ORIGINAL RESEARCH

Cumulative Radiation Exposure and Lifetime Cancer Risk in Patients With Tetralogy of Fallot Requiring Early Intervention

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ABSTRACT

BACKGROUND Neonates with tetralogy of Fallot and symptomatic cyanosis (sTOF) require early intervention, utilizing either a staged repair (SR) or primary repair (PR) approach. They are exposed to several sources of low-dose ionizing radiation, which may contribute to increased cancer risk.

OBJECTIVES The purpose of this study was to compare cumulative radiation exposure and associated lifetime attributable risk (LAR) of cancer between treatment strategies in sTOF.

METHODS Neonates with sTOF who underwent SR or PR from 2012 to 2017 were retrospectively reviewed from the Congenital Cardiac Research Collaborative. Radiation exposure from all radiologic studies prior to 18 months of age was converted to organ-equivalent doses and projected LAR of cancer incidence using the National Cancer Institute dosimetry tools.

RESULTS There were 242 neonates from 8 centers, including patients with 146 SR and 96 PR. Cumulative total effective dose was significantly higher for SR (median 8.3 mSv, IQR: 3.0-17.4 mSv) than PR (2.1 mSv, IQR: 0.8-8.5 mSv; $P < 0.001$). Cumulative organ-level doses were significantly higher in SR compared to PR. Regardless of treatment strategy, LARs were higher in females compared to males. Among organs with median exposure >1 mGy in females, the LAR was highest for breast in SR (mean 1.9/1,000 patients). The highest proportion of cancers attributable to radiation exposure was projected for thyroid cancer in females undergoing SR (7.3%).

CONCLUSIONS Cumulative radiation exposure and LARs were higher among those undergoing SR compared to PR. This will be an important factor to consider in determining the preferred neonatal treatment strategy and should substantiate efforts to reduce radiation exposure in this vulnerable population. (JACC Adv. 2024;3:101239) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ALARA = as low as reasonably achievable

CHD = congenital heart disease

CT = computed tomography

DLP = dose-length product

IR = interventional radiology

LAR = lifetime attributable risk

LDIR = low-dose ionizing radiation

NCI = National Cancer Institute

NM = nuclear medicine

NCIRF = NCI dosimetry system for radiography and fluoroscopy

PR = primary repair

PDA = patent ductus arteriosus

RadRAT = radiation risk assessment tool

RVOT = right ventricular outflow tract

SR = staged repair

sTOF = symptomatic tetralogy of Fallot

Improvement in survival among children with congenital heart disease (CHD) has been attributed to advancements in diagnosis, treatment, and periprocedural management.[1] However, many of these advancements involve exposure to low-dose ionizing radiation (LDIR). Studies of adult patients with CHD have demonstrated a two-fold increased cancer risk compared to the general population.[2-6] This risk of cancer persists despite adjustment for genetic syndromes,[7,8] fueling ongoing conversations about the implications of LDIR exposure and cancer risk in the population with CHD. LDIR exposure is associated with increased cancer risk among adult patients with CHD.[6,9-11] As children are more sensitive to the carcinogenic effects of ionizing radiation and are generally expected to live longer than adults,[12,13] radiation exposure from select medical procedures, including cardiac catheterization, during childhood may have an especially pronounced influence on lifetime cancer risk.[14,15]

A comparison of outcomes between neonates born with tetralogy of Fallot and symptomatic cyanosis (sTOF) who were managed with staged repair (SR) versus primary repair (PR) reported no significant difference in 5-year cumulative mortality with select benefits for each strategy.[16] While patients were exposed to LDIR related to the need for early intervention and ongoing management, differences in cumulative exposure have not been evaluated. Therefore, we sought to compare cumulative radiation exposure and radiation-related lifetime attributable cancer risk in PR and SR infants with sTOF from a multicenter collaborative study.

METHODS

STUDY POPULATION. Patients who underwent initial intervention at ≤30 days of age from January 1, 2012, through November 30, 2017, and were enrolled in a multicenter retrospective observational cohort study at 8 centers of the Congenital Cardiac Research Collaborative were eligible for inclusion.[17] While the parent study includes patients as early as 2005, patients who underwent intervention before 2012 were excluded from this study due to concerns for incomplete radiation dose data capture from cardiac catheterizations. This study was approved by the Institutional Review Board at Cincinnati Children's Hospital in Cincinnati, Ohio, which acted as the single Institutional Review Board, with a waiver of the need for informed consent. A data use agreement was in place among all participating centers and the data-coordinating center.

RADIATION DOSE DATA EXTRACTION AND ORGAN-SPECIFIC DOSE CALCULATION. Exam-specific radiation dose data were collected from radiologic studies performed in the first 18 months of life. These studies included cardiac catheterizations, interventional radiology (IR) and fluoroscopy, computed tomography (CT), nuclear medicine (NM), and x-ray. For cardiac catheterizations and IR studies, the dose-area-product in frontal and lateral projections was extracted from each procedure. For CT, the radiation output, measured as dose-length product (DLP), and study type were extracted from imaging reports. For NM studies, the study performed, radioactive isotope administered, dose metric and volume administered were collected from electronic health records. Finally, the number of studies of each x-ray subtype was extracted from the patient's electronic health records. Chart abstraction was performed at the center level, with deidentified data

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entered into an electronic database at the Congenital Cardiac Research Collaborative data coordinating center at Children's Healthcare of Atlanta, in Atlanta, Georgia.

The National Cancer Institute (NCI) has a collection of medical radiation dosimetry tools that estimate organ-equivalent doses received by patients undergoing diagnostic radiation procedures.[18-20] We utilized the technical parameters of the NCI dosimetry tools to make reasonable assumptions in the calculation of organ-equivalent doses, further outlined below. All dosimetry calculations were performed on a newborn phantom.

1. Cardiac catheterization and IR: The NCI dosimetry system for radiography and fluoroscopy (NCIRF) calculated organ-equivalent doses from dose-area-product (Gy-cm^2) values.[18] Technical parameters were defined with the assistance of the NCIRF graphical user interface for x-ray beam alignment and expected exposure field.
2. CT: The NCI dosimetry system for CT estimated organ-equivalent doses from DLP (milligray [mGy]-cm) values.[19] The DLP was converted to the volume CT dose index (CTDI$_{vol}$) using standardized CT scanner lengths for a newborn phantom, which was subsequently used to generate organ-equivalent dose estimations.
3. NM: The standard radiopharmaceutical was identified for each NM study, as defined by the International Commission on Radiological Protection.[21] The NCI dosimetry system for NM estimated organ-equivalent doses using the corresponding radiopharmaceutical and volume administered in millicuries (mCi).[20]
4. X-ray: Individual radiation dose data for each study were not available. Instead, effective doses for x-ray studies estimated using the Monte Carlo method with commercially available software (PCXMC, version 2.0, STUK) are available.[22] The exposure field for each x-ray study was defined using the NCIRF graphical user interface. Organ-equivalent doses were then obtained with retrograde calculations using the effective dose from the previous PCXMC estimations.

Effective dose, defined as the tissue-weighted sum of radiation doses to each organ, was quantified in millisieverts (mSv) with organ-equivalent doses in mGy. Following organ-equivalent dose calculations for each radiation-emitting study, the cumulative total effective and organ-equivalent doses were summated across all studies and by study type for each patient.

PROJECTION OF RADIATION-RELATED CANCER RISK. The NCI radiation risk assessment tool (RadRAT) estimates sex-specific lifetime attributable risk (LAR) of cancers attributable to radiation exposure.[23] RadRAT projects LAR from the time when an individual was exposed until the end of expected lifetime using age- and sex-specific excess risk per dose unit depending on age at and time since exposure. Baseline risk and life expectancy was estimated based on cancer incidence rates and survival function for the 2015 to 2019 U.S. population. To account for uncertainties in dose estimation, we considered a log-triangular probability distribution with the minimal, median, and maximal values defined as the 25th, 50th, and 75th percentiles of the dose distributions for each treatment strategy, respectively. Because uncertainties are high at very low doses (<1 mGy), LARs were only estimated for organs that received a cumulative dose >1 mGy.[23]

STATISTICAL ANALYSES. Comparisons between categorical baseline patient characteristics and treatment strategy were performed using a chi-square test or Fisher's exact test when expected cell counts were <5. Approximate normality for continuous variables was determined using the Shapiro-Wilk test. The Kruskal-Wallis one-way analysis of variance was used to compare continuous variables when the normality assumption was not met.

Additional secondary analyses were performed to evaluate differences in the utilization of radiologic studies between treatment strategies. Trends in utilization of specific studies and cumulative radiation exposure by study type over time were assessed using the Cochran-Armitage test for categorical and the Jonckheere-Terpstra test for continuous variables.

Multivariable linear regression was used to identify factors independently associated with cumulative radiation exposure. Cumulative radiation exposure was logarithmically transformed to produce a normal distribution for the linear regression analyses. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute), and statistical significance was assessed at the 0.05 level.

RESULTS

STUDY POPULATION. After exclusion of patients who underwent intervention before 2012, 242 patients with sTOF who required intervention at ≤30 days of age were included in the analyses. A total of 146 neonates underwent SR strategy versus 96 neonates who underwent PR (**Table 1**). Baseline patient characteristics were similar between treatment

TABLE 1 Baseline Characteristics of the Study Population by Treatment Strategy (N = 242)

	Primary Repair (N = 96)	Staged Repair (N = 146)	P Value
Sex			
Male	51 (53)	74 (51)	0.71
Female	45 (47)	72 (49)	
Anatomy			
Tetralogy of Fallot with pulmonary stenosis	57 (59)	81 (55)	0.55
Tetralogy of Fallot with pulmonary atresia	39 (41)	65 (45)	
Prematurity (<37 weeks)	16 (17)	36 (25)	0.14
Birthweight, kg	3.0 (2.6-3.4)	2.8 (2.4-3.3)	0.17
Genetic syndrome	25 (26)	39 (27)	0.91
DiGeorge	10 (10)	17 (12)	0.84
Trisomy 21	3 (3)	7 (5)	0.75
VACTERL	4 (4)	3 (2)	0.44
Other[a]	7 (7)	13 (9)	0.81
Inotrope use before index procedure	7 (7)	25 (17)	0.03
Invasive ventilation before index procedure	9 (9)	37 (25)	0.002
Year of index procedure			
2012	20 (21)	17 (12)	0.45
2013	17 (18)	24 (16)	
2014	12 (13)	23 (16)	
2015	11 (11)	24 (16)	
2016	16 (17)	26 (18)	
2017	20 (21)	32 (22)	
Age at index procedure, days	10 (6-19)	7 (5-13)	0.002
Initial palliation			
RVOT stent		4 (3)	
PDA stent		21 (14)	
Balloon pulmonary valvuloplasty		19 (13)	
Systemic to PA shunt		97 (66)	
Surgical RVOT patch, no VSD closure		5 (3)	
Reintervention	44 (46)	79 (54)	0.21

Values are n (%) or median (IQR). [a]Other genetic syndromes included Alagille syndrome, CHARGE, trisomy 18, sex chromosome and partial aneuploidy, microdeletion, microduplication, and syndrome but unspecified.

PDA = patent ductus arteriosus; PA = pulmonary artery; RVOT = right ventricular outflow tract; VSD = ventricular septal defect.

groups except patients with SR were significantly younger at index procedure and more likely to receive inotropic support and invasive ventilation prior to index procedure. There was no significant difference in the proportion of patients who underwent reintervention(s). Of those in the SR group, 44 and 102 patients underwent a transcatheter or surgical palliation, respectively. When comparing surgical to transcatheter palliation, surgical palliation was more commonly employed among female neonates, and those with pulmonary atresia, but otherwise there were similar baseline patient characteristics (Supplemental Table 1).

OBSERVED RADIATION EXPOSURE. Combining exposure across all radiologic studies, patients with SR had significantly higher cumulative radiation exposure (median 8.3 mSv, IQR: 3.0-17.4 mSv) compared to PR (2.1 mSv, IQR: 0.8-8.5 mSv; $P < 0.001$) (Central Illustration). This difference was consistently observed across organ-equivalent doses, with the highest dose appreciated in lung for SR (15.9 mGy, IQR: 4.0-33.0 mGy). In a subgroup analysis of patients with SR, there was no significant difference in cumulative radiation exposure between those treated by transcatheter versus surgical palliative procedures (Supplemental Table 2). However, patients undergoing initial transcatheter palliation had significantly higher radiation exposure to the lung (18.3 mGy, IQR: 9.0-36.9) and stomach (17.5 mGy, IQR: 9.3-33.2) compared to surgical palliation (lung: 11.2 mGy, IQR: 3.1-32.6; $P = 0.04$, and stomach: 10.3 mGy, IQR: 3.6-33.5; $P = 0.04$).

PROJECTED LIFETIME CANCER RISK. Projection of LAR and the proportion of risk attributable to early radiation exposure, defined by the ratio of the LAR to the total future risk (LAR plus baseline risk), for select organs are provided in Table 2 for females and Table 3 for males. The highest LAR was appreciated for breast cancer among patients managed with SR (1.9 per 1,000 females) and PR (0.7 per 1,000 in females), followed by thyroid and lung cancer. Females had higher LARs for thyroid and lung cancer compared to males. The highest proportion of attributable risk was for thyroid cancer, with 1.1% to 2% and 3.8% to 7.3% of cancers attributable to early radiation exposure among patients managed with PR and SR, respectively.

By projected attained age, an increase in excess radiation-related cancer was evident from ages 20 to 30 for female thyroid and breast cancer and somewhat later for male cancers (Figure 1), reflecting similar patterns in age-specific baseline cancer rates in the U.S. general population.

In a multivariable linear regression model, SR ($P < 0.001$), genetic syndrome ($P = 0.004$), need for invasive ventilation before index procedure ($P = 0.007$), and need for reintervention ($P < 0.001$) were independently associated with total cumulative radiation exposure during the first 18 months of life (Table 4).

TRENDS IN UTILIZATION OF RADIOLOGIC STUDIES. Utilization and frequency of radiation-emitting studies varied by treatment strategy. Subjects with SR were more likely to undergo cardiac catheterization, IR, or CT compared to those who underwent PR (Table 5). However, among patients who had at least one of these studies performed, there was no significant difference in the number of studies obtained by treatment strategy. There was also no significant

CENTRAL ILLUSTRATION Cumulative Radiation Exposure in Tetralogy of Fallot Patients Requiring Early Intervention
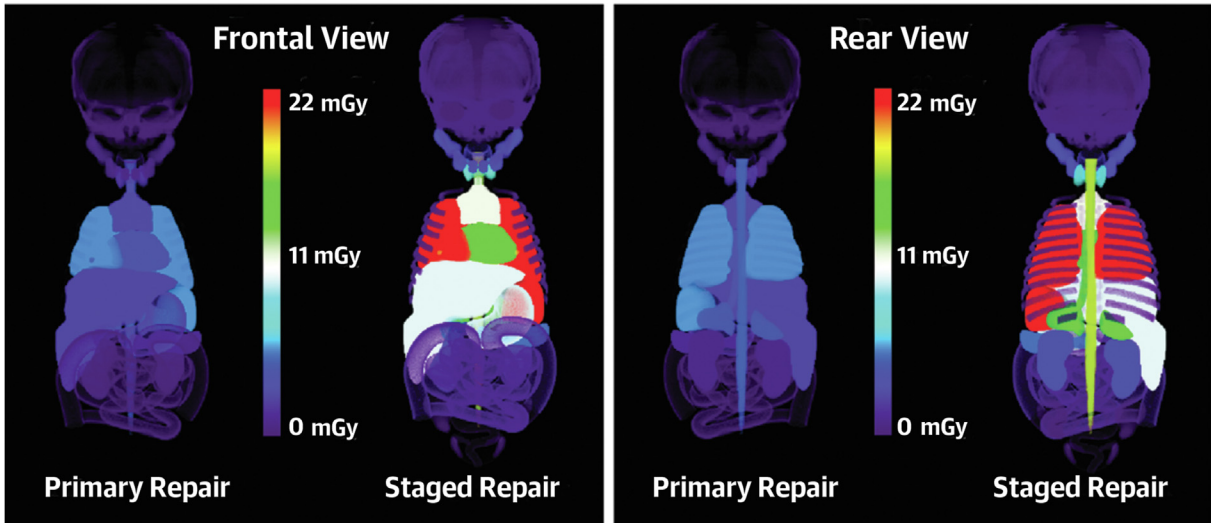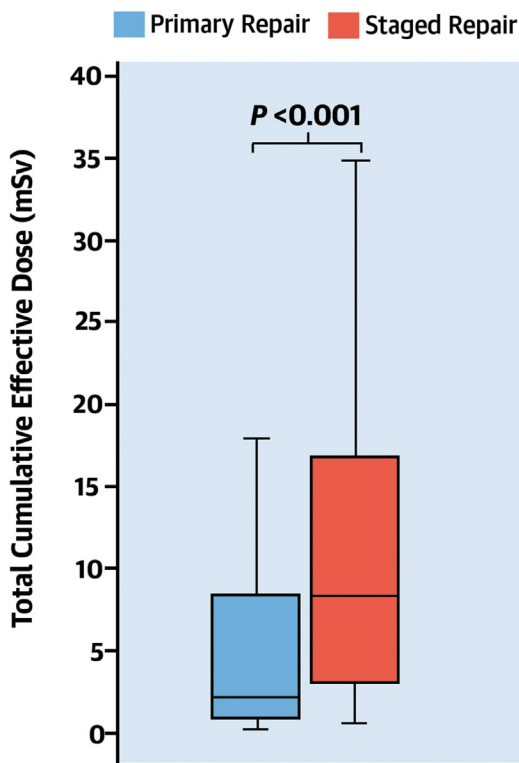
Select Organ-Equivalent Doses (mGy)		
	Primary Repair (n = 96)	**Staged Repair (n = 146)**	**P Value**
Brain	0.0 (0.0-0.4)	0.2 (0.0-0.5)	<0.001
Thyroid	0.0 (0.0-0.4)	7.4 (2.3-15.4)	<0.001
Lung	2.0 (0.6-17.1)	15.9 (4.0-33.0)	<0.001
Breast[a]	4.5 (1.8-12.6)	11.6 (5.3-29.0)	<0.001
Stomach	2.4 (1.0-13.1)	14.2 (4.6-33.5)	<0.001
Liver	2.6 (0.9-10.3)	11.0 (3.9-28.7)	<0.001
Pancreas	1.7 (0.8-5.3)	5.6 (2.5-12.6)	<0.001
Testes	0.1 (0.0-0.2)	0.2 (0.1-0.5)	0.001
Ovary	0.8 (0.4-1.8)	1.4 (0.6-2.9)	0.002
Marrow	0.4 (0.1-3.7)	3.2 (0.8-7.2)	<0.001

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Distribution of cumulative radiation exposure by organ and treatment strategy in (A). The total cumulative effective and select organ-equivalent doses are provided in (B). Boxes represent the 25th to 75th percentiles, with the median depicted as a horizontal line. The whisker represents 1.5x the interquartile range or the minimum and maximum values, whichever is shorter. Values are median (interquartile range). P values comparing between treatment strategies are provided. The primary repair group is displayed in blue, and the staged repair group is in red. [a]Female patients only, n = 45 (primary repair) n = 72 (staged repair).

TABLE 2 Projected Lifetime Risks of Developing Cancer by Organ Site and Treatment Strategy (Females)[a]

Organ/Tissue	Baseline Risk (Cancers per 1,000 Patients)	Number of Excess Cancers per 1,000 Patients Attributable to Radiation Exposure[b]		Proportion of Cancers Attributable to Radiation Exposure (%)	
		Primary Repair	Staged Repair	Primary Repair	Staged Repair
Thyroid	17.6	0.4 (0.0-1.2)	1.4 (0.2-4.4)	2.0	7.3
Lung	63.3	0.3 (0.0-0.9)	1.3 (0.4-3.1)	0.5	2.1
Breast	139.6	0.7 (0.2-1.5)	1.9 (0.7-3.8)	0.5	1.4
Stomach	6.6	0.1 (0.0-0.4)	0.4 (0.0-1.5)	1.3	5.2
Liver	6.8	0.0 (0.0-0.1)	0.1 (0.0-0.3)	0.4	1.5
Pancreas	16.4	0.0 (0.0-0.0)	0.0 (0.0-0.1)	0.1	0.3
Active marrow	8.0	NA	0.1 (0.0-0.1)	NA	1.1

[a]Risks provided where median cumulative organ-equivalent dose >1 mGy. [b]Values given as mean (90% uncertainty range).

difference in the proportion of patients who had an NM study, but among those who did, patients with PR had significantly more NM studies compared to SR ($P = 0.02$). While all patients had x-rays, patients with SR had significantly more studies compared to PR ($P < 0.001$).

For patients who received at least one study, there was no significant difference by cumulative radiation exposure for cardiac catheterizations, IR, or CT studies (Figure 2). Cardiac catheterizations contributed the highest cumulative radiation exposure while IR studies had the least. Patients with PR had significantly higher cumulative radiation exposure for NM (median 5.1 mSv, IQR: 2.0-7.0) than SR (median 2.2 mSv, IQR: 1.7-2.8; $P = 0.02$). Patients with SR had significantly higher cumulative radiation exposure for x-ray (median 1.8 mSv, IQR: 1.1-3.1) than PR (median 1.1 mSv, IQR: 0.7-2.0; $P < 0.001$). Furthermore, despite higher doses generally associated with CT studies compared to x-rays, patients received significantly more x-rays than CTs, resulting in similar cumulative total effective dose from CT studies and x-rays in both treatment strategies.
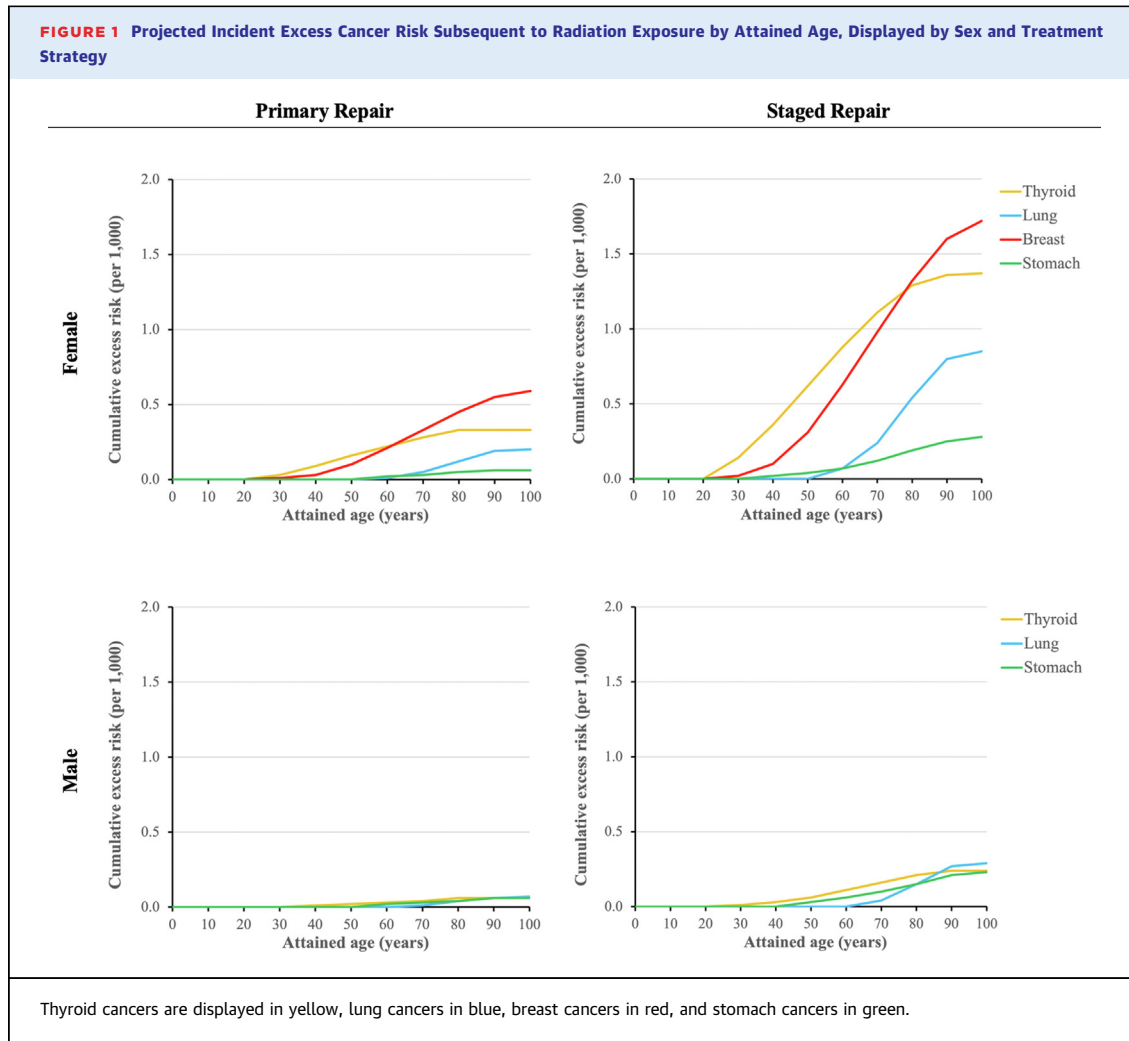
A significantly higher proportion of patients with SR underwent a major radiologic study, defined as a cardiac catheterization, CT, or NM study, than patients with PR (84% vs 51%, $P < 0.001$) (Figure 3). In secondary analyses excluding patients who did not undergo a major radiologic study, no significant difference was observed in cumulative total effective dose for PR (median 7.9 mSv, IQR: 4.5-12.6) versus SR (median 9.7 mSv, IQR: 5.4-21.2; $P = 0.21$) (Supplemental Table 3). The duration of follow-up and other patient characteristics were not significantly different between patients with PR who did and did not undergo a major radiologic study (data not shown).

TRENDS IN UTILIZATION OF MAJOR RADIOLOGIC STUDIES. A significant decline in total effective dose from cardiac catheterizations (among patients who had at least one study) was observed across the study period by year of index procedure ($P = 0.001$) (Supplemental Figure 1). Total effective dose for CT among patients who had at least one study was significantly increased ($P = 0.05$) with no change in NM effective dose appreciated. While there was a

TABLE 3 Projected Lifetime Risks of Developing Cancer by Organ Site and Treatment Strategy (Males)[a]

Organ/Tissue	Baseline Risk (Cancers per 1,000 Patients)	Number of Excess Cancers per 1,000 Patients Attributable to Radiation Exposure[b]		Proportion of Cancers Attributable to Radiation Exposure (%)	
		Primary Repair	Staged Repair	Primary Repair	Staged Repair
Thyroid	6.6	0.1 (0.0-0.2)	0.3 (0.0-0.8)	1.1	3.8
Lung	67.3	0.1 (0.0-0.4)	0.6 (0.1-1.3)	0.2	0.9
Stomach	10.1	0.1 (0.0-0.3)	0.3 (0.0-1.2)	0.8	2.9
Liver	15.3	0.1 (0.0-0.2)	0.2 (0.0-0.5)	0.3	1.2
Pancreas	16.8	0.0 (0.0-0.0)	0.1 (0.0-0.1)	0.1	0.3
Active marrow	10.9	NA	0.1 (0.0-0.1)	NA	0.9

[a]Risks provided where median cumulative organ-equivalent dose >1 mGy. [b]Values given as mean (90% uncertainty range).

FIGURE 1 Projected Incident Excess Cancer Risk Subsequent to Radiation Exposure by Attained Age, Displayed by Sex and Treatment Strategy

Thyroid cancers are displayed in yellow, lung cancers in blue, breast cancers in red, and stomach cancers in green.

decline in total effective dose, there was a significant increase in the proportion of patients who received a cardiac catheterization ($P = 0.04$) or CT ($P = 0.01$) across the study period (Supplemental Figure 2).

DISCUSSION

This multicenter retrospective cohort study is, to our knowledge, the first to describe early life exposure to ionizing radiation in a cohort of neonates with tetralogy of Fallot and symptomatic cyanosis. Overall, early cumulative effective and organ-equivalent radiation exposure were higher in those selected for a SR strategy compared to those for PR. Lifetime attributable cancer risks were also higher for SR, and especially for females, with excess thyroid, lung, breast, and stomach cancers representing the majority of radiation-attributable cases.

Radiation exposure has been characterized in other populations with CHD and correlated with cancer incidence or projection of cancers attributable to radiation exposure.[9,11,24] Patients with CHD are also increasingly exposed to ionizing radiation from medical studies, and this exposure is occurring at progressively younger ages.[24,25] Increased tissue sensitivity to radiation in children has been associated with higher relative risks for cancer, including breast and thyroid, compared to the same level of exposure in adults.[26,27] This is particularly relevant for our studied population, who required neonatal cardiovascular imaging and intervention and thus were obligately exposed to radiation-emitting studies very early in life.

Previous studies have identified populations at risk for higher radiation exposure, and thus at theoretically higher risk for developing cancer, including a

TABLE 4 Linear Regression Models to Examine Clinical Variable Associations With Cumulative Radiation Exposure

	Dependent Variable: Cumulative Total Effective Radiation Dose (mSv)					
	Univariable			Multivariable		
	Estimate	95% CI	P Value	Estimate	95% CI	P Value
Treatment						
Primary repair	(ref.)	(ref.)		(ref.)	(ref.)	
Staged repair	2.80	(2.00-3.92)	<0.001	2.27	(1.71-3.01)	<0.001
Sex						
Male	(ref.)	(ref.)				
Female	1.00	(0.70-1.43)	0.99			
Genetic syndrome	1.80	(1.24-2.62)	0.002	1.16	(1.15-2.06)	0.004
Anatomy						
Tetralogy of Fallot with pulmonary stenosis	(ref.)	(ref.)				
Tetralogy of Fallot with pulmonary atresia	1.41	(0.99-2.02)	0.05			
Prematurity	1.26	(0.82-1.94)	0.29			
Inotrope use before index procedure	1.19	(0.71-2.00)	0.52			
Invasive ventilation before index procedure	2.08	(1.34-3.24)	0.001	1.20	(1.14-2.31)	0.007
Reintervention	4.37	(3.23-5.90)	<0.001	3.90	(2.97-5.13)	<0.001
Procedure year						
2012-2014	(ref.)	(ref.)				
2015-2017	1.09	(0.77-1.55)	0.63			

The log(10) transformation of the effective dose was used as the dependent variable, with reported results referring to the back-transformed data (10^x). Statistical analyses were performed to confirm the model's fit and validity.

Abbreviation as in Table 1.

single ventricle population followed from birth through Fontan palliation and a single-center cohort of patients with pulmonary hypertension with a cumulative median effective dose of 25.7 mSv and 19 mSv, respectively.[11,28] Indeed, the United States Department of Energy has advised a limit of 1 mSv/year for minors.[29] Here in our neonatal sTOF cohort, a cumulative effective dose from the first 18 months of life was 2 and 8 times this limit in patients with PR and SR, respectively. Comparing this further to common sources of radiation, patients with SR received 19 times the average dose of a mammogram.[29] Underlying anatomy and physiology alone may not be enough to predict the potential radiation exposure a

patient may receive but may be more so dependent on the treatment strategy that was pursued.

Cardiac catheterizations consistently account for the highest proportion of overall cumulative exposure.[11,22,28] Otherwise, we found that almost half and nearly 20% of patients with PR and SR , respectively, did not receive a major radiologic study. Differences in utilization of these radiologic studies may reflect institutional preferences more so than the necessity of the study for diagnostic or therapeutic purposes. The ALARA (as low as reasonably achievable) concept represents a practice mandate to: 1) optimize imaging equipment to reduce radiation dose rates; and 2) advocate for optimal operation of any radiation-

TABLE 5 Utilization of Radiation-Emitting Studies in the First 18 Months of Life by Treatment Strategy

|	Number of Patients Who Received Study			Frequency of Studies per Patient Who Received Study		
	Primary Repair (N = 96)	Staged Repair (N = 146)	P Value	Primary Repair	Staged Repair	P Value
Cardiac catheterization	34 (35)	104 (71)	<0.001	1 (1-2)	2 (1-2)	0.18
Interventional radiology	32 (33)	75 (51)	0.008	2 (1-3)	2 (1-3)	0.98
Computed tomography	17 (18)	47 (32)	0.02	1 (1-2)	1 (1-2)	0.81
Nuclear medicine	21 (22)	25 (17)	0.40	2 (1-3)	1 (1-1)	0.02
X-ray	96 (100)	146 (100)	NA	23 (15-37)	35 (25-55)	<0.001

Values are n (%) or median (IQR).

FIGURE 2 Cumulative Effective Dose Across Type of Radiation-emitting Study, by Treatment Strategy
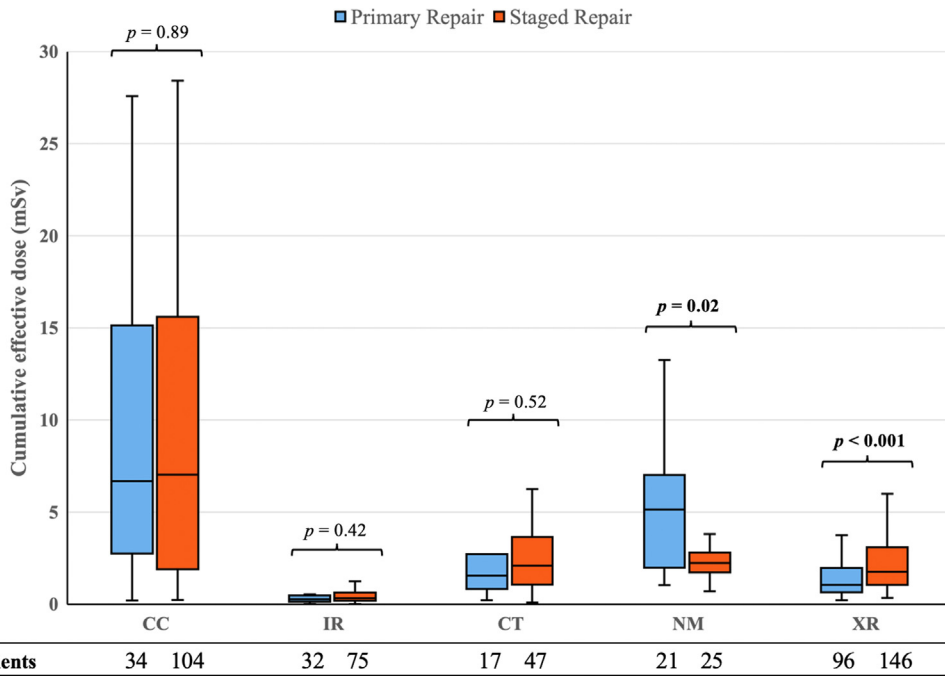
Boxes represent the 25th to 75th percentiles, with the median depicted as a horizontal line. The whisker represents 1.5x the interquartile range or the minimum and maximum values, whichever is shorter. *P* values comparing treatment strategies are displayed above. the number of patients included within each category are listed below. The primary repair group is displayed in blue, and the staged repair group is in red. CC = cardiac catheterization; CT = computed tomography; IR = interventional radiology; NM = nuclear medicine; XR = x-ray.

FIGURE 3 Distribution of the Proportion of Patients Who Had a Cardiac Catheterization, CT, or NM Study by Treatment Strategy
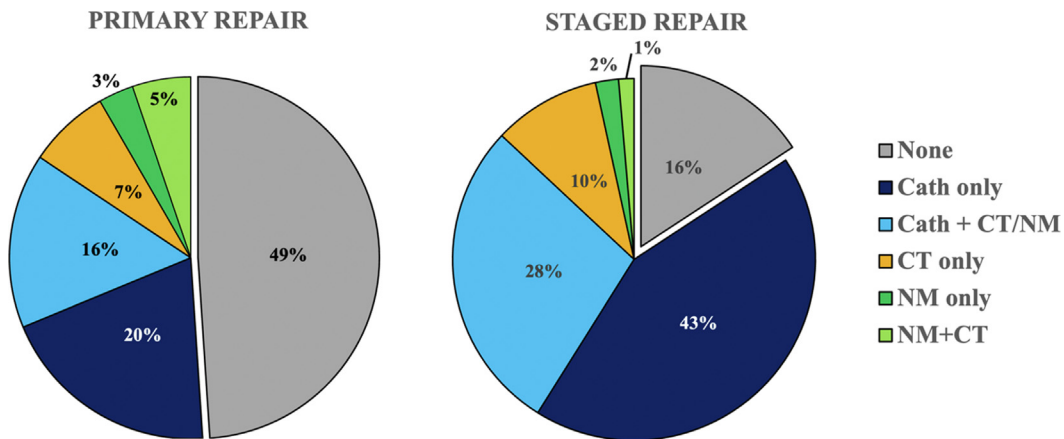
Use of none of these studies is displayed in gray, cardiac catheterizations only in dark blue, cardiac catheterization with CT and/or NM in blue, CT only in orange, NM only in dark green, and NM and/or CT in green.

emitting equipment to reduce duration of fluoroscopic radiation as it pertains to cardiac catheterizations and IR studies[30-33] Newer models of fluoroscopy and CT systems tout decreased radiation exposure to the patient compared to historical models. These technological enhancements in medical imaging equipment may account for the observed lower effective dose in cardiac catheterizations over time as appreciated in our study. Similar trends in procedure doses have been observed across multiple centers participating in quality improvement measures in an effort to minimize radiation exposure.[34]

However, as noted here, cardiac catheterizations and CT studies have been more frequently employed in this population over time. The ALARA concept should be further extended beyond specific procedures and studies to the treatment approach as a whole, in order to understand the optimal strategies available for patients with CHD. For example, magnetic resonance imaging studies may be able to replace CT as a cross-sectional imaging modality in some cases, as it is already utilized for diagnostic and procedural planning purposes in tetralogy of Fallot. Here, while one x-ray may not seem significant, the accumulation of repeated x-rays over the first 18 months of life resulted in similar cumulative radiation exposure to the small number of CT scans received.

Patients with CHD may benefit from additional radiation protection measures, especially during cardiac catheterizations. We estimated that about 7% of thyroid cancers over the lifetime of female patients undergoing SR will have been attributable to early radiation exposure. The thyroid gland is more sensitive to the long-term effects of IR exposure in infancy and early childhood compared to exposures at older ages.[35,36] While there is ongoing debate about the benefits of shielding, it may be prudent to provide additional thyroid protection to our patients with CHD as long as the quality of the imaging is not compromised.[37]

Another important observation is the relationship between CHD, genetic syndromes, radiation exposure, and cancer risk. Patients with trisomy 21 are well-known to have an increased risk for developing leukemia, but that risk is even further elevated in patients with concurrent CHD.[8] However, an increased cancer risk among patients with CHD without chromosomal abnormalities has also been recognized.[4] In our study, genetic syndrome was independently associated with higher cumulative radiation exposure, possibly due to the presence of other comorbidities requiring additional radiologic studies. Underlying genetic variations associated

with CHD may inherently increase risk of cancer or result in greater vulnerability of DNA to ionizing radiation.[6] Patients with CHD and a genetic diagnosis may require additional LDIR dose reduction measures to protect against a potential susceptibility and may be considered for PR over SR when appropriate.

It is interesting to note that patients with SR more often underwent surgical shunt than transcatheter palliation in this historical cohort. Since this cohort was assembled, patent ductus arteriosus (PDA) and right ventricular outflow tract (RVOT) stenting to establish adequate pulmonary blood flow are now more commonly offered in the neonatal period for sTOF. Indeed, our data capture an inflection point where PDA or RVOT stenting frequency increased and became nearly as frequent as surgical shunts. We found no significant difference in overall cumulative radiation exposure between surgical versus transcatheter palliation in the SR group. However, between the obligate radiation exposure from the index transcatheter palliation and increased risk for early transcatheter reintervention, patients undergoing PDA or RVOT stenting may ultimately be at increased risk for higher early cumulative radiation exposure compared to those undergoing surgical shunt. As these transcatheter therapies continue to evolve, this clearly becomes an issue that warrants ongoing study.

Finally, when traditional cohort follow-up approaches are not feasible due to a limited number of patients in the study, projection of future cancer risks attributable to radiation exposure can be estimated under specific exposure parameters using radiation risk models derived from studies of populations exposed to radiation.[23] We projected excess cancer risk starting as early as age 20 for thyroid and 30 for breast cancer without accounting for additional radiation exposure in early childhood and adolescence. Similar to our results, females also had higher LAR estimates compared to males in previous studies.[11,14] Females appear to be at greater risk for morbidity and mortality from radiation-induced cancers than males exposed to the same radiation dose.[12] While larger prospective cohorts are needed to further characterize total radiation exposure and provide adequate power to identify incident cancer cases, studies such as ours provide estimates suggestive of the need for earlier enhanced cancer screening protocols in select populations with CHD where radiation exposure is known.

STUDY LIMITATIONS. First, while there was very limited loss to follow-up over the first 18 months of life, there may still be incomplete radiation data capture and underestimation of cumulative exposure.

As site-specific equipment parameters were not available, organ-equivalent dose estimations relied on many assumptions. Cardiac catheterizations and IR studies do not have fixed exposure fields during the procedure, but specific duration and location of exposure fields were not available. We presumed fixed exposure fields that may overestimate the regions of exposure but utilized other conservative measures, such as energy beam and distance of source to patient, to minimize overestimations or underestimations of the organ-equivalent doses. Comparison of our organ-equivalent doses to published reference values for select IR studies noted overall similar or slightly underestimated values.[38] Further evaluation of radiation dose variation may need to be considered in relation to equipment and operator preferences, specifically for cardiac catheterizations and IR studies.

Second, quantification of LAR attributable to radiation exposure in RadRAT relied on several assumptions as well. Baseline cancer risk does not include the impact of genetic syndromes, which may have a higher cancer predisposition as previously discussed and result in overestimation of attributable risk. Furthermore, the prevalence of smoking in the population with CHD may be different than the general population, which would impact baseline cancer risk for cancers associated with tobacco use (eg lung). Finally, survival to adulthood is lower for people with CHD compared to the general population.[39] LARs may be overestimated when assuming life expectancy of the general U.S. population but the excess risk by attained age remains unchanged.

CONCLUSIONS

In spite of these acknowledged limitations, SR is associated with higher early cumulative radiation exposure and projected lifetime attributable cancer risk. While the PR group had lower radiation exposure, utilization of any major radiologic study (cardiac catheterization, CT, or NM) resulted in similar early cumulative radiation exposure to the SR group.

While there is relative value to each potential treatment strategy, PR may be favored and selected in regard to less radiation exposure when appropriate. These findings suggest the need for effective radiation protection practices in the management of patients with CHD, especially in the early childhood period. Thoughtful justification for all radiologic examinations and therapeutic interventions should continue, and operators should closely adhere to radiation dose minimization practices as per the ALARA concept. Additionally, select populations with CHD may benefit from enhanced cancer screening protocols beginning in the third decade of life.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: SR in symptomatic neonatal TOF is associated with higher early cumulative radiation exposure and higher lifetime attributable cancer risks compared to PR.

TRANSLATIONAL OUTLOOK: Additional follow-up is needed to evaluate the ongoing radiation exposure received in this and other populations with CHD and its correlation to lifetime cancer risk.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.