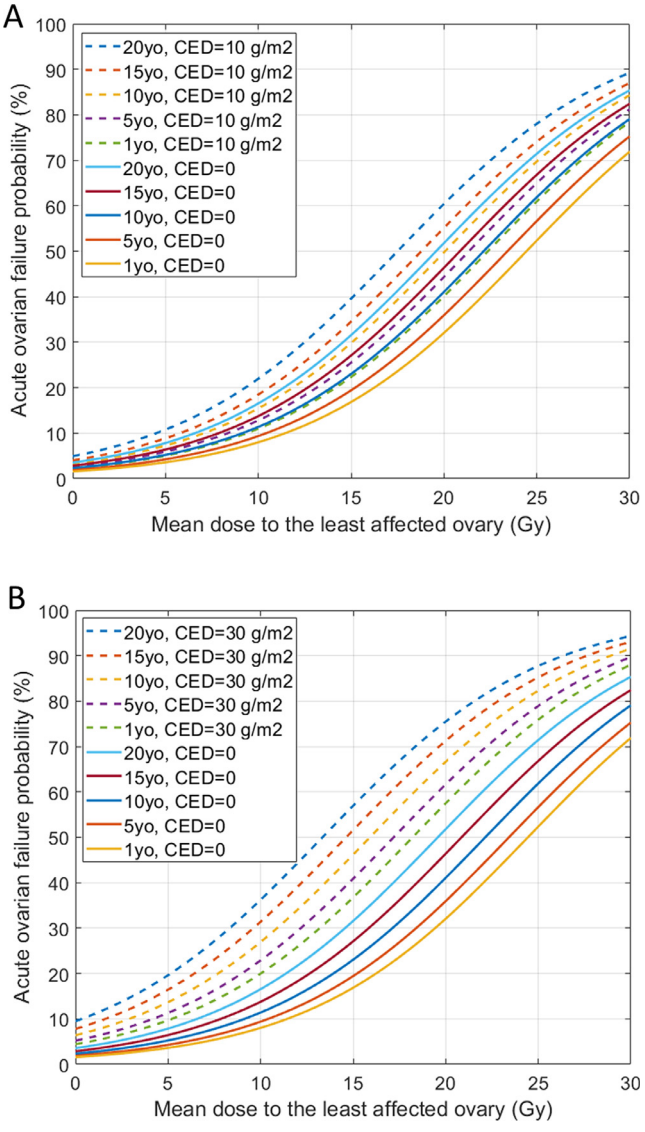

Fig. 4. Calculated probability of acute ovarian failure in childhood cancer survivors as a function of ovary dose (Gy), age (years) at diagnosis, and cyclophosphamide equivalent dose (CED; g/m^2) of alkylating chemotherapy, reproduced based on the logistic regression model in the Clark study[19] (Table E2). Acute ovarian failure is defined as loss of ovarian function within 5 years of radiation therapy. The graph was generated by the PENTEC team assuming no hematopoietic stem cell transplant. Solid curves represent no exposure to alkylating agent chemotherapy. Dash curves are for intermediate-dose alkylating chemotherapy dose of 10 g/m^2 CED (A) and high-dose alkylating chemotherapy of 30 g/m^2 CED (B).

exposure (0, 10 g/m^2, and 30 g/m^2) and 5 different ages (1, 5, 10, 15, 20 years) at the time of diagnosis.

POI model

In a cross-sectional study, Chemaitilly et al[18] evaluated the SJLIFE cohort of 921 childhood cancer survivors (200 with ovarian exposure to radiation) at median age of 31.7 years, and a median of 24 years after cancer diagnosis. A total of 100 survivors had experienced POI at the time of evaluation. The study defines POI as "persistent amenorrhea with evidence of a primary ovarian origin before the age of 40 years." This definition implies that a subgroup of these patients will have had AOF (within 5 years of treatment). Dosimetry in the Chemaitilly study[18] was reconstructed from age-appropriate computer phantoms, and ovary position was assumed to correspond to the average position from 10 patient CT scans, specifically selecting scans on which ovaries were visualized. The authors note that ovaries were not visible on all scans, and the use of select scans and assumption of average position may be a limitation of the study. The published article (Table 3, primary publication)[18] provides a multivariable Cox regression model fit with the hazard ratio (HR) for each risk factor that was considered. Radiation dose is presented in 3 bins: 0, >0 to <10 Gy, and ≥10 Gy, and alkylating agent dose in 5 bins: 0, <8 g/m^2, 8 to 12 g/m^2, 12 to 20 g/m^2, ≥20 g/m^2. No special provision was made for survivors who had received HSCT. The PENTEC team log-transformed the HR to obtain the Cox model coefficients (log-hazard per unit change in the independent predictor). The primary authors also kindly shared with PENTEC via personal communication the unpublished baseline cumulative hazard function, $h_0(t)$, at specific evaluation ages of 20, 30, and 40 years of age. By dropping the nonsignificant terms ($P \geq .05$), we approximated the expected cumulative hazard h(t) and the probability, P, of having POI at the time of assessment, t, as follows.

$$\begin{aligned} h(t) = h_0(t) \times e\text{^}(&-0.84082 \times \text{BMI}{\geq}30 + 2.62841 \\ &\times D_{\text{ovary}} \langle 10 \text{ Gy and} \rangle 0 + 4.88541 \\ &\times D_{\text{ovary}}{\geq}10 \text{ Gy} + 1.01727 \times \text{CED 8 to 11.99} \\ &+ 1.35983 \times \text{CED 12 to 19.99} + 1.41842 \\ &\times \text{CED}{\geq}20) \end{aligned} \quad (2)$$

$$p = 1 - e\text{^}(-h(t)) \quad (3)$$

where D_{ovary} is the dose (Gy) to least affected ovary, BMI (body mass index) is in units of kg/m^2, and CED is in units of g/m^2. Every categorical variable in Equation 2 is coded as 0 or 1 based on its applicability to a particular patient. $h_0(t)$ is 0.0093, 0.0132, and 0.0505 for t = 20, 30, and 40 years of age at assessment (obtained from personal communication with primary author group). To simplify the graphical representation of POI probability versus ovary dose, we modeled risk for a survivor with a normal BMI between 18.5 and 25 kg/m^2 at evaluation. As displayed in Figure 5, the POI probability was calculated for 2 scenarios of alkylating agent exposure (none and ≥20 g/m^2) and 3 ovarian dose groups (0, >0 to <10, ≥10 Gy) as defined in the published study.[18]

Toxicity Risk Analysis

Ovarian toxicity risk

Based on the models detailed previously, we are able to describe risk of ovarian toxicity (AOF and POI) within specific clinical contexts.

Risk of AOF

The risk of AOF was found to increase with RT dose to least affected ovary, CED, and age at RT (Fig. 4). Radiation dose to least affected ovary corresponding to a 5% AOF risk decreased with age at the time of RT and decreased with increasing alkylating chemotherapy exposure. Representative discrete data from Figure 4 are shown in Table 4. Two Gy to the least affected ovary resulted in AOF risk of 1% to 5% (no CED, risk increasing with age), 4% to 7% (CED = 10 gm/^{2}, risk increasing with age), and 6% to 13% (CED = 30 g/m^2, risk increasing with age). AOF risk was ≥50% at doses of 24 Gy and 20 Gy for a 1-year-old and a 20-year-old, respectively, with no alkylating chemotherapy, 22.5 Gy and 17 Gy (aged 1 and 20 years) with intermediate alkylator dose (10 g/m^2), 17 Gy and 13 Gy, (aged 1 and 20 years) with high alkylator dose (30 g/m^2; Fig. 4).

Risk of POI

The risk of POI with neither RT nor alkylating chemotherapy exposure is <5% in childhood cancer survivors (Fig. 5). Age at diagnosis/RT was not found to be a significant variable for POI by Chemaitilly et al.[18] Risk of POI increases with survivor age, radiation dose to least affected ovary, and alkylator dose. Representative discrete data from Figure 5 are shown in Table 5.

Uterine late toxicity risk

Articles that were relevant to the topic of uterine radiation in children are summarized in Table 3; data were not sufficient for modeling. Small uterine size after radiation therapy has been associated with pregnancy loss, difficulty with implantation (likely due to endometrial dysfunction), preterm birth, and delivery of low birth-weight infants.[14] Five articles[14,17,20,23,25] presented information on dependence of uterine volume on the estimated amount of radiation to the uterus. Volume measurements were performed with transabdominal or transvaginal ultrasound, well after treatment, and results are summarized in Figure 6. Four studies[14,17,20,23] found reduced volume when the uterus had received radiation but one[25] did not. Three

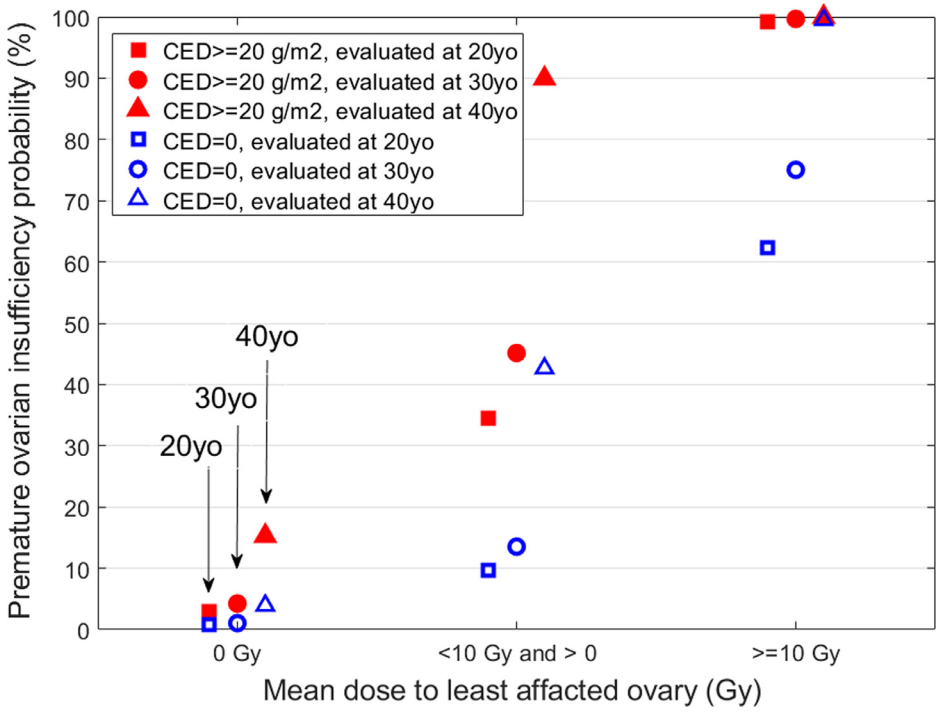

Fig. 5. Calculated probability of premature ovarian insufficiency in childhood cancer survivors as a function of radiation dose (Gy) to least affected ovary and cyclophosphamide equivalent dose (CED, g/m^2) of alkylating chemotherapy based on the Cox regression model published in Chemaitilly et al.[18] Premature ovarian insufficiency refers to loss of ovarian function before age 40 years old. This graph was generated by the PENTEC team assuming normal body mass index at 3 evaluation timepoints when the survivor ages are 20, 30, and 40 years old with no history of oophoropexy; median age at the time of radiation was 8 years old in the modeled patient cohort. Red symbols represent those receiving high dose (≥20 g/m^2) alkylating chemotherapy. Blue symbols are for patients who did not receive alkylating chemotherapy.

articles[14,17,23] reported lower measured uterine volumes for patients treated at younger ages. The relationship of uterine size and radiation is confounded by both a wide range in "normal" uterine size between individuals (Fig. 3B),[36,37] and changes in uterine size that occur naturally at puberty, after pregnancy, and at menopause in a given individual. Despite these limitations, when taken in summary, these publications suggest that higher radiation doses are associated with smaller uterine size, with uterine size considerably restricted after 12 Gy.

Uterine size[23] in adult survivors of childhood cancer who have received RT may be related to decreased arterial blood flow, which can be measured with ultrasonography, and which may result from radiation-induced vascular change. This RT-associated vascular injury (along with reduced flexibility related to fibrosis) may affect the potential for a survivor to carry a pregnancy to full term. Indeed, this was reported on by the International Late Effects of Childhood Cancer Guidelines Harmonization Group in their comprehensive review of articles on obstetrical and fertility outcomes in childhood, adolescent, and young adult cancer survivors published between 1990 and 2018.[38] From 2772 abstracts on pregnancy and delivery risks, and 2492

Table 4 Radiation dose to least affected ovary corresponding to 5% risk of acute ovarian failure, based on age at treatment and alkylating chemotherapy dose, extracted from Figure 4

Age (y)	Ovarian dose (Gy) with CED = 0	Ovarian dose (Gy) with CED = 10 g/m^2	Ovarian dose (Gy) with CED ≥30 g/m^2
1	7	5	<2
5	6	4	<2
10	4.5	3	<2
15	3.5	2	<2
20	2	<1	<2

Dose/risk correlation may be of use during radiation planning as well as patient and survivor counseling.
Abbreviation: CED = cyclophosphamide equivalent dose.

Table 5 Risk of premature ovarian insufficiency after radiation exposure in childhood (median age 8 years) based on age at assessment (survivor age), radiation dose to least affected ovary, and alkylating chemotherapy exposure, extracted from Figure 5

	No alkylating chemotherapy		CED ≥20 g/m^2	
Age (y)	<10 Gy	≥10 Gy	<10 Gy	≥10 Gy
20	12%	71%	41%	Approaching 100%
30	17%	83%	53%	Approaching 100%
40	50%	100%	94%	Approaching 100%

Abbreviation: CED = cyclophosphamide equivalent dose.

abstracts on congenital abnormalities, they selected 98 publications for full-text review and base their recommendations on 28 of these. The authors used a published grading scheme (GRADE[39]), to evaluate the quality of published evidence for each of 113 outcomes and made counseling recommendations for outcomes with moderate through very high evidence. There was moderate to high-quality evidence that survivors who had uterine radiation exposure were at increased risk for adverse outcomes, including miscarriage, premature birth, and low birthweight children; sufficient evidence was not available to determine a safe uterine dose, although high quality evidence indicated that cancer-survivorship did not increase the risk of congenital abnormalities in births to survivors.

Vaginal late toxicity risk

Very little published data exist examining vaginal toxicity after radiation in childhood; however, the sparse literature and clinical observations confirm the risks of vaginal fibrosis, stenosis, dryness, and mucosal thinning in survivors after vaginal radiation. For example, in a group of 23 female survivors treated for pelvic rhabdomyosarcoma in childhood, the

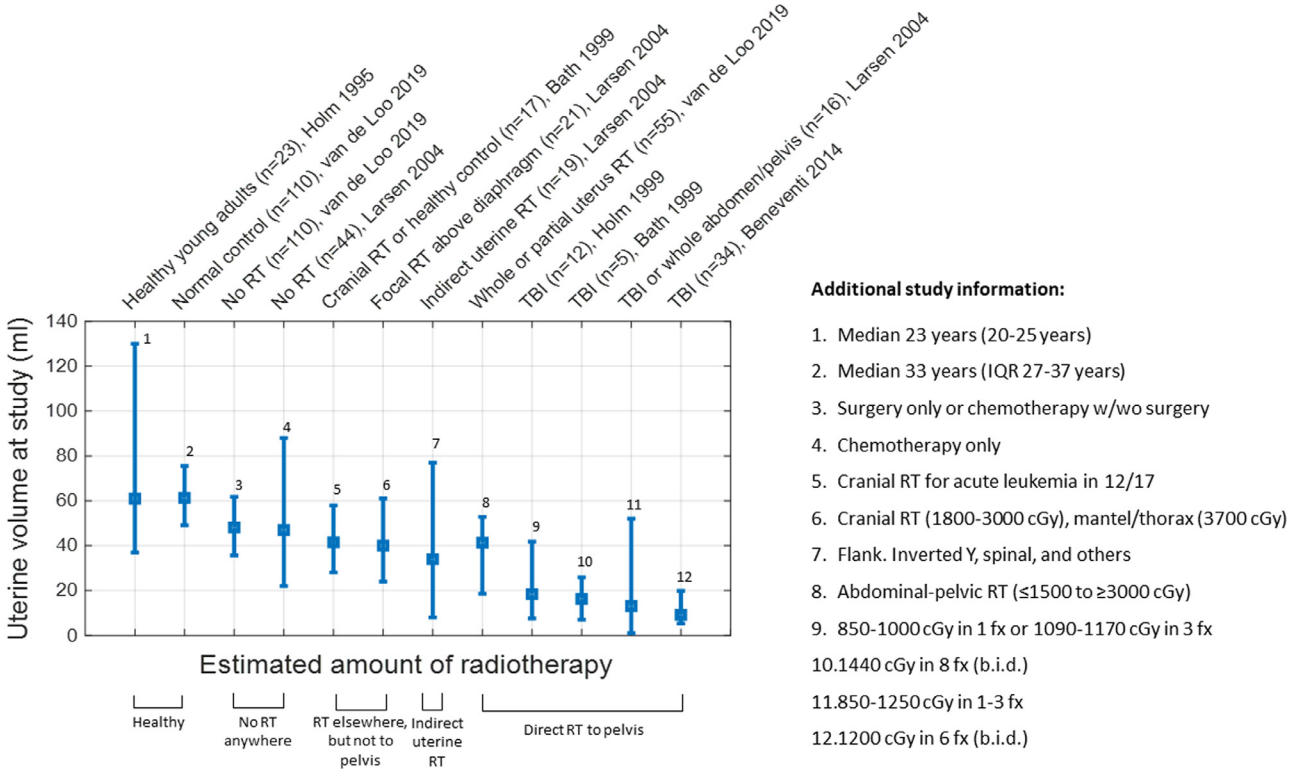

Fig. 6. Ultrasound measured uterine volumes (median and range) of healthy females and childhood cancer survivors from reviewed studies. Labels on the top describe the study and subpopulation. Because different studies have different subpopulations (Table 2), additional study information is provided on the right side of the plot. Median age at study for survivors ranged from 17 to 30 years. Unlike other studies, the van de Loo et al[25] and Beneventi et al[17] studies reported interquartile range instead. *Abbreviations*: bid = twice a day; fx = fractions; IQR = interquartile range; n = sample size; RT = radiation therapy; SCT = stem cell transplant; TBI = total body irradiation; w/wo = with or without.

risk of late effects was high, with 15 patients experiencing grade 3 or 4 gynecologic toxicity.[26] In this study, vaginal toxicity often required surgical treatment, including dilation or reconstruction for vaginal stenosis, procedures to relieve ureteral obstruction, and fistula repair. Of note, patients who received RT experienced a median of 9.5 late effects per patient compared with median of 1 per patient for those who did not require RT. Findings from the Gustave-Roussy brachytherapy experience suggest that treating smaller rhabdomyosarcoma tumor volumes (postchemotherapy or postsurgical volume) may reduce late effect risk,[27,28] although dosimetric data were not published, and clinical decisions regarding treatment volumes must be balanced with target coverage. Risk of vaginal stenosis in the adult population is more widely reported. It appears to be related to dose to vaginal wall and shorter vaginal reference length: The EMBRACE I study[40] demonstrated that in women with cervical cancer, higher doses to posterior-inferior border of symphysis (PIBS), PIBS + 2 cm, PIBS − 2 cm, and recto-vaginal reference point were associated with increased risk for grade ≥2 vaginal stenosis. Adult patients who received >5 Gy to PIBS-2 cm (lower vagina) were more likely to develop grade 2/3 stenosis (42% vs 21%). Dose to PIBS (midvagina) was also related to stenosis risk, with risk of grade 2/3 stenosis being 44% at >50 Gy, 26% at 15 to 50 Gy, and 12% at <15 Gy.

Comparison With Previously Published Adult Data

Even in adult practice, true standards for protection of normal tissues within the female reproductive tract are lacking. These topics were not addressed within the QUANTEC effort published in 2010 and are also not addressed by the American Society for Radiation Oncology practice guidelines or within Children's Oncology Group treatment protocols. In response to the EMBRACE I study findings mentioned above, the EMBRACE-II study[41] aims to standardize dose reporting in adult patients with cervical cancer as well as to dose de-escalate where appropriate in attempt to spare the upper vagina, with an optimization, nonevidence based constraint of 5 Gy maximum dose to PIBS-2 cm when vagina is not involved with tumor, and an optional ovarian constraint of <5 to 8 Gy. Published data examining total body irradiation in a small cohort of adult patients (n = 20) suggests that maintaining maximum ovarian dose <2.4 Gy through use of shielding provides menstrual preservation for most patients.[42] These data are in keeping with those presented here.

Recommendations for Nominal Dose-Volume Goals

Given the exquisite radiosensitivity of ovarian tissue, the PENTEC task force recommends maintaining dose as low as possible to at least one ovary for all patients. Even so, treatment of life-threatening malignancy remains a priority over ovarian preservation and families should be counseled regarding this specific risk-benefit balance. Several possibilities for sparing of at least one ovary exist: radiation field modification may reduce exposure of reproductive organs; particle therapy may minimize exposure from exit dose; surgical relocation of one or both ovaries may allow ovarian sparing[43]; and surgical consultation should be obtained well in advance of anticipated RT to allow for discussions of risk/benefit profile of this approach when desired. Egg "harvesting" (although logistically challenging for some patients and not possible premenarche) and cryopreservation of ovarian tissue may be available options before radiation. For some patients, ovarian relocation and cryopreservation may be performed simultaneously. Each option has its own risk/benefit profile, and applicability depends on the specific clinical situation. Maximum radiation dose to least affected ovary to maintain <5% AOF risk varies inversely with age. Based on the findings shown in Figure 4, we recommend maximum dose to the least affected ovary of 5, 4, 3, and 2 Gy for patients ≤5, 5 to 10, 10 to 15, and 15 to 20 years of age at RT, respectively, when this approach does not compromise coverage of tumor or target volumes (Table 4). With alkylator dose of up to 10 g/m^2, we recommend reduction in ovarian maximum dose to 4, 3, 2, and <1 Gy for patients <5, 5 to 10, 10 to 15, and 15 to 20 years. With high alkylator dose (CED ≥30 g/m^2), AOF risk is >5% for all patients even at doses of 1 to 2 Gy.

Data do not exist to support firm dose/volume limits to uterus or vagina; however, based on our review of the existing literature and practice guidelines, risk of toxicity to these organs remains high, and dose should be kept as low as reasonably achievable. Of note, suggestion within the literature exists that considerable uterine size restriction occurs after dose of 12 Gy, and data in the adult population suggests that radiation dose >5 Gy is more likely to contribute to vaginal toxicity.

Recommendations for Survivorship Care After Radiation Exposure of Female Reproductive Organs

Survivors who have undergone pelvic RT should receive care from an endocrinology team for sequelae of decreased estrogen production to be addressed. In addition, after RT, risk of POI increases as survivors approach their fourth decade of life. Early counseling is important for reproductive options to be maximized. Children's Oncology Group Guidelines, which include pelvic ultrasound as well as care from a high-risk maternal fetal medicine team, should be followed for all survivors desiring pregnancy.[44] Use of vaginal dilator therapy is considered part of best practice to safely delay or prevent vaginal stenosis,[45] although both survivor use and outcomes assessment are challenging.[46,47]

Limitations

Data regarding outcomes after radiation to the pediatric female reproductive organs are limited and currently do not allow for systematic dosimetric analysis. Although we are able to understand ovarian risk in the context of radiation dose and other clinical factors, data regarding dose-volume related toxicity to the uterus are minimal, and to the vagina are essentially nonexistent. As noted previously, the present analysis is limited due to several factors. Most studies have relatively small numbers of subjects, likely due to the relative rareness of diagnosis of pelvic malignancy in children, as well as the fact that survivorship outcomes require very long-term follow-up over a period during which survivors become adults and often relocate several times. Gathering information on menstrual cycles, hormone levels, and fertility outcomes is very challenging in the years to decades after childhood radiation, and information on vaginal outcomes even more so. These issues are not always possible to study in the setting of relapsed disease, when patients receive further systemic therapy and often do not survive; hence, only a subset of radiated patients can provide data on female reproductive outcomes. In addition, topics such as vaginal health, sexual function, fertility, and pregnancy loss are very personal and may be difficult for some survivors and health care providers to discuss. Outcomes reported by health care providers are likely different from those experienced by survivors, particularly in the circumstance of toxicities that may be sensitive or stigmatized, as is unfortunately often the case for sexual and fertility health.[48]

In addition to these challenges are inconsistencies in dose reporting and endpoints, as well as lack of patient-reported outcomes. Most of the studies we reviewed report prescription doses, and not doses to particular organs at risk. In some settings, such as TBI or whole abdomen radiation, the ovaries and uterus are recognized to receive the full prescription dose, but in the setting of a pelvic sarcoma or localized Wilms tumor, the dose received by the reproductive structures may vary considerably compared with the prescription dose. The female reproductive structures, in particular ovaries, are quite difficult to accurately identify on CT scan, and many studies were conducted before the CT era, meaning that accuracy of dose reporting is essentially limited to prescription dose versus no dose. As a result, data do not exist regarding exposure of part of an ovary, the uterus, or the pediatric vagina. Coupled with these challenges at the level of an individual person or a specific study is considerable inconsistency in the endpoints used to assess toxicity, as discussed earlier in this article. Use of different endpoints means that pooled analyses of published data are not possible and makes data interpretation very challenging.

Recommended Data Reporting Standards

The significant limitations outlined previously emphasize the need for improved data gathering on a larger number of patients, as well as consistent outcomes assessment. Having said this, given the low incidence of childhood cancers requiring pelvic RT, and the challenge in following patients long term, for single institutions to independently generate high-quality dose/volume response data are extremely difficult. Adherence of published data sets to rigorous reporting standards to allow pooling of results is thus essential. We propose reporting of the following information in future studies:

- Patient race
- BMI at treatment and evaluation
- Age when treated with radiation therapy and at evaluation
- Prescribed radiation therapy dose and fractionation
- Dose-volume radiation exposure of ovaries, uterus, and vagina when feasible
- Use of alkylating agents (including dose as CED)
- Receipt of HSCT
- Clinical and laboratory follow-up for endocrine function
- Clinical and laboratory follow-up for reproductive interventions, pregnancy, and complications of pregnancy
- Clinical and laboratory follow-up for uterine size and function
- Clinical follow-up for pregnancy outcomes, including infant health and delivery method

To facilitate this robust data gathering, treating clinicians should use imaging that allows them to identify and contour ovaries, uterus, and vagina for treatment planning. This will require evolution in radiology protocols as well as those within radiation oncology. For example, diagnostic pelvic MRI is usually obtained clinically for patients with pelvic malignancies before RT. If institutional clinical protocols required it, ovaries could be identified and marked with arrows by the radiologist reading the diagnostic scan. This would help to ensure that the radiation oncologist contouring the ovaries could do so accurately. A combined effort between radiology and radiation oncology to produce contouring atlases and guidelines would also be of great use. These efforts would greatly facilitate ability to report dose-volume data for uterus and vagina where at minimum, maximum, and mean dose should be reported; mean ovarian dose is likely sufficient given the small and potentially mobile nature of ovaries.

Future Directions

Our analysis revealed a dearth of information regarding outcomes after ovarian, vaginal, and uterine radiation therapy exposure in childhood cancer survivors. As a first step, institutions can begin to address this need by adding contours of reproductive structures which will allow dosimetric analysis. To address concerns regarding small patient numbers, we recommend standardization of patient data gathering at the

time of diagnosis, as well as during long-term follow-up. This could be best achieved by robust participation in national registries of childhood cancer patients and survivors such as the Pediatric Proton/Photon Collaborative Registry.[49] Such registries would allow radiation doses and plans to be recorded and maintained for all female patients treated with pelvic radiation therapy, and for long-term outcomes to be documented and studied with dose correlation. Although the Pediatric Proton/Photon Collaborative Registry is an existing resource, further support will be needed to maximize the scope of patient enrollment and follow-up. The same standardizations should be applied to patients treated on clinical trials, with long-term toxicity data gathered as part of such trials. Female reproductive organs should be included as organs at risk on cooperative group studies with dose-volume information recorded, even in circumstances where data-driven constraints or recommended maximum doses are not available. These needs will require significant resource investment at the federal and international levels to support infrastructure and institutional participation in registries and clinical trials, as well as long-term follow-up that accounts for many patients undergoing geographic relocation by the time of desired childbearing age. Registries that allow correlation of dose-volume relationships with outcomes related to endocrine function, fertility, and pregnancy outcomes would allow significant steps forward within 1 to 2 decades.

Beyond these recommendations is the necessity that the field of cancer survivorship become increasingly patient-centered, with recognition that long-term toxicity from cancer treatment is a common experience, but that individual experiences are unique and often best described by survivors themselves. To this end, patient-reported outcomes, particularly with regard to sexual and fertility outcomes, would be expected to be quite informative, particularly if gathered longitudinally. Further data on patient-centered outcomes, such as effect on maturation and pregnancy outcomes, would be of value during patient and family counseling. We recommend that survivors be monitored closely for clinical endpoints including menarche, menopause, pregnancy, and live birth, and that patient-reported outcomes be assessed at all survivorship visits and recorded in the same comprehensive registry in order to be correlated with prior cancer treatments.

Finally, as our understanding of the profound effect of radiation on the female reproductive tract continues to evolve, patient-centered language will be essential. This movement will require elimination of terms such as "failure," which imply fault or shortcoming on the part of the cancer survivor. In order to center discussions on the function of certain organs, and not the potential for the survivor to be a whole person, or a successful parent, we suggest use of the terms "diminished ovarian reserve," characterized as acute or chronic to replace AOF and POI, respectively; "pregnancy loss" should replace the term "miscarriage." The terms "reduced fertility" with risk grading applied may assist survivors in understanding options, while also minimizing use of the blanket and confusing word "infertility."[50] As patient-centered language becomes adopted and recommended by cooperative groups, it can also be implemented into educational programs for oncology care providers. Standardization of terms and endpoints with a focus on patient-centered outcomes will facilitate understanding within the oncology community of the effect of the treatments that we offer, as well as options to promote comprehensive survivorship care.

References

1. Chemaitilly W, Mertens AC, Mitby P, et al. Acute ovarian failure in the childhood cancer survivor study. *J Clin Endocrionl Metab* 2006;91:1723-1728.
2. Byrne J. Infertility and premature menopause in childhood cancer survivors. *Med Pediatr Oncol* 1999;33:24-28.
3. Sklar CA, Mertens AC, Mitby P, et al. Premature menopause in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2006;98:890-896.
4. Green DM. Preserving fertility in children treated for cancer. *BMJ* 2001;323:1201.
5. Williams SA. Female reproductive tract and oocyte development. Textbook of Clinical Embrology, *Chapter 4*. Cambridge University Press; 2013.
6. Cohen HL, Shapiro MA, Mandel FS, Shapiro ML. Normal ovaries in neonates and infants: A sonographic study of 77 patients 1 day to 24 months old. *AJR Am J Roentgenol* 1993;160:583-586.
7. Ivarsson SA, Nilsson KO, Persson PH. Ultrasonography of the pelvic organs in prepubertal and postpubertal girls. *Arch Dis Child* 1983;58:352-354.
8. Yoneda A, Fujii H, Tanaka Y. Location of the ovaries in children and efficacy of gonadal shielding in hip and pelvis radiography. *J Orthop Sci* 2023;28:1165-1168.
9. Bardo DME, Black M, Schenk K, Zaritsky MF. Location of the ovaries in girls from newborn to 18 years of age: reconsidering ovarian shielding. *Pediatr Radiol* 2009;39:253-259.
10. LaRiviere M, James P, Clegg K, et al. Pencil beam scanning (PBS) proton therapy for children requiring radiotherapy with anesthesia (GA) for rhabdomyosarcoma. *Int J Rad Oncol Biol Phys* 2022;114:E489-E490.
11. Ahmed SE, Shalet SM, Campbell RHA, et al. Primary gonadal damage following treatment of brain tumors in childhood. *J Pediat* 1983;103:562-565.
12. Thibaud E, Rodriguez-Macias K, Trivin C, Espérou H, Michon J, Brauner R. Ovarian function after bone marrow transplantation during childhood. *Bone Marrow Transplant* 1998;21:287-290.
13. Blask ARN, Nicholson HS, Markle BM, et al. Sonographic detection of uterine and ovarian abnormalities in female survivors of Wilms' tumor treated with radiotherapy. *AJR Am J Roentgenol* 1999;172:759-763.
14. Bath LE, Critchley HOD, Chambers SE, Anderson RA, Kelnar CJ, Wallace WH. Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: Response to sex steroid replacement. *Br J Obstet Gynaecol* 1999;106:1265-1272.
15. Chiarelli AM, Marrett LD, Darlington G. Early menopause and infertility in females after treatment for childhood cancer diagnosed in 1964-1988 in Ontario, Canada. *Am J Epidemiol* 1999;150:245-254.
16. Schuck A, Hamelmann V, Brämswig JH, et al. Ovarian function following pelvic irradiation in prepubertal and pubertal girls and young adult women. *Strahlenther Onkol* 2005;181:534-539.
17. Beneventi F, Locatelli E, Giorgiani G, et al. Gonadal and uterine function in female survivors treated by chemotherapy, radiotherapy, and/or bone marrow transplantation for childhood malignant and non-malignant diseases. *BJOG* 2014;121:856-865.

18. Chemaitilly W, Li Z, Krasin MJ, et al. Premature ovarian insufficiency in childhood cancer survivors: A report from the St. Jude Lifetime Cohort. *J Clin Endocrinol Metab* 2017;102:2242-2250.
19. Clark RA, Mostoufi-Moab S, Yasui Y, et al. Predicting acute ovarian failure in female survivors of childhood cancer: A cohort study in the Childhood Cancer Survivor Study (CCSS) and the St. Jude Lifetime Cohort (SJLIFE). *Lancet Oncol* 2020;21:436-445.
20. Holm K, Nysom K, Brocks V, Hertz H, Jacobsen N, Müller J. Ultrasound B-mode changes in the uterus and ovaries and Doppler changes in the uterus after total body irradiation and allogeneic bone marrow transplantation in childhood. *Bone Marrow Transplant* 1999;23:259-263.
21. Critchley HOD, Wallace WHB, Shalet SM, Mamtora H, Higginson J, Anderson DC. Abdominal irradiation in childhood: The potential for pregnancy. *Br J Obstet Gynaecol* 1992;99:392-394.
22. Critchley HOD, Bath LE, Wallace WHB. Radiation damage to the uterus: Review of the effects of treatment of childhood cancer. *Hum Fert (Camb)* 2002;5:61-66.
23. Larsen EC, Schmiegelow K, Rechnitzer C, Loft A, Müller J, Andersen AN. Radiotherapy at a young age reduces uterine volume of childhood cancer survivors. *Acta Obstet Gynecol Scand* 2004;83:96-102.
24. Inagaki J, Fukano R, Kodama Y, Nishimura M, Okamura J. Gonadal function in patients with severe aplastic anaemia and refractory cytopenia of childhood who undergo bone marrow transplantation after receiving 3-Gy total body irradiation and high-dose cyclophosphamide. *Br J Haematol* 2013;163:127-129.
25. van de Loo LEXM, van den Berg MH, Overbeek A, et al. Uterine function, pregnancy complications, and pregnancy outcomes among female childhood cancer survivors. *Fertil Steril* 2019;111:372-380.
26. Spunt SL, Sweeney TA, Hudson MM, Billups CA, Krasin MJ, Hester AL. Late effects of pelvic rhabdomyosarcoma and its treatment in female survivors. *J Clin Oncol* 2005;23:7143-7151.
27. Magne N, Oberlin O, Martelli H, Gerbaulet A, Chassagne D, Haie-Meder C. Vulval and vaginal rhabdosarcoma in children: Update and reappraisal of Institut Gustave Roussy brachytherapy experience. *Int J Radiat Oncol Biol Phys* 2008;72:878-883.
28. Levy A, Martelli H, Fayech C, et al. Late toxicity of brachytherapy after female genital tract tumors treated during childhood: Prospective evaluation with a long-term follow-up. *Radiother Oncol* 2015;117:206-212.
29. Wallace WHB, Shalet SM, Hendry JH, Morris-Jones PH, Gattamaneni HR. Ovarian failure following abdominal irradiation in childhood: The radiosensitivity of the human oocyte. *Br J Radiol* 1989;62:995-998.
30. Wallace WHB, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. *Hum Reprod* 2003;18:117-121.
31. Wallace WHB, Kelsey TW. Human ovarian reserve from conception to the menopause. *PLoS One* 2010;5:e8772.
32. Wallace WHB, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys* 2005;62:738-744.
33. St. Jude Children's Research Hospital. Acute ovarian failure risk prediction calculator. Available at: https://ccss.stjude.org/tools-documents/calculators-other-tools/ccss-ovarian-risk-calculator.html. Accessed July 12, 2021.
34. Green DM, Nolan VG, Goodman PJ, et al. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: A report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer* 2014;61:53-67.
35. Mertens AC, Ramsay NK, Kouris S, Neglia JP. Patterns of gonadal dysfunction following bone marrow transplantation. *Bone Marrow Transplant* 1998;22:345-350.
36. Holm K, Mosfeldt Laursen E, Brocks V, Müller J. Pubertal maturation of the internal genitalia: an ultrasound evaluation of 166 healthy girls. *Ultrasound Obstet Gynecol* 1995;6:175-181.
37. Kelsey TW, Ginbey E, Chowdhury MM, Bath LE, Anderson RA, Wallace WHB. A validated normative model for human uterine volume from birth to age 40 years. *PLOS One* 2016;11:e0157375.
38. van der Kooi A-LLF, Mulder R, Hudson MM, et al. Counseling and surveillance of obstetrical risks for female childhood, adolescent, and young adult cancer survivors: Recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Am J Obstet Gynecol* 2021;224:3-15.
39. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:388-394.
40. Westerveld H, Kirchheiner K, Nout R, et al. Dose-effect relationship between vaginal dose points and vaginal stenosis in cervical cancer: An EMBRACE-I sub-study. *Radiother Oncol* 2022;168:8-15.
41. Potter R, Tanderup K, Kirisits C, et al. The EMBRACE II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018;9:48-60.
42. Akahane K, Shirai K, Wakatsuki M, et al. Dosimetric evaluation of ovaries and pelvic bone associated with clinical outcomes in patients receiving total body irradiation with ovarian shielding. *J Radiat Res* 2021;62:918-925.
43. Hoekman EJ, Knoester D, Peters AW, Jansen FW, de Kroon CD, Hilders CGJM. Ovarian survival after pelvic radiation: Transposition until the age of 35 years. *Arch Gynecol Obstet* 2018;298:1001-1007.
44. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers, version 5.0. Available at: https://survivorshipguidelines.org/. Accessed October 10, 2022.
45. International Clinical Guideline Group. International guidelines on vaginal dilation after pelvic radiotherapy. Available at: https://owenmumford.com/us/wpcontent/uploads/sites/3/2014/11/Dilator-Best-Practice-Guidelines.pdf. Accessed October 10, 2022.
46. Schlover LR, van der Kaaij M, van Dorst E, Creutzberg C, Huyghe E, Kiserud CE. Sexual dysfunction and infertility as late effects of cancer treatment. *EJC Suppl* 2014;12:41-53.
47. Cullen K, Fergus K, Dasgupta T, Fitch M, Doyle C, Adams L. From "sex toy" to intrusive imposition: A qualitative examination of women's experiences with vaginal dilator use following treatment for gynecological cancer. *J Sex Med* 2012;9:1162-1173.
48. Moss HA, Havrilesky LJ. The use of patient-reported outcome tools in gynecologic oncology research, clinical practice, and value-based care. *Gynecol Oncol* 2018;148:12-18.
49. Pediatric Proton/Proton Consortium Registry. Available at: https://www.pediatricradiationregistry.org/. Accessed December 2, 2022.
50. Habbema JD, Collins J, Leridon H, Evers JL, Lunenfeld B, te Velde ER. Towards less confusing terminology in reproductive medicine: A proposal. *Hum Reprod* 2004;19:1497-1501.