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PENTEC ORGAN SYSTEM REVIEW

Breast Hypoplasia and Decreased Lactation From Radiation Therapy in Survivors of Pediatric Malignancy: A PENTEC Comprehensive Review

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Purpose: Breast hypoplasia and impaired lactation are poorly studied sequelae of chest radiation therapy (RT) in children. The Pediatric Normal Tissue Effects in the Clinic female breast task force aimed to quantitate the radiation dose-volume effects on these endpoints.

Methods and Materials: A literature search was conducted of peer-reviewed manuscripts evaluating breast hypoplasia and lactation after chest RT in children, yielding 789 abstracts. Only 2 studies on children irradiated at <4 years of age for angioma of the breast provided dosimetric data correlated with breast hypoplasia. For patients who received brachytherapy, the dose was converted to external beam RT in equivalent 2 Gy fractions (D_{EBRT}), although the limitations of this type of mathematical conversion need to be recognized. We calculated relative risks (RR) and 95% confidence intervals (95% CIs) based on these data. Only 1 study was relevant to the lactation endpoint, in which patients were given RT for Hodgkin lymphoma at age 14 to 40 years.

Results: The 3 studies involved 206 patients in total. In patients <4 years old at the time of RT, the prevalence of patient-perceived breast hypoplasia was 38% (RR 2.5; 95% CI, 1.3-4.6) after D_{EBRT} of <0.34 Gy, 61% (RR 4.0; 95% CI, 2.1-7.4) after D_{EBRT} 0.34-0.97 Gy, and 97% (RR 6.3; 95% CI, 3.6-10.8) after D_{EBRT} ≥0.97 Gy to the breast anlage. A simple linear regression model ($r = 0.72$; $P < .001$) showed that the treated breast was smaller than the untreated breast by 13% at $D_{EBRT} = 0.5$ Gy, 20% at

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D_{EBRT} = 1 Gy, 32% at D_{EBRT} = 2 Gy, 51% at D_{EBRT} = 4 Gy, 66% at D_{EBRT} = 6 Gy, 79% at D_{EBRT} = 8 Gy, and 90% at D_{EBRT} = 10 Gy. The risk of unsuccessful breastfeeding was 39% after a median mediastinal dose of 41 Gy, compared with 21% in a sibling control group (P = .04). RT dose of ≥42 Gy was not associated with less breastfeeding success compared with <42 Gy, and data on lower doses were unavailable.

Conclusions: Based on extremely limited data, young adults exposed to thoracic RT as children seem to be at significant risk of breast hypoplasia and impaired lactation. Doses as low as 0.3 Gy to immature breasts can cause breast hypoplasia. Additional studies are needed to quantify dose and technique effects with modern RT indications. Prospective collection of clinical outcomes and dosimetric factors would enhance our understanding of RT-induced breast hypoplasia and impaired lactation.

Introduction

Radiation therapy (RT) involving the chest is critical in the management of several pediatric malignancies but often results in incidental exposure of the breasts, predisposing long-term survivors to complications. This comprehensive review from the Pediatric Normal Tissue Effects in the Clinic (PENTEC) initiative aims to describe the risk of breast hypoplasia and lactation impairment in female survivors of cancer who were treated with chest RT as children.

Clinical Significance

Many pediatric malignancies require chest irradiation that partially or fully exposes the breast tissue. The more common clinical scenarios include mediastinal RT in Hodgkin lymphoma, total body irradiation before stem cell transplantation, and bilateral lung RT for metastatic Wilms tumor (nephroblastoma) or sarcoma.

As would be expected, RT-induced breast hypoplasia is age-dependent because it can only occur in children with undeveloped or underdeveloped mammary tissue. Impaired lactation results from impaired breast development or damage to the apparatus necessary for milk production and expression.

The risks of breast hypoplasia and an impaired ability to breastfeed after chest-directed RT are important quality-of-life issues for female survivors of pediatric malignancies. It has been well documented that breast hypoplasia and asymmetry can lead to social discomfort and psychological distress.[1,2] Further, many survivors who become pregnant may wish to breastfeed, which is regarded as a biologic norm.[3,4] Not breastfeeding has been associated with modest increases in risks of common infections, obesity, and sudden infant death syndrome in the child, as well as breast cancer, ovarian cancer, and osteoporosis in the mother.[5,6] Thus, the World Health Organization recommends exclusive breastfeeding up to 6 months of age, with continued breastfeeding along with appropriate complementary foods up to 2 years of age or beyond.[7]

Endpoints and Toxicity Scoring

Based on previous literature, the severity of breast hypoplasia has been scored according to 2 different endpoints. The first endpoint is patient-reported subjective breast asymmetry graded on a 0 to 4 scale, in which 0 = no difference, 1 = hardly visible difference, 2 = small difference, 3 = moderate difference, and 4 = large difference. The second endpoint concerns actual measurements of the percentage difference in breast volume, such as a water measurement system that involves assessing the volume displaced by immersion of each breast in water.[8,9]

The advantages of the former subjective self-reported scoring system are that it does not require any measurement and can be reported by the patient. The advantage of the second endpoint is that it is more objective, likely resulting in less interobserver variability when grading this toxicity. Reassuringly, the 2 endpoints are strongly associated with each other (ie, a correlation coefficient of 0.72 on simple linear regression).[8] A limitation common to both scoring systems is that they apply only to unilateral breast RT, because it relies on having an unirradiated breast for comparison. Previous studies have not reported on, or scored, breast hypoplasia after bilateral breast RT, but this can be done using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading system for breast atrophy (see section "Toxicity Scoring Recommendations").

The endpoint that has been used for lactation outcomes after pediatric RT is "successful breastfeeding," defined as at least 1 breastfeeding attempt from the treated breast that was successful.[10] The advantage of this endpoint is that it is simple to report; the major limitation is that it does not account for the volume of breast milk produced nor for the intention to breastfeed. Possible methods to measure breast milk production include test weighing (ie, weighing the infant before and after breastfeeding), recording of expressed/pump milk volume, computerized measurements of breast volume,[11] and deuterium tracer studies,[12,13] though the latter 2 methods are complicated and time-consuming.

An indirect measure of breast milk production is weight gain of the infant in the setting of exclusive breastfeeding; the most important drawback of this endpoint is that it may not accurately capture the reduction of milk production in a treated breast if an untreated contralateral breast provides an adequate supply of breast milk. On the other hand, infant weight gain is a more clinically relevant and all-

encompassing endpoint than the actual volume of milk produced by 1 or both breasts. For patients aiming to exclusively breastfeed, its duration is also a clinically important endpoint, as well as the reason for stopping breastfeeding.

Anatomy and Developmental Dynamics

The duct system of the female breast develops as a result of invagination of embryonal ectoderm, beginning at the sixth week of development. At birth, the breast rudiment is formed by 10 to 12 primitive ductal elements located beneath the nipple-areola complex. These ducts slowly grow and branch during the prepubertal years, with canalization into ductal structures.[14] Puberty in girls usually begins about 10 to 12 years of age, during which several changes occur in the breast, including external appearance, larger tissue volume, increased number of structures present in the mammary gland, and increased degree of branching or differentiation of the individual structures. During pregnancy and lactation, the maximum branching capability of the breast is expressed, and the full extent of glandular differentiation is achieved.[15] Breast hypoplasia, also known as mammary hypoplasia or insufficient glandular tissue, is defined as underdevelopment of the breast.[15] It may be unilateral or bilateral and can be congenital or acquired from causes such as irradiation.[16] The tissue in a hypoplastic breast tends to microscopically resemble that of a prepubertal breast, consisting of fibrous stroma and ductal structures without acinar differentiation.[16] The lack of or diminished amount of glandular tissue in breast hypoplasia has been associated with decreased milk production in the postpartum period.[17]

Animal studies suggest that the duct system in the breast undergoes alterations in its resistance to radiation depending on the endocrine activity of the female. It has been shown in rabbits that before estrogen stimulation, ducts are relatively radioresistant; after estrogen stimulation (ie, during puberty), the sensitivity of the duct epithelium increases by 30% to 50%, with irradiation causing inhibition of lobule growth and hyperplasia of the mammary gland. After puberty, the duct system becomes relatively radioresistant again.[14,18] The variation in radiosensitivity related to endocrine activity in the human female breast is less clear.[19]

Defining Volumes: Pediatric Imaging Issues

When the breast region is irradiated in pediatric patients, standard planning procedures (including noncontrasted axial computed tomography [CT] images) are sufficient for defining the breasts or chest wall as organs at risk. Before breast development (ie, in the absence of evident breast tissue), the relevant volume to define is the breast bud, which is approximately 5 mm deep to the nipple in patients <2 years of age and 3 mm deep to the nipple in patients who are ≥2 years of age[8,20]; in addition, we suggest defining the chest wall for dose-reporting in future studies. In prepubertal patients, a radio-opaque marker should be placed on the nipple to facilitate localizing the breast bud. In a postpubertal patient, the total glandular breast tissue should be delineated. As a guide, radio-opaque markers may be placed around the breast for CT scanning, though these markers do not necessarily represent the true borders of the breast because visible/palpable clinical borders may not correspond with CT-defined borders (eg, based on tissue density[21] and/or the true anatomic borders. In defining the breasts or chest wall, we suggest using an adapted version of the European Society for Radiotherapy and Oncology (ESTRO) consensus guidelines on target volume delineation for breast cancer.[21] Modifications of the original guidelines are necessary to adjust for inherent differences between the postmastectomy versus prepubertal chest wall, as well as target-volume versus organs at risk delineation (see Table 1[21,22]). Because the breast is a parallel-type organ, in which each region functions relatively independently, a planning organ at risk volume (eg, to account for geometric uncertainties[23]) might be most pertinent for outcomes such as

Table 1 Recommended guidelines for delineating breast and chest wall as organs at risk[21,24]

	Breast	Chest wall
Cranial	Upper border of palpable/visible breast tissue; typically up to the inferior edge of the sterno-clavicular joint	Inferior edge of the sterno-clavicular joint
Caudal	Most caudal computed tomography image with visible breast	Anterior aspect of the sixth rib
Anterior	Skin	Skin
Dorsal	Major pectoral muscle, or costae and intercostal muscles where no major pectoral muscle	Major pectoral muscle, or costae and intercostal muscles where no major pectoral muscle
Lateral	Lateral breast fold; anterior to the lateral thoracic artery	Midaxillary line; typically excludes latissimus dorsi muscle[24]
Medial	Lateral to the medial perforating mammary vessels; maximally to the edge of the sternal bone	Lateral to the medial perforating mammary vessels; maximally to the edge of the sternal bone

cancer induction, but perhaps less useful for outcomes such as hypoplasia and lactation.

In the relevant studies for breast hypoplasia, only absorbed dose in the breast bud was calculated, and this parameter was found to be predictive of the rate and severity of hypoplasia.[8,24] However, the dose distribution to the adjacent tissue may also be important for both breast hypoplasia and lactation outcomes[14] (as well as subsequent malignancies). Thus, in addition to reporting dose to the breast bud for future studies, we recommend contouring the breast/chest wall so that additional dose-volume endpoints can be investigated, including mean breast dose, and volumes receiving at least 1 Gy, 5 Gy, 10 Gy, 20 Gy, and 30 Gy (V1, V5, V10, V20, and V30). For patients treated before breast development, dose to the breast bud should be determined as previously described. This is based on the developmental changes in the thickness of the breast bud.[8,20]

Review of Dose Volume Response Data and Risk Factors

Identification of eligible studies

This PENTEC systematic review of radiation-induced breast hypoplasia and lactation deficiency was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[25]

The medical literature was queried to identify peer-reviewed manuscripts evaluating breast hypoplasia and lactation among young women who received chest RT as children (see Supplement). For the breast *hypoplasia* endpoint, no studies on survivors of childhood cancer were identified. Therefore, it was decided that the experience of children who received chest RT for nonmalignant conditions might provide valuable data that could potentially be extrapolated to survivors of childhood cancer, in the absence of direct evidence. The search yielded 789 abstracts. Abstracts were reviewed by 2 authors each (K.M., C.R.). Thirty-one articles passed the title-abstract selection and were further inspected based on full text review. Six studies[8,10,24,26-28] fulfilled the inclusion criteria and were submitted to PENTEC data review (see Fig. 1). Two studies were identified that contained dosimetric data correlated with hypoplasia.[8,24] Only 1 study from the literature search was relevant to the *lactation* endpoint, in which patients were given RT for Hodgkin lymphoma at age 14 to 40 years.[10]

Breast hypoplasia

The study by Fürst et al included 129 women irradiated during infancy or childhood, aged 1 to 47 months, for hemangioma in the breast region.[8] Most patients were irradiated

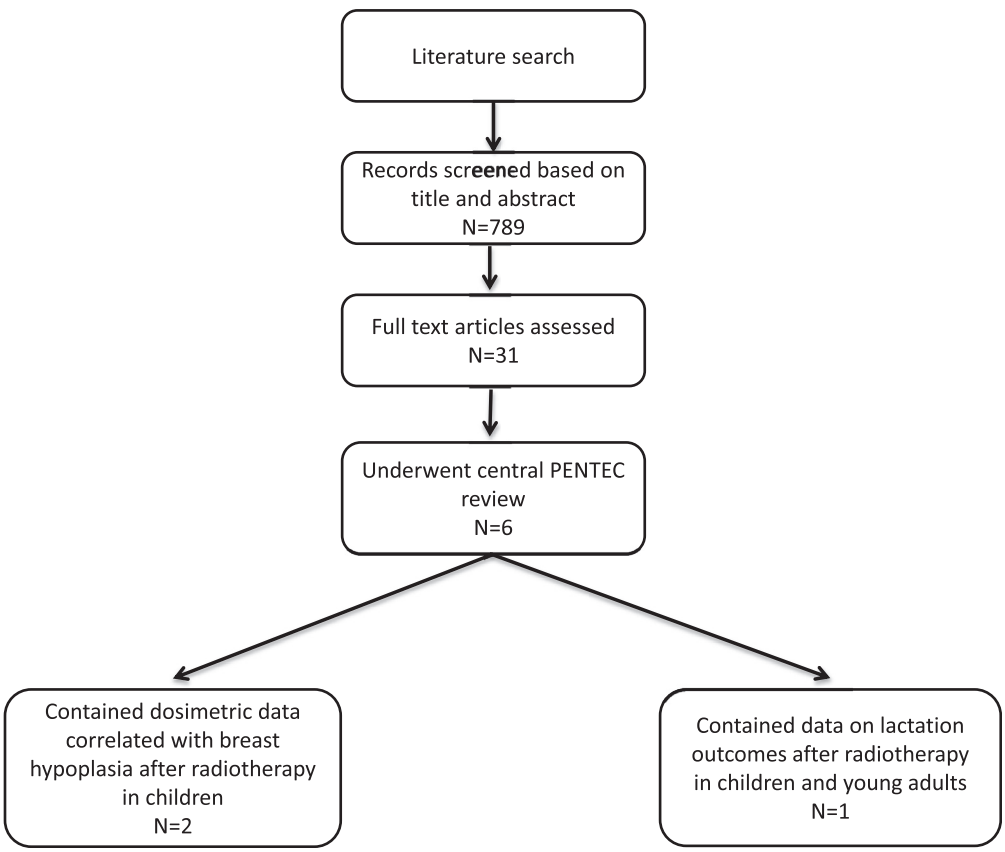

Fig. 1. Identification of eligible studies.

with a single treatment of brachytherapy using ^{226}Ra surface applicators or needles and/or tubes. From 1934 to 1939, the prescribed skin dose was 17 to 18 Gy. Thereafter, the dose was prescribed as the average dose in the first 10 mm of tissue, which was 7 Gy. The mean skin dose was 11 Gy (range 6-25 Gy). At a tissue depth of 5 mm, the dose was 3% (0.4 Gy) of the surface dose. Estimated absorbed dose to the center of the "breast anlage" (ie, breast bud) was reported as ranging from 0.01 to 18.3 Gy. However, subsequent dosimetric reanalyses for this cohort adjusted these doses down by, on average, about one-half[29,30] (ie, to the range of 0.005-9.15 Gy). Therefore, a correction factor of one-half has been applied to the available reported doses. Further details about the dose adjustment are included in section "Dose/Volume/Outcome Associations."

It has been suggested that brachytherapy doses can be converted into estimated equivalent external beam RT (EBRT) equivalent doses at 2 Gy per fraction (D_{EBRT}) as follows[31]:

$$D_{EBRT} = \frac{d + g\{d^2/(\alpha/\beta)\}}{1 + 2/(\alpha/\beta)} \quad g = \frac{2}{(\mu T)^2}\left(\mu T - 1 + e^{-\mu T}\right)$$

in which d is the brachytherapy dose, μ = 0.693/$T_{1/2}$, and $T_{1/2}$ is half-life time for repairing of tissues, which is 1.5 hours for late responding tissues, α/β = 3 Gy for late responding tissues, and T was treatment duration; treatments of hemangioma with radium typically lasted 2.5 hours.[32] As a result, a dose range of 0.005 to 9.15 Gy in brachytherapy is equivalent to D_{EBRT} of 0.003 to 17.29 Gy. We recognize the limitations of this type of mathematical conversion and acknowledge that this description does not reflect the marked heterogeneity of most brachytherapy dose distributions.

The severity of breast hypoplasia was scored according to 2 different endpoints based on the following data: (1) All patients answered a questionnaire subjectively grading breast asymmetry (0 = no difference, 1 = hardly visible difference, 2 = small difference, 3 = moderate difference, and 4 = large difference); (2) 53 of the 67 patients living in the geographic vicinity also participated in a clinical breast examination including measurement of breast volume.

In patients with brachytherapy doses (D_B) at the breast bud <0.5 Gy (D_{EBRT} <0.34 Gy) resulted in 38% (27/71) of patients reporting a smaller breast on the treated side and 15% (11/71) reporting the opposite. The proportion of patients reporting a smaller breast on the treated side was 61% (16 of 26) after D_B = 0.5 to 1.25 Gy (D_{EBRT} = 0.34-0.97 Gy), 100% (10 of 10) after D_B = 1.25 to 2.5 Gy (D_{EBRT} = 0.97-2.38 Gy), and 95% (21 of 22) after D_B ≥2.5 Gy (D_{EBRT} ≥2.38 Gy). None of the 58 patients who received D_B >0.5 Gy (D_{EBRT} >0.34 Gy) reported a smaller breast on the untreated side. Prevalence of patient-perceived breast hypoplasia according to estimated equivalent external beam dose, D_{EBRT}, is shown in Figure 2.

For the 53 patients whose breast volume was measured, Fürst et al described the dose-effect relationship as a simple linear regression line (% difference in breast volume = 3.12 + 6.65x; in which x = absorbed D_B in Gy) with a correlation coefficient of 0.72 (P < .001). Thus, based on this model, differences in breast volume would be 13% at D_{EBRT} = 0.5 Gy, 20% at D_{EBRT} = 1 Gy, 32% at D_{EBRT} = 2 Gy, 51% at D_{EBRT} = 4 Gy, 66% at D_{EBRT} = 6 Gy, 79% at D_{EBRT} = 8 Gy, and 90% at D_{EBRT} = 10 Gy (see Fig. 3).

A series on patients with angiomas by Kolar et al reported on 14 girls who received unilateral chest RT at the age of 2 to 16 months, in 8 of whom the absorbed doses in

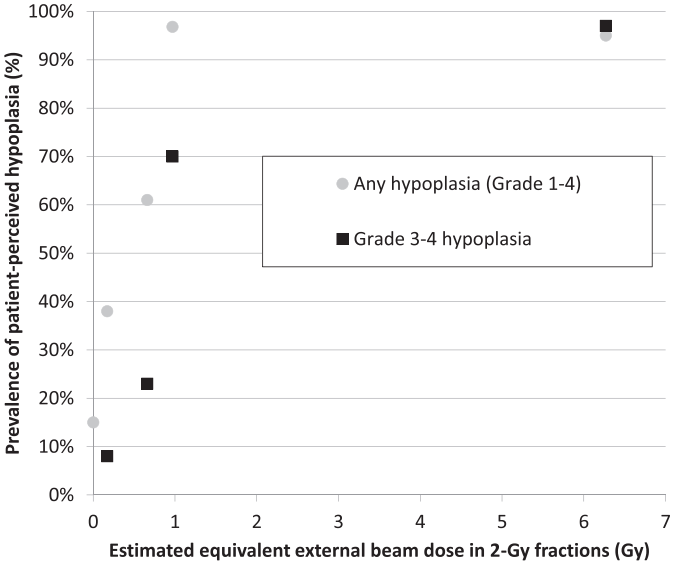

Fig. 2. Prevalence of patient-perceived hypoplasia in the treated breast in patients <4 years old at the time of radiation therapy versus the estimated equivalent external beam radiation therapy dose in 2 Gy fractions, based on data from Fürst et al[8] (see section "Review of Dose Volume Response Data and Risk Factors" for details). Grade 1 = hardly visible difference; grade 2 = small difference; grade 3 = moderate difference; and grade 4 = large difference.

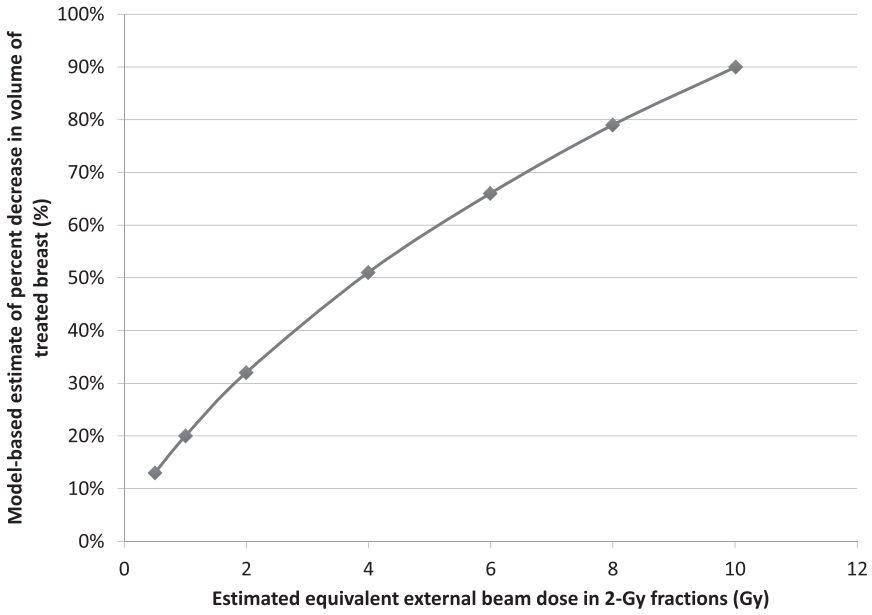

Fig. 3. Model-based prediction of the percent decrease in volume of treated breast in patients <4 years old at the time of radiation therapy versus estimated equivalent external beam dose in 2 Gy fractions, based on data from Fürst et al[8] (see section "Review of Dose Volume Response Data and Risk Factors" for details).

the breast bud could be calculated with sufficient accuracy.[24] Doses were administered in 3 or 5 fractions per week using kilovoltage x-rays. Fraction size was not stated for every patient, but based on the total dose and duration of treatments, fraction size ranged from 40 to 108 Roentgen (R), which converts to 0.35 to 0.95 Gy. The calculated depth dose in the breast bud (defined as 1 cm below the skin surface) was 30% of the skin surface dose. None of the 3 patients with total absorbed doses in the breast bud of ≤100 R (ie, ≤0.88 Gy) developed hypoplasia (n = 3). Three patients who received 300 to 660 R (2.63-5.79 Gy) for 1 to 3 weeks experienced a <1/3 decrease in breast volume (compared with the contralateral side). The remaining 2 patients each received 2 courses of radiation separated by 4 months, with total doses being 1100 R and 1180 R (ie, 9.65 Gy and 10.35 Gy), which was associated with a one-third to one-half decrease in breast volume (compared with the contralateral side). The amount of breast volume reduction is less than would have been expected based on the dose-response relationship reported in the Fürst study. Unlike the Fürst study, however, the doses reported in the Kolar study were not verified with modern dosimetry to our knowledge.

The impact of fractionated doses higher than 15.7 Gy on breast development in children is poorly studied. There are no studies among survivors of childhood cancer. Moss' textbook of RT reports that in the prepubertal breast, 30 to 40 Gy to the skin in 30 days permanently arrests growth of the duct system and produces an associated severe fibrosis and shrinkage of the breast.[14]

In determining the risk of radiation-induced breast hypoplasia, the underlying rate of breast asymmetry without any RT must be considered. It has been reported that approximately 25% of adult women have visible breast asymmetry.[2] Assuming this asymmetry is distributed equally between left and right breasts, approximately 12.5% of women would have a smaller breast when either side is considered. We lack a control group of patients with childhood angioma who did not receive RT to inform us accurately about the underlying rate of breast asymmetry in this specific population. However, 15% of women in Fürst's study reported a smaller breast on the untreated side (of those receiving D_B <0.5 Gy to the treated side), evidence of asymmetry that is unrelated to the RT. This suggests that without any RT, at least 15% of such patients would develop a smaller breast on 1 given side, serving as our best estimate of a control rate of breast asymmetry for this population.

The risk factors contributing to the occurrence and severity of breast hypoplasia from RT are largely unknown. In the study by Fürst et al,[8] patient age ranged from 1 to 47 months with a mean age of 9 months, with 94% of patients treated at <2 years of age. In the study by Kolar et al,[24] 12 of 14 patients were <12 months at the time of RT, and the other 2 were <16 months. Given the young age of patients in both studies, the effect of age at radiation exposure and RT −induced breast hypoplasia could not be determined. We do not know if hypoplasia effects are more profound in younger girls than in those >4 years of age when treated with RT. Although biologically an additional effect of puberty is likely, as shown in animal experiments, there are no human data on this topic.

In addition, there is no information on the attained age of the girls/women at the time of the outcome assessment, so that the potential confounding impact of age and/or reproductive phase cannot be assessed.

The effect of race is also unknown, because this cohort consisted of patients living in Sweden in the 1930s and

1940s who were presumably mostly white. Similarly, the cohort described by Kolar et al was very young (≤16 months) and likely largely white as well, having received treatment from 1946 to 1952 in Prague.

Lactation

The effect of RT on lactation has been scarcely investigated in survivors of childhood cancer. The only study that included pediatric patients was by McCullough et al, reporting on 83 children and young adults with Hodgkin lymphoma receiving chest RT between the ages of 14 to 40 years (median 23 years) and who had at least 1 live birth after RT.[10] Of note, 37% of the patients in this cohort (ie, n = 30) were survivors of pediatric disease and aged <21 years at RT, which is not fully representative of the target population for treatment planning nor PENTEC. Nonetheless, because this is the only reported evidence, it was decided to describe the evidence. Also, the treatment exposure typically concerns bilateral chest exposure, in contrast to unilateral exposure in the studies previously cited addressing breast hypoplasia.

Overall, 61% of breastfeeding attempts were successful compared with 79% in a sibling control group ($P = .04$) who also had at least 1 live birth.[10] Among 30 survivors aged ≤21 years at the time of diagnosis, 23 of 35 (66%) breastfeeding attempts were successful (these data include some women with ≥1 subsequent births and breastfeeding attempts). Eight patients received chest RT between ages 14 and 16 years, all of whom attempted to breastfeed, with 75% (6 of 8) being successful.

The median prescribed radiation dose to mantle plus mediastinal boost was 41 Gy (range, 27-46 Gy). Prescription RT dose ≥42 Gy was not found to be associated with less success at breastfeeding, suggesting that the percent volume of breast tissue incidentally irradiated might be more important than the prescribed doses. In considering the breast dose distribution from mantle field irradiation, a previous study demonstrated that the measured dose was 72% to 91% of the prescribed dose in the primary beam, 4% to 70% near the block or collimator edges, 8% to 14% under the blocks, and 2% to 25% out of the beam; however, breast volume encompassed in these respective sections was not specified.[33]

Because the youngest patients were 14 years old at the time of RT, the effect of thoracic RT on lactation in children <14 years old was not determined in this study, nor has it been reported elsewhere in the literature. Further, given that the lowest prescribed dose was 27 Gy, the impact of even lower doses on lactation is unknown. Previous literature has suggested that cranial RT is separately associated with a high risk of lactation impairment, perhaps related to growth hormone insufficiency[34]; however, this association was not explored in McCullough's study, as cranial RT is not a typical part of Hodgkin lymphoma management.

Dose/Volume/Outcome Associations

The modeled association between estimated breast dose and the prevalence of breast hypoplasia and breastfeeding success is summarized in Table 2. The statistical models for

Table 2 Summary of model-based dose/outcome associations for breast hypoplasia in patients treated at <4 years of age and lack of breastfeeding success in patients treated at 14 to 40 years of age

Outcome: Breast hypoplasia					
		Risk of patient-perceived hypoplasia			Expected difference in volume compared with untreated breast (%)[‡]
Brachytherapy dose to breast bud[*] (Gy)	Estimated equivalent EBRT dose[†] (Gy)	Reported prevalence	Relative risk (95% CI)	*P* value	
0	0	15%[§]	1.0		
0 to <0.5	0 to <0.34	38%	2.5 (1.3-4.6)	.0045	<10%
0.5 to <1.25	0.34-0.97	61%	4.0 (2.1-7.4)	< .0001	10-20%
1.25 to <5	≥0.97	97%	6.7 (3.7-11.1)	< .0001	20-70%
≥5	≥6.27	95%	6.2 (3.4-10.3)	< .0001	≥70%
Outcome: Unsuccessful breastfeeding					
Dose to mediastinum[‖]		**Absolute risk**		**Odds ratio (95% CI)**	
27-46 Gy (median 41 Gy)		39%		2.4 (1.0-5.0)	

Abbreviations: CI = confidence interval; EBRT = external beam radiation therapy.

[*] Doses administered using ^{226}Ra surface applicators or needles and/or tubes.

[†] Estimated equivalent external beam radiation therapy dose at 2 Gy per fraction: see text section "Review of Dose Volume Response Data and Risk Factors" for assumptions and calculations used.

[‡] Based on data from Fürst et al,[8] % difference in breast volume = $3.12 + 13.3D_B$, in which D_B = brachytherapy dose in Gy. This converts to % difference in breast volume = $1.27\sqrt{783(D_{EBRT}) + 500} - 25.19$, in which D_{EBRT} = external beam radiation therapy in equivalent 2 Gy fractions.

[§] See section "Review of Dose Volume Response Data and Risk Factors."

[‖] Doses administered using standard fractionation external beam radiation therapy.

the respective dose/outcome associations are based on the original data reported by Fürst et al[8] (with aforementioned dose adjustments) and McCullough et al.[10] Because the Kolar et al[24] study was not verified by modern dosimetry, it was not included in our dose volume recommendations. In McCullough et al's study on breastfeeding, data on a sibling control group were available, which allowed for calculation of an odds ratio. Owing to the lack of a control group for breast hypoplasia, relative risks were calculated based on a 15% underlying rate of breast asymmetry as explained previously. It is obviously desirable to limit the incidental dose to the breast tissue as much as possible, but one needs to balance these risks with the potential toxicity to other at-risk organs and success in curing the malignancy.

Limitations

The dose/volume/outcome data are limited by uncertainty in the correction factor applied to the brachytherapy doses used in the study by Fürst et al.[8] In this study, doses to the breast anlage from ^{226}Ra needles and tubes were estimated using a combination of thermoluminescent dosimeter measurements and calculations with an early-generation treatment planning system (SIDOS-Brachy, Siemens). Lundell et al observed that SIDOS simplified the geometry of the ^{226}Ra applicators used and did not include a correction for tissue inhomogeneity: they recalculated the doses using 2 different Monte Carlo codes, showing that SIDOS overestimated the doses to the breast anlage by up to a factor of 4.[29] The discrepancy between SIDOS and Monte Carlo dose increased with decreasing distance between the applicator and the breast anlage, that is, the discrepancy was largest for high doses. Individual dose corrections were not provided, but Lundell et al suggest that, for the whole cohort, the doses actually delivered are half of the doses reported by Fürst et al. This simple and pragmatic correction (applying a factor of one-half to the doses reported by Fürst) is the one used by Eidemuller et al[30] in their update of the risk model from the Fürst cohort, and is also the one we have applied in this work. However, as the true correction factor could be greater or less than one-half, we might have underestimated or overestimated the doses that lead to hypoplasia.

Furthermore, brachytherapy is characterized by steep dose gradients (eg, 10% per mm),[35] which can result in high variations of dose within the treated region[36] and is not adequately described by mean dose or prescribed dose. As a consequence, when calculating the D_{EBRT} used for modeling, we could not account for the heterogeneous dose distribution by using the Equivalent Uniform Dose[37] concept, for instance. Because the effect of heterogeneous dose distribution could not be considered, the effect of small volumes receiving high doses on the risk of adverse effects is an issue appropriate for investigation.

Another study limitation is that the dose to the breast bud is the only dosimetric parameter that was examined, yet the dose distribution to the adjacent tissue may also be a significant factor to hypoplasia risk. Of note, the skin dose was much greater than the breast bud dose in both series by Fürst et al and Kolar et al, and it is possible that this contributed to the occurrence of hypoplasia. Unfortunately, the lack of dosimetric data on the skin and adjacent tissue in individual patients prohibits us from drawing any further conclusions.

Toxicity Scoring Recommendations

Toxicity scoring is important to describe the extent of injury and to standardize gradations of severity for both clinical application and research. For a complete assessment of RT-induced effects, both pre- and posttreatment scoring should be performed when feasible; however, in many cases, baseline breast development and lactation assessment are not applicable owing to the child being prepubertal and nulliparous.

Our recommendation is to score breast hypoplasia using a descriptive system that does not require measurements, as well as a volumetric system whenever possible. For the former, we suggest using the CTCAE version 5.0 grading system for breast atrophy: grade 1, minimal asymmetry, minimal atrophy; grade 2, moderate asymmetry, moderate atrophy; and grade 3, asymmetry greater than one-third of breast volume, severe atrophy. The advantage of this scoring system is that it can be used after either unilateral or bilateral breast RT, although assigning a grade can be quite difficult in the latter scenario when asymmetry is not expected.

The volumetric system is best applied after unilateral RT, because the contralateral breast size serves as a control. For the volumetric system, we recommend reporting the percent difference in breast volume as was previously done.[8,24]

$$\text{Percent difference}\,(\%) = \frac{\text{Difference between both breast volumes}}{\text{Best volume of larger side}}$$

We recommend determining breast volumes based on mammography[38] for patients in whom a mammogram is indicated for breast cancer screening. Using mammography, breast volume can be approximated as $\pi/4 \times$ width $\times$ height $\times$ compression thickness in craniocaudal mammography.[38,39] If compression thickness is not reported on the mammography report, breast volume can be estimated with the formula, $1/3\pi$[8,24] $(\text{width}/2)^2 \times$ height.[40] Alternatively, breast volume can be computed from serial magnetic resonance imaging scans using an inversion recovery pulse sequence.[41] In cases in which a CT image is available, that can also be used to compute objective volume differences. However, owing to radiation exposure, this is not otherwise recommended.

For patients in whom mammographic or magnetic resonance imaging screening is not indicated, we suggest considering using the Archimedes (water displacement) procedure in scenarios in which time and resources allow for it, as it is economical, highly accurate, and has an acceptable level of patient tolerability.[38,42]

For lactation, we recommend using the CTCAE version 5.0 grading system for lactation disorder: grade 1, mild changes in lactation, not significantly affecting production or expression of breast milk; and grade 2, changes in lactation, significantly affecting breast production or expression of breast milk.

In addition, the following measures would be useful for a more comprehensive evaluation of lactation toxicity:

- Whether the woman intended to breastfeed before delivery
- Whether the woman attempted to breastfeed after delivery
- The reasons for not attempting to breastfeed
- In case of unsuccessful breastfeeding, the main reasons for not sustaining attempts
- Whether at least 1 attempt at breastfeeding or expressing milk from the treated breast was successful
- Whether infant weight gain was satisfactory in the context of exclusive breastfeeding[43]
- Duration of exclusive breastfeeding
- Reasons underlying the decision to stop exclusive breastfeeding
- If exclusively pumping, daytime volume of milk produced from the treated breast versus untreated breast (ie, from 8:00 AM to 4:00 PM on the fourth day after delivery, which is highly related to the 24-hour output[44,45])

Recommendations for Data Reporting

RT can adversely affect breast development and lactation when the thorax of a prepubertal or adolescent female individual is being irradiated. Although avoiding radiation exposure to the breast would be ideal to reduce the risk of breast hypoplasia, impaired lactation, and second malignancy, this may not be possible depending on the location of the target volume and other organs at risk. Nevertheless, it is helpful to estimate the dose-related likelihood of impaired breast development and function to offer the patient and family insight into the predicted impact of a proposed treatment on breast development and lactation, as part of a global assessment of potential late adverse effects.

In reporting data on risk of breast hypoplasia and lactation disorder after RT, we recommend reporting the patient demographic, oncologic, and dosimetric information listed as follows:

- Patient race
- Cancer diagnosis
- Age when treated with RT and age at evaluation
- Presence of endocrinopathies
- Prescribed RT dose to target
- Fractionation schedule
- RT technique
- Additional therapies received, such as systemic therapies, cranial RT, pelvic RT, endocrinologic therapies
- In prepubertal patients:
  - Minimum dose to the hottest 0.03-cc volume (D0.03cc) of the breast bud
  - Dose to skin of chest wall
    - D0.03cc, mean dose, V2, V5, V10, V20, V30
  - Dose to chest wall
    - D0.03cc, mean dose, V2, V5, V10, V20, V30
- In postpubertal patients:
  - Dose to breast
    - Mean dose, V2, V5, V10, V20, V30

Future Investigations

Many questions remain unanswered regarding breast hypoplasia and lactation impairment after RT. Of high priority are the impact of age, breast development stage, and hormonal stimulation on the incidence and severity of these toxicities. With the published studies for breast hypoplasia being limited to patients treated at <4 years old and for breastfeeding limited to patients receiving RT at >14 years old, significant age gaps exist in the populations investigated. Moreover, there are no published studies describing breast hypoplasia in female survivors irradiated for childhood cancer, as opposed to those irradiated for angiomas. Although animal studies demonstrate that the breast undergoes alterations in its resistance to radiation depending on the endocrine activity of the female, data are lacking to confirm whether the human breast is subject to the same pattern of alteration in radiation resistance.

The impact of additional dose-volume parameters is an important area for future investigation, particularly the effect of breast volume; for example, we lack knowledge on what volume of the breast bud needs to be spared to what dose to preserve lactation. In addition, the importance of dose distribution to the skin and tissue adjacent to the breast bud is unknown. Further, dose fractionation is an important area for future investigation; the bulk of the dosimetric information we have on breast hypoplasia is based on treatment with brachytherapy, and pediatric RT to the lungs or mediastinum in the current era is typically delivered for 1 to 4 weeks using conventionally fractionated EBRT. Given the uncertainties associated with the correction of Fürst brachytherapy doses, future EBRT studies are important for validation. Specific dosimetric data pertaining to lactation after pediatric RT are completely lacking, warranting focused studies on this topic. A better understanding on dose effect would help guide the selection of treatment modalities when chest RT is needed, for example, intensity-modulated protons versus volumetric-modulated photons versus fixed photon fields.

After a study population of adequate size and diversity has been identified with appropriate dosimetric information, investigation of other factors should also be considered, including race, impact of chemotherapy on radiation sensitivity, and genetic predisposition, as well as the role of adequate and tailored support during breastfeeding initiation and sustainment for female survivors of cancer. Such comprehensive studies are required to properly inform practitioners, patients, and families about the risks of breast hypoplasia and decreased lactation from RT for pediatric malignancies, and to minimize these risks whenever possible.

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