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PENTEC ORGAN SYSTEM REVIEW

Kidney Disease in Childhood Cancer Survivors Treated With Radiation Therapy: A PENTEC Comprehensive Review

Matthew M. Poppe, MD,[*] An Tai, PhD,[†] X. Allen Li, PhD,[†] Moyed Miften, PhD,[‡] Arthur Olch, PhD,[§] Lawrence B. Marks, MD,[‖] Bilal Mazhar Qureshi, MBBS,[¶] Sheri L. Spunt, MD, MBA,[#] Margarett Shnorhavorian, MD, MPH,[**] Geoff Nelson, PhD,[*] Cecile Ronckers, PhD,[††,‡‡] John Kalapurakal, MD,[§§] Brian Marples, PhD,[‖‖] Louis S. Constine, MD,[‖‖,1] and Arthur K. Liu, MD, PhD[¶¶,1]

[*]*Department of Radiation Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah;* [†]*Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin;* [‡]*Department of Radiation Oncology, University of Colorado School of Medicine, Denver, Colorado;* [§]*Department of Radiation Oncology, Keck School of Medicine, University of Southern California, and Children's Hospital Los Angeles, Los Angeles, California;* [‖]*Department of Radiation Oncology, University of North Carolina, Chapel Hill, North Carolina;* [¶]*Radiation Oncology Section, Department of Oncology, Aga Khan University, Karachi, Pakistan;* [#]*Stanford University School of Medicine, Department of Pediatrics, Stanford, California;* [**]*Department of Urology, Seattle Children's Hospital, University of Washington, Seattle, Washington;* [††]*Princess Máxima Center for Paediatric Oncology, Utrecht, Netherlands;* [‡‡]*Division of Organisational Health Care Research, Departement of Health Care Research, Carl von Ossietzky University of Oldenburg, Oldenburg, Germany;* [§§]*Department of Radiation Oncology, Northwestern University Feinberg School of Medicine, Chicago, Illinois;* [‖‖]*Department of Radiation Oncology, University of Rochester Medical Center, Rochester, New York; and* [¶¶]*UC Health – Poudre Valley Hospital, Radiation Oncology, Fort Collins, Colorado*

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Purpose: Kidney injury is a known late and potentially devastating complication of abdominal radiation therapy (RT) in pediatric patients. A comprehensive Pediatric Normal Tissue Effects in the Clinic review by the Genitourinary (GU) Task Force aimed to describe RT dose-volume relationships for GU dysfunction, including kidney, bladder, and hypertension, for pediatric malignancies. The effect of chemotherapy was also considered.

Methods and Materials: We conducted a comprehensive PubMed search of peer-reviewed manuscripts published from 1990 to 2017 for investigations on RT-associated GU toxicities in children treated for cancer. We retrieved 3271 articles with 100 fulfilling criteria for full review, 24 with RT dose data and 13 adequate for modeling. Endpoints were heterogenous and grouped according to National Kidney Foundation: grade ≥1, grade ≥2, and grade ≥3. We modeled whole kidney exposure from total body irradiation (TBI) for hematopoietic stem cell transplant and whole abdominal irradiation (WAI) for patients with Wilms tumor. Partial kidney tolerance was modeled from a single publication from 2021 after the comprehensive review revealed no usable partial kidney data. Inadequate data existed for analysis of bladder RT-associated toxicities.

Results: The 13 reports with long-term GU outcomes suitable for modeling included 4 on WAI for Wilms tumor, 8 on TBI, and 1 for partial renal RT exposure. These reports evaluated a total of 1191 pediatric patients, including: WAI 86, TBI 666, and

Corresponding author: Matthew M. Poppe, MD; E-mail:; E-mail: Matthew.Poppe@hci.utah.edu

Louis S. Constine and Arthur K. Liu were cosenior authors.

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[1] Co-senior authors.

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439 partial kidney. The age range at the time of RT was 1 month to 18 years with medians of 2 to 11 years in the various reports. In our whole kidney analysis we were unable to include chemotherapy because of the heterogeneity of regimens and paucity of data. Age-specific toxicity data were also unavailable. Wilms studies occurred from 1968 to 2011 with mean follow-ups 8 to 15 years. TBI studies occurred from 1969 to 2004 with mean follow-ups of 4 months to 16 years. We modeled risk of dysfunction by RT dose and grade of toxicity. Normal tissue complication rates ≥5%, expressed as equivalent doses, 2 Gy/fx for whole kidney exposures occurred at 8.5, 10.2, and 14.5 Gy for National Kidney Foundation grades ≥1, ≥2, and ≥3, respectively. Conventional Wilms WAI of 10.5 Gy in 6 fx had risks of ≥grade 2 toxicity 4% and ≥grade 3 toxicity 1%. For fractionated 12 Gy TBI, those risks were 8% and <3%, respectively. Data did not support whole kidney modeling with chemotherapy. Partial kidney modeling from 439 survivors who received RT (median age, 7.3 years) demonstrated 5 or 10 Gy to 100% kidney gave a <5% risk of grades 3 to 5 toxicity with 1500 mg/m^2 carboplatin or no chemo. With 480 mg/m^2 cisplatin, a 3% risk of ≥grade 3 toxicity occurred without RT and a 5% risk when 26% kidney received ≥10 Gy. With 63 g/m^2 of ifosfamide, a 5% risk of ≥grade 3 toxicity occurred with no RT, and a 10% toxicity risk occurred when 42% kidney received ≥10 Gy.

Conclusions: In patients with Wilms tumor, the risk of toxicity from 10.5 Gy of WAI is low. For 12 Gy fractionated TBI with various mixtures of chemotherapy, the risk of severe toxicity is low, but low-grade toxicity is not uncommon. Partial kidney data are limited and toxicity is associated heavily with the use of nephrotoxic chemotherapeutic agents. Our efforts demonstrate the need for improved data gathering, systematic follow-up, and reporting in future clinical studies. Current radiation dose used for Wilms tumor and TBI appear to be safe; however, efforts in effective kidney-sparing TBI and WAI regimens may reduce the risks of renal injury without compromising cure.

Introduction

Radiation therapy (RT) is critical in the treatment of several pediatric malignancies, but direct or incidental radiation exposure to the genitourinary (GU) system can be toxic and predisposes survivors to complications that may affect duration and quality of life. This comprehensive review from Pediatric Normal Tissue Effects in the Clinic (PENTEC) aims to describe the risk of renal toxicity in pediatric cancer survivors who had radiation exposure to the kidney during therapeutic RT.

Clinical Significance

Almost any malignancy in the lower chest, abdomen, or upper pelvis can result in radiation exposure to 1 or both kidneys, and in these settings the kidneys can be the dose-limiting organ during treatment planning. It is critical to know radiation-tolerance of the kidney to make treatment decisions that are not overly protective, thus compromising the therapy to cure the cancer; conversely, renal toxicities can have long-lasting implications, particularly because chemotherapy, antibiotics, and other toxins can be additive in compromising renal function.[1,2] In light of the multiagent and high-dose chemotherapy regimens and antibiotic exposures to which these patients are typically exposed, the cause of renal dysfunction is multifactorial.[1,2] Published in 2010, the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) report describes the dose relationship to the kidney in adults.[3] In their analysis, the prescribed radiation dose associated with a 5% risk of toxicity, without nephrotoxic drug exposure, was 9.8 Gy, regardless of fractionation, although severity of toxicity was not defined.

Volume, fraction size, and total dose are critical factors affecting risk.[4] In an analysis of 126 5-year survivors with a variety of diseases in which portions of 1 or both kidneys were exposed to radiation, Bolling et al[4] reported increasing rates of grade 1 toxicity with increasing volumes of both kidneys receiving ≥20 Gy (V20) and ≥30 Gy (V30) among patients mostly treated with intensity modulated RT (IMRT) since 2001. When the V20 was low, no severe toxicities were observed. The QUANTEC report concluded that partial volume radiation tolerances on the pediatric kidney were not available in the published literature. Analyzing both adult and pediatric data, QUANTEC concluded that the nontotal body irradiation (TBI) whole kidney response data associated with a 5% toxicity risk at 5 years ranged from 18 to 23 Gy, and the 50% risk was 28 Gy. In their analysis, toxicity endpoints were defined by individual publications and were not grouped or uniformly graded.[3] Timing to renal dysfunction and hypertension (HTN) in relation to radiation exposure is also important, as publications show a general trend of decreased glomerular function rate (GFR) over time, especially after the third through fifth decades.[5,6]

Wilms tumor (nephroblastoma) is the most common childhood primary renal tumor. Others include malignant rhabdoid tumor, various soft tissue sarcomas, and renal cell carcinoma.[7] Local management of childhood renal tumors usually includes radical nephrectomy except for those patients with bilateral involvement. For patients with unilateral stage III Wilms tumors, RT is delivered to the post-nephrectomy tumor bed or flank (extending to cover the entire vertebral bodies up to the contralateral kidney) and results in only low-dose radiation exposure to the medial portion of the remaining contralateral kidney.[8] For certain

stage III Wilms tumors where whole abdomen radiation (WAI) is required, the remaining kidney is uniformly exposed to doses of at least 10.5 Gy, but this can be higher depending on histology, extent of abdominal disease, and other patient-specific parameters.[8] Several reports have demonstrated risks of renal dysfunction that range from 0% to 100% after WAI with prescribed doses of 8 to 35 Gy after unilateral nephrectomy, depending on the chosen endpoints and toxicity scoring system used (Table E1).[4,6,9-20] Aside from Wilms tumor, WAI is used in desmoplastic small round cell tumor and rarely for peritoneal metastases of various sarcomas, for which substantially higher RT doses are used and the benefits of radiation are less certain.[21,22]

In the setting of TBI, both kidneys are uniformly exposed to radiation in preparation for bone marrow transplant. TBI is usually delivered in 6 to 9 fractions of 1.5 to 2 Gy to total doses of 12 to 14 Gy over 3 to 4 days but was historically delivered in a single fraction of 7 to 10 Gy.[23-26] When converted to an equivalent single daily dose of 2 Gy per fraction (EQD2), using an α:β ratio of 3.4 Gy for late effects (details in the following sections), the reported TBI doses range from 9 to 23 EQD2 Gy.[27] Total kidney exposures in this dose range result in a rate of renal dysfunction of 0% to 66%, depending on the severity of toxicity reported (Table E2).[23-26,28-33] Abboud et al[28] reported on a series of 148 adults and children undergoing allogenic hematopoietic stem cell transplant who were relapse-free at least 2 years posttransplant. TBI (which was delivered in 50 of these patients in 2 Gy fractions twice daily to 12 Gy) was statistically associated with chronic kidney disease (CKD). The publication does not describe the incidence of TBI by age but notes that none of the 57 patients ≤15 years of age experienced CKD compared with 11% of older patients. This could be a consequence of decreased renal vulnerability to damage in younger patients or additional causes of renal toxicity in older patients.

Neoplasms near the kidney may require therapeutic RT that exposes the kidneys to significant radiation doses. Hodgkin lymphoma involving the para-aortic nodes and/or spleen is often treated with doses of 20 to 36 Gy.[34,35] High risk neuroblastoma arising in the adrenal gland or in the region of the celiac and superior mesenteric arteries is generally treated with 21.6 Gy, often after autologous stem cell transplant.[36] Many types of sarcoma developing in the retroperitoneum, peritoneal cavity, paraspinal region, and body wall near the kidney, including rhabdomyosarcoma and other soft tissue and bone sarcomas, are irradiated to 45 to 63 Gy.[37-39] Carcinomas, although rare in children, occasionally arise in regions around the kidney and may also require high doses of RT. In these settings, portions of 1 or both kidneys can be exposed to significant radiation doses. Historically, hand-placed kidney blocks have been used intermittently to reduce the radiation exposure to the kidneys.[13,18,32,33] In the modern era, kidney sparing is mostly achieved using imaging-based conformal blocking, IMRT planning, and/or proton beam RT.[22,40] Green et al[41] reported kidney function in 2753 survivors of childhood cancer from the St. Jude Lifetime Cohort Study, in which 439 received partial kidney radiation. They concluded that 2.1% of the cohort developed significant (≥grade 3) chronic kidney dysfunction with significant risk factors including older age; grade ≥2 HTN; high cumulative ifosfamide, cisplatin, or carboplatin; use of a calcineurin inhibitor; and volume of the kidney exposed to radiation doses ≥5 or 10 Gy of radiation (V5 or V10). Interestingly, V15 and V20 were not statistically significant risk factors (Table E3).

Radiation to the bladder can result in impaired bladder function and hemorrhagic cystitis (HC), particularly in patients also treated with cyclophosphamide[42,43]; however, this is not commonly observed at doses used in pediatric cancer (Table E4).[44,45] Martelli et al[44] describe the experience of pediatric patients with bladder-prostrate rhabdomyosarcoma. From 1991 to 2007, patients were treated with partial prostatectomy with urethral preservation and/or partial cystectomy and 60 Gy interstitial brachytherapy. With a median follow-up of 10 years, complications included bladder stones (9%), obstruction (5%), and urinary dribbling (50%). Riachy et al[45] reported on the Memorial Sloan Kettering experience of 6119 pediatric patients from 1986 to 2010 to evaluate causes of HC. Overall, 1.6% of children experienced HC, and this rate was 2.7% in the subsets receiving cyclophosphamide, 3.6% busulfan, 5.5% allogenic bone marrow transplant, and 29.5% with pelvic RT.[45] The odds ratio (OR) of developing HC was 59 with pelvic radiation in multivariate analysis, but no analysis by dosage to the bladder was performed. Unfortunately, there were limited usable dose/volume/outcome data for bladder toxicity in children, therefore a dose model could not be generated.

Endpoints and Toxicity Scoring

Several toxicity scoring systems were used in the papers we analyzed and complicate probability modeling because the heterogeneity of endpoints and criteria for different degrees of severity (Tables E1-2, 4). These include classification and scoring systems reported by the National Kidney Foundation (NKF), Radiation Therapy Oncology Group (RTOG)/European Organization for the Research and Treatment of Cancer (EORTC), and the American Heart Association, as well the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).[46-52]

The NKF in 2002 published their expert consensus clinical practice guidelines for the evaluation and classification of CKD.[49] The goals included defining and classifying the stage of CKD and stratifying risk for loss of kidney function and subsequent cardiovascular disease. CKD is stratified into 5 stages/grades, according to GFR (Table 1), and GFR rates are correlated with renal failure complications. Most of the publications eligible for our analysis were completed before this 2002 NKF consensus guideline.

The RTOG and EORTC grading systems (Table E5) were used in the study by Bolling et al.[4] This system grades

Table 1 Chronic kidney disease scoring

NKF[49]	CTCAE v5[47,53]	Description	GFR (mL/min/1.73 m^2)	Action
1	1	Kidney damage with normal or increased GFR	≥90	Treat comorbid condition. Slow progression.
2	1	Kidney damage with mild decreased GFR	60-89	Estimating progression
3	2	Moderate decrease GFR	30-59	Evaluate and treat complications
4	3	Severe decrease GFR	15-29	Prepare for transplant
5	4	Kidney failure	<15 (or dialysis)	Replacement

Because of limited data, we had to group our data and considered NKF stage ≥1 as ≥mild, stage ≥2 as
Abbreviations: CTCAE = common terminology criteria for adverse events; GFR = glomerular filtration rate; NKF = National Kidney Foundation.

patients based on serum creatinine and creatinine clearance, as well as the presence and severity of proteinuria and hematuria but does not use GFR.[48]

Van Dijk et al[20] used National Cancer Institute's CTCAE V3.0, which is a set of standardized criteria for reporting adverse effects of cancer therapy, currently in its fifth version.[50,53] Version 3 and older, like that used by Van Dijk et al, differs from the NKF grading and recommendations.[49,51] Starting with CTCAE version 4.0, the grading for renal toxicity is based on GFR, in line with the NKF recommendations.[46,49] Although both systems have 5 grades of severity, the systems are not directly interchangeable.

HTN can be an important sign of renal disease and results from the stimulation of the renin-angiotensin-aldosterone system that occurs when the kidney detects inadequate blood flow. Renal function can remain adequate with only 1 functioning kidney. One functional and 1 injured kidney, while adequate for filtration, can lead to the nonfunctioning kidney stimulating the renin-angiotensin-aldosterone system, resulting in HTN. In the pediatric population, normal blood pressure varies by age and therefore diagnosis of stage 1 and 2 HTN is based on the variation in an age-specific reference/norm population. According to the 2017 American Heart Association guidelines, pre-HTN is 90% to 95% of normal, stage 1 HTN is ≥95% of normal, and stage 2 is ≥95% normal + 12 mm Hg.[52] Two of our referenced studies include their criteria for the diagnosis of HTN, including that blood pressure measurements be obtained on 2 separate readings[13,24]; however, most do not describe this level of detail.[16,18,23,33]

Although these various toxicity scoring systems are useful, as a practical matter, our review was limited to the scoring systems used in the identified reports. Of 25 included publications that we formally reviewed, 12 describe renal dysfunction as a decrease in predicted GFR, calculated according to validated formulas.[54] Of those, 4 publications describe renal toxicity using a cut-off of 90 mL/min per 1.73 m^2,[6,11,13,33] 3 use 60 mL/min per 1.73 m^2,[23,25,28] and 5 report a variable range of GFRs.[12,14,15,19,41] The 13 other included publications describe kidney dysfunction based on a heterogenous collection of functional and external indicators of renal injury, such as elevated blood urea nitrogen and/or creatinine, albuminuria, electrolyte derangements, HTN, or abnormal kidney imaging, which may or may not correlate with GFR.[4,9,10,16-18,20,24,26,29-32] Given the NKF recommendations, we grouped patients when possible into NKF grades. Grades ≥3 represented chronic renal failure, chronic dialysis, kidney transplant, or GFR <60 mL/min per 1.73 m^2. Grade ≥2 toxicity occurred if patients had a GFR 60 to 90 mL/min per 1.73 m^2 or had an elevated creatinine > 1.5 times normal. The remaining patients with only abnormal laboratory values but normal GFR were grouped into grade 1.[49]

Anatomy and Developmental Dynamics

The renal cortex, renal medulla, and renal pelvis are the 3 main internal components of the kidney. Nephrons, the basic structural and functional unit of the kidneys, are largely located in the medulla and receive fluid from the blood vessels in the renal cortex.[55] The renal cortex produces erythropoietin. The renal pelvis contains the hilum, which is where blood vessels and nerves enter and exit the kidney; this is also the point of exit for the ureters that drain urine and empty into the urinary bladder. The kidneys perform several critical functions including: filtering waste metabolites from the blood into urine, regulating electrolyte levels in the blood, secreting renin to control blood pressure, releasing erythropoietin to stimulate red blood cell production, and secreting the active form of vitamin D to add calcium to bone.[56]

The kidneys at birth and the postnatal period are marked by growth and physiological functional changes that adapt to extrauterine life and progress to adult renal function.[57] In term neonates, nephrogenesis is complete at birth and comprises the glomerulus, tubules, and the renal collecting system. Postnatal maturation of glomerular structure consists of an increase in glomerular membrane permeability, filtration surface area, corpuscular glomerular diameter, and intrarenal redistribution of blood flow. Glomerular size reaches adult values at 3 years of age. Postnatal maturation of renal tubules

mirrors the maturation of GFR and is characterized by a 10-fold increase in proximal tubular length and diameter.[58]

The mechanism of RT-associated renal dysfunction is generally thought to result from direct nephron, renal tubular damage, and/or renal artery narrowing (which can result in hyper-renin HTN). Nephrons, the radiobiological functional subunit, are architecturally arranged in parallel, rendering the organ sensitive to RT dose and volume effects.[3,59-62] The low mitotic index of the radiosensitive tubular epithelial cells and/or endothelial cells confers a long latency.[59] During the latent period and the early stages of radiation nephropathy, injury remains subclinical and includes glomerular alterations, along with reduced vessel perfusion, loss of small blood vessels, and capillary dilation.[63] These events also make the organ sensitive to retreatment with a tolerance that decreases with time, indicating continuous progression of occult damage.[64] Irradiation also modifies the tissue microenvironment, leading to increased expression of proinflammatory and profibrotic cytokines promoting tissue fibrosis.[65-67] Although there might be regional differences in the sensitivity of regions within the kidney, specific analysis of hilar versus cortical radiation dose sensitivity is lacking despite the expectation that the elegant renal cortex is more vulnerable.

Defining Volumes: Pediatric Imaging Issues

The kidneys are typically easy to delineate on the radiation planning computed tomography (CT) scans. The RTOG provides a CT kidney contour atlas in the Upper Abdominal Normal Organ Contouring Consensus Guidelines.[68] Modern CT scanners have improved imaging capabilities, while delivering lesser radiation doses, inspired in large part by Brenner et al,[69] who linked CT scans with increased cancer risk. Adaptive bow-tie filters, iterative reconstruction, and pediatric- specific protocols with lower voltage and amperage settings allow less kidney dose while maintaining, or even improving, the image quality. Efforts should be made with pediatric patients to use all tools available to decrease the CT dose.

For RT-associated image guidance of the abdomen, if the bony anatomy is a sufficient surrogate for positioning and 4 degrees of freedom table correction is acceptable, orthogonal kV images are dosimetrically preferred because they have can have a far lower dose than cone beam CT.[70,71] Ultra low-dose cone beam CT is a good alternative when full 6 degree of freedom corrections are used.[72]

Kidney motion in children has been assessed by several groups, whether interfractional motion or with 4-dimensional CT (4DCT).[73-76] At St. Jude Children's Research Hospital, 20 pediatric patients who underwent 4DCT had motion reported based on the kidney center of mass. [76] The largest motion was in the supero-inferior direction, with a mean motion of 12 to 25 mm in children aged 2 to 8, and 21 to 52 mm in children aged 9 to 18. In another study from Oncology Centre King Faisal Specialist Hospital, 9 pediatric patients with neuroblastoma underwent 42 4DCTs.[75] The largest motion was also found in the supero-inferior direction and ranged from 4 to 10 mm. This motion envelope can be used to create an expanded planning organ at risk volume when optimizing a radiation plan for renal protection.

Review of Dose Volume Response Data and Risk Factors

The PENTEC systematic review of RT-associated genitourinary dysfunction aimed to assess the dose response of the kidney and bladder in childhood cancer survivors. Because of the limited data available regarding bladder injury, we focused our efforts on radiation-related kidney dysfunction and HTN (though the few bladder studies are included in Table E4 for completeness). Search methodology is described in Supplementary Materials, including inclusion criteria and data extraction.

Based on the final focus of kidney dysfunction and HTN, from a total of 2652 titles reviewed for renal dysfunction, 98 were included for qualitative review. Of those, 13 reports fulfilled criteria for quantitative modeling (Tables 2-5).[6,13,16,18,23-26,29,30,32,33,41]

To determine the accuracy of the dosimetry reported in the articles we reviewed, the task force medical physicist (M. M.) objectively reviewed dose accuracy for each of the studies formally reviewed (Table E6). A dosimetry grade and accuracy score were assigned based on the ability to determine dose to the kidney versus prescribed dose. For the majority of studies, the prescribed dose was specified and correlated with toxic events.[24,26,30,41] For studies in which doses were given as a range, mean dose was used when possible.[6,13,16,18,31] We recognize that there were inconsistencies in dosimetric reporting, which is a limitation in the model. There are several important TBI studies in which the majority of patients received a single large fraction of radiation and a few patients received a lower or fractionated dose or a partial transmission kidney block was used. When toxicity was not correlated by dose or use of a kidney block, we made an assumption that a toxicity event was likely from the larger (more common) biological equivalent dose (see Table E6).[23,25,31-33] For the purposes of biologically effective dose calculations in our modeling, twice and 3 times daily fractions were modelled as daily exposure, given uncertainly in time between fractions and assumption of near complete repair after 6 hours.[29] We ultimately modeled 13 studies based on acceptable dosimetric accuracy. In the Supplementary Materials is a bias assessment of the 13 studies ultimately modeled, which still demonstrates moderate to severe bias.

Dose-effect relationship

Normal tissue complication probability (NTCP), that is, the incidence of radiation-associated renal failures or HTN as a

Table 2 Summary of studies estimating the risk of severe toxicity

Study, first author	Diagnosis	Patients (n)	Total dose (Gy)	Dose (Gy)/Fx	Fx/D	EQD2 (Gy)	Toxicity (%)
Bradley[29]	TBI, leukemia	52	13.5	1.5	2	12.2	3.9
Chou[30]		58	12	2	2	12.0	1.7
Frisk[23]		26	7.5	7.5	2	15.8	0
Gerstein[32]		43*	12	2	2	12.0	0
Leisner[25]		7†	9	9	1	21.6	14.3
Tarbell[26]		20	13-14	2	2	14.0	15.0
Levitt[13]	Wilms	17‡	11-17	1.5	1	13.8	5.9
Paulino[16]		6	10-24 WAI	1.5	1	12.0	0
Sasso[18]		13	<12 WAI	1.5	1	10.8	0
		6§	12-35	2		20.0	16.7

GFR <60 mL/min/1.73 m^2 (NKF grades 3-5). Total dose is estimated kidney dose, not necessarily prescribed dose.

Abbreviations: D = day; EQD2 = equivalent dose in 2 Gy/fx calculated assuming an α:β ratio of 3.4 Gy (see text for details and justification); GFR = glomerular filtration rate; NKF = National Kidney Foundation; TBI = total body irradiation; WAI = whole abdominal irradiation.

* One patient had renal shielding to 10 Gy but toxicity data do not account for this, therefore not used in EQD2 data.

† One of 7 patients received 14 Gy in 7 fx over 3 days. The EQD2 data are shown for the 6 receiving the dose shown.

‡ We used an average total dose of 15 Gy and assumed daily 1.5 Gy in EQD2 data.

§ Kidneys were stated to be "totally" blocked at 12 Gy; however, 6 patients received an unstated higher dose to the kidney because of diffuse macroscopic residual or protocol. As prescribed doses were 15 to 35 Gy, we chose a dose of 20 Gy in our model.

function of radiation dose was analyzed based on the Lyman-Kutcher-Burman model as formulated[77,78]:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx$$

$$t = \frac{D - TD_{50}}{mTD_{50}}$$

where D is the dose that is delivered uniformly to the entire volume. TD_{50} is the uniform dose given to the entire organ volume that results in 50% complication risk, and m is a measure of the slope of the sigmoid dose-response curve. EQD2 was used to consider the fractionation sizes other than 2 Gy. The EQD2 was calculated according to the linear-quadratic (LQ) model as:

$$EQD_2 = D_d \frac{\frac{\alpha}{\beta} + d}{\frac{\alpha}{\beta} + 2},$$

where D_d is the total dose delivered at d Gy/fraction. Time is not considered in the equivalent dose equation and thus we are inherently assuming 1 fraction per day. The α:β ratio is the LQ parameter and assumed fixed at 3.4 Gy.[27,79-81] The work from Brenner[82] suggests the LQ model is appropriate for high dose fractions certainly up to 10 Gy. The maximum likelihood method was used to fit the available data using the Lyman-Kutcher-Burman model.[83] Particularly, the values of TD_{50} and m were determined by maximizing the following log likelihood function:

$$L = \sum_i \{r_i \ln(P_i) + (n_i - r_i) \ln(1 - P_i)\}$$

Where P_i is the calculated NTCP, n_i is the number of patients, and r_i is the number of responders for the i-th data.

Figs 1 through 4 through present the renal toxicity data by grade and HTN data, along with the NTCP model fitting lines. The error bars represent a 95% confidence level calculated with a Poisson distribution based on dose error estimations from the dosimetry scores found in Table E6.

Radiation technique and diagnosis considerations

The preponderance of available kidney toxicity data came from 2 indications for radiation therapy: Wilms tumor, in which 1 kidney had been removed and the remaining kidney was exposed to radiation as part of WAI, and TBI, in which both kidneys were exposed to radiation. We found insufficient data to model other scenarios, including bilateral Wilms tumor and unilateral Wilms tumor treated by flank-only RT. As we modeled radiation dose-response for situations in which only 1 kidney is present or where both kidneys were equally exposed to radiation, GFR tests should be a valid measure of kidney toxicity. Studies were excluded if flank RT versus WAI could not be distinguished, because we did not want to underestimate the toxicity of WAI by including patients who received flank-only RT, which does not expose the contralateral kidney to significant radiation. Wherever possible, we attempted to model based on organ-specific RT doses. Most investigations reported prescribed dose rather than estimated dose to the kidney because of a lack of 3D planning.[6,16,24-26,29-33] The task force medical physicists performed a dose accuracy evaluation for each

Table 3 Summary of studies estimating the risk of moderate toxicity

Study, first author	Diagnosis	Patients (n)	Total dose (Gy)	Dose (Gy)/Fx	Fx/D	EQD2 (Gy)	Toxicity (%)
Bradley[29]	TBI, leukemia	76	13.2-13.5	1.5	2	12.4	5.3
Frisk[23]		26	7.5	7.5	1	15.8	7.7
Gerstein[32]		43*	11-12	2	2	12.0	7.0
Leisner[25]		7†	9	9	1	19.5	28.6
Tarbell[26]		5	12	2	2	12.0	20.0
		6	13	2.16	2	13.3	50.0
		12	14	1.75	2	13.4	33.0
		5	8.5	8.5		17.7	20.0
Watanabe Nemoto[33]		1	8	2.67	1	8.9	0
		2‡	10	2.5	2	10.8	50.0
		6	12	2	2	12.0	0
Tarbell[26]	TBI, neuroblastoma	10	12	2	2	12.0	60.0
		1	13	2.16	2	13.3	100
Kostel Bal[6]	Wilms	8	15	1.5	1	13.6	0
Levitt[13]		13	No RT	0	0	0.0	31
		23§	1-12	1.5	1	7.3	8.7
		17‖	12-17	1.5	1	13.8	23.5
Sasso[18]		13	<12	1.5	1	10.8	0
		6¶	12-35	2	1	20.0	33.3

GFR <90 mL/min/1.73 m^2 (NKF grades ≥2). Total dose is estimated kidney dose, not necessarily prescribed dose.

Abbreviations: D = day; EQD2 = equivalent dose in 2 Gy/fx calculated assuming an α:β ratio of 3.4 Gy (see text for details and justification); GFR = glomerular filtration rate; NKF = National Kidney Foundation; RT = radiation therapy; TBI = total body irradiation.

* One patient had renal shielding to 10 Gy but toxicity data do not account for this, therefore not used in EQD2 data.

† One of the 7 patients received 14 Gy in 7 fx over 3 days. The EQD2 data are shown for the 6 receiving the doses shown.

‡ One patient is described with a kidney and liver block with left adrenal neuroblastoma. There is no description of the thickness of the block or dose to the kidney under the block, therefore discarded in EQD2 data.

§ We used an average total dose of 8 Gy and assumed daily 1.5 Gy in EQD2 data.

‖ We used an average total dose of 15 Gy and assumed daily 1.5 Gy in EQD2 data.

¶ Kidneys were stated to be "totally" blocked at 12 Gy; however, 6 patients received an unstated higher dose to the kidney because of diffuse macroscopic residual or protocol. As prescribed doses were 15 to 35 Gy, we chose a dose of 20 Gy in our model.

investigation analyzed for dose-response modeling that included a categorization of the reported doses as well as an estimate, when possible, of the accuracy of those doses (Table E6). Most commonly, dose to organ accuracy (either prescribed dose or estimated organ dose) was estimated to be within 5% to 10% of the modeled dose. In the publications reviewed, doses were often binned[13,29,32,33,41] and/or only expressed in medians.[6,25,26,31] Our dose-response model used the midpoint dose of the bins for analysis. Not knowing the distribution of doses within each bin increases the uncertainty in the shape of the dose-response. The data were synthesized into tables for modeling purposes and translated into EQD2 (Tables 2-6).

Partial kidney tolerance was modeled based on a single report that was obtained outside of this formal search.[41] From the reported ORs in Table E3 of the report by Green et al, the coefficients in the logistic regression models can be calculated, that is, coefficient = ln (OR). The intercepts of the logistic regression models were not reported but were obtained directly from the authors. Fig 5 demonstrates the V10 partial kidney modeling. The 95% confidence intervals for the V10 model are available in Fig E1. Because V5 was similar in our model to V10 and as it was reported by Green et al that V15 and V20 are not statistically significant when predicting stages 3 to 5 CKD, models are not included for these dose levels.

Recommendations for Nominal Dose/Volume Goals

Based on these data, we anticipate clinically acceptable toxicity with commonly prescribed doses used today (Table 7). The risk of any renal toxicity from 10.5 Gy in 7 fractions (EQD2 = 9.6 Gy) of whole abdomen RT (as is routinely given to the remaining kidney in the postoperative setting in patients with Wilms tumor) is low, with a generally acceptable <5% risk of chronic moderate or

Table 4 Summary of studies estimating the risk of any toxicity

Study, first author	Diagnosis	Patients (n)	Total dose (Gy)	Dose (Gy)/Fx	Fx/D	EQD2 (Gy)	Toxicity (%)
Bradley[29]	TBI, leukemia	52	13.5	1.5	2	12.2	7.7
Chou[30]		58	12	2	2	12.0	3.5
Frisk[23]		26	7.5	7.5	1	15.8	34.6
Gerstein[32]		43*	11-12	2	2	12.0	28.0
Tarbell[26]		5	12	2	2	12.0	20.0
Tarbell[26]		6	13	2.16	2	13.3	50.0
Tarbell[26]		12	14	1.75	2	13.4	33.0
Tarbell[26]		5	8.5	8.5	1	17.7	20.0
Watanabe Nemoto[33]		1	8	2.67	1	8.9	0
		2†	10	2.5	2	10.8	50.0
		6	12	2	2	12.0	66.7
Tarbell[26]	TBI, neuroblastoma	10	12	2	2	12.0	60.0
		1	13	2.16	2	13.3	100
Sasso[18]	Wilms	28	<12	1.5	1	10.8	0
	Wilms	6‡	12-35	2	1	20.0	100

Any GFR (NKF grades ≥1). Total dose is estimated kidney dose, not necessarily prescribed dose.

Abbreviations: D = day; EQD2 = equivalent dose in 2 Gy/fx calculated assuming an α:β ratio of 3.4 Gy (see text for details and justification); GFR = glomerular filtration rate; NKF = National Kidney Foundation; TBI = total body irradiation.

* One patient had renal shielding to 10 Gy but toxicity data do not account for this, therefore not used in EQD2 data.

† One patient is described with a kidney and liver block with left adrenal neuroblastoma. There is no description of the thickness of the block or dose to the kidney under the block, therefore discarded in EQD2 data.

‡ Kidneys were stated to be "totally" blocked at 12 Gy; however, 6 patients received an unstated higher dose to the kidney because of diffuse macroscopic residual or protocol. As prescribed doses were 15 to 35 Gy, we chose a dose of 20 Gy in our model.

Table 5 Summary of studies estimating the risk of hypertension

Study, first author	Diagnosis	Patients (n)	Total dose (Gy)	Dose (Gy)/Fx	Fx/D	EQD2 (Gy)	Toxicity rate (%)
Frisk[23]	TBI, leukemia	26	7.5	7.5	1	15.8	7.7%
Watanabe Nemoto[33]		1	8	2.67	1	8.9	0%
Watanabe Nemoto[33]		2*	10	2.5	2	10.8	50.0%
Watanabe Nemoto[33]		6	12	2	2	12.0	0%
Hoffmeister[24]	TBI, various	10	2-6	2	2	6.0	0%
Hoffmeister[24]		356	12-15.75	2	2	12.0	18.0%
Hoffmeister[24]		79	10	10	1	23.3	35.4%
Levitt[13]	Wilms	23†	0-12	1.5	1	7.3	4.4%
Levitt[13]		17‡	12-17	1.5	1	13.8	23.5%
Paulino[16]		36	No RT	0	0	0.0	8%
Paulino[16]		6	10-24	1.5	1	12.0	0%
Sasso[18]		13	<12	2	1	10.8	0%
Sasso[18]		6§	12-35	1.8	1	20.0	66.7%

Total dose is estimated kidney dose, not necessarily prescribed dose.

Abbreviations: D = day; EQD2 = equivalent dose in 2 Gy/fx calculated assuming an α:β ratio of 3.4 Gy (see text for details and justification); RT = radiation therapy; TBI = total body irradiation.

*One patient is described with a kidney and liver block with left adrenal neuroblastoma. There is no description of the thickness of the block or dose to the kidney under the block, therefore discarded in EQD2 data.

† We used an average total dose of 8 Gy and assumed daily 1.5 Gy in EQD2 data.

‡ We used an average total dose of 15 Gy and assumed daily 1.5 Gy in EQD2 data.

§ Kidneys were stated to be "totally" blocked at 12 Gy; however, 6 patients received an unstated higher dose to the kidney because of diffuse macroscopic residual or protocol. As prescribed doses were 15 to 35 Gy, we chose a dose of 20 Gy in our model.

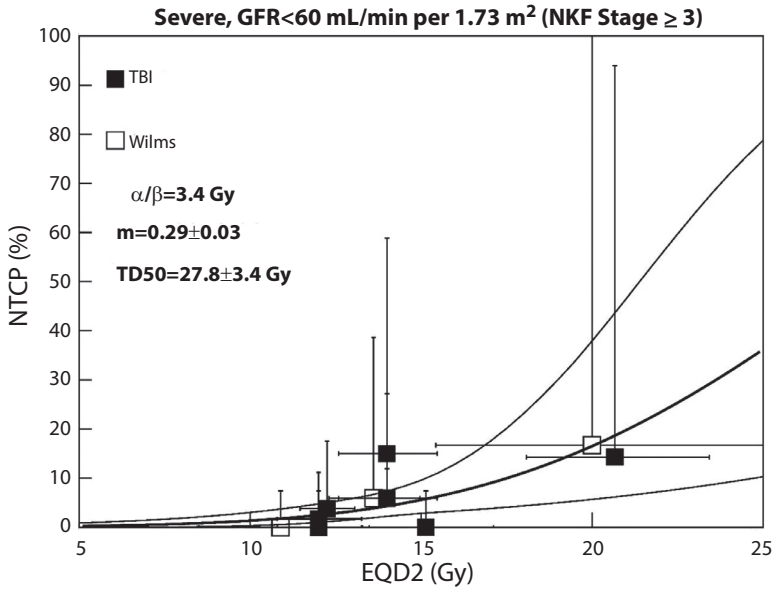

Fig. 1. Severe renal toxicity as a function of equivalent single daily dose of 2 Gy per fraction and model fitting results (thick lines) and 95% confidence levels (thin lines) for total body irradiation and Wilms. *Abbreviations:* GFR = Glomerular Filtration Rate, NKF = National Kidney Foundation, TD50, Total Dose in which 50% of patients experience toxicity. EQD2 = Equivalent Dose in 2 Gy per fraction.

severe toxicity. In the setting of 12 to 14 Gy TBI (11-12 Gy EQD2) the risk is higher with ≥ chronic moderate toxicity risk of 6% to 8% and severe toxicity or renal failure 2% to 3%.

Based on the single publication used for partial kidney modeling,[41] we suggest cautious interpretation of partial kidney results. Based on these data, even with 100% of kidney receiving 5 to 10 Gy of radiation, the risk of severe renal toxicity is low (<5%) with 1500 mg/m^2 carboplatin (neuroblastoma, medulloblastoma, hepatoblastoma) or no chemotherapy. With 480 mg/m^2 of cisplatin (osteosarcoma, neuroblastoma, medulloblastoma, hepatoblastoma), we estimate a 5% risk of severe toxicity with a volume of 26% of the kidney receiving greater than 10 Gy of radiation. With 63 g/m^2 of ifosfamide (sarcoma), we estimate a 5% risk of severe toxicity occurring in the absence of any radiation and a 10% risk with a volume of 42% of the kidney receiving greater than 10 Gy of radiation.

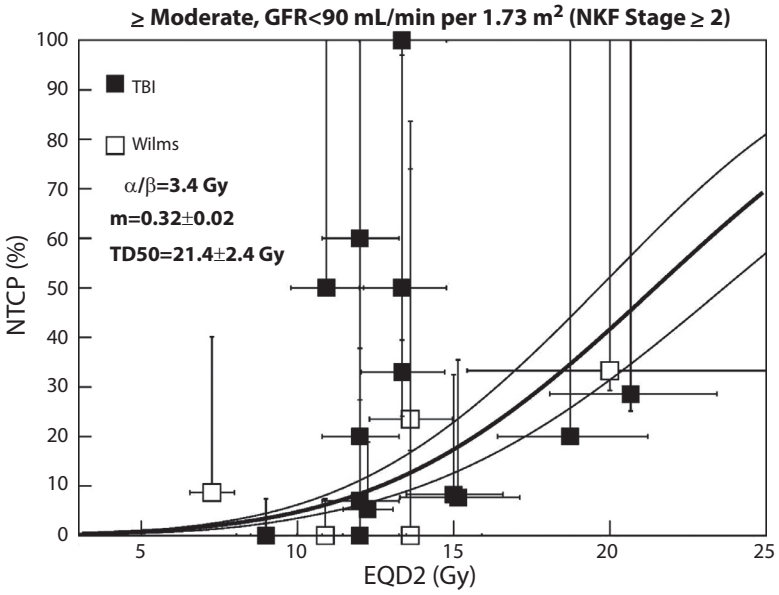

Fig. 2. Moderate renal toxicity as a function of equivalent single daily dose of 2 Gy per fraction and model fitting results (thick lines) and 95% confidence. *Abbreviations:* GFR = Glomerular Filtration Rate, NKF = National Kidney Foundation, TD50, Total Dose in which 50% of patients experience toxicity. EQD2 = Equivalent Dose in 2 Gy per fraction.

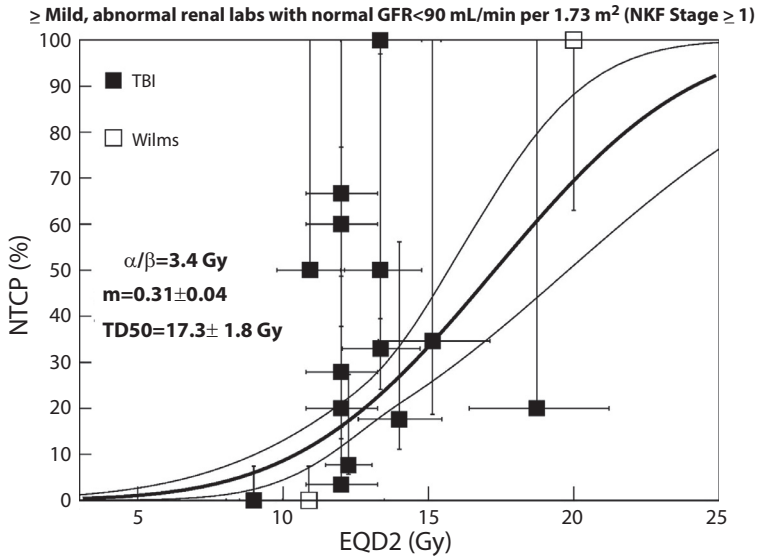

Fig. 3. Mild renal toxicity as a function of equivalent single daily dose of 2 Gy per fraction and model fitting results (thick lines) and 95% confidence levels (thin lines) for total body irradiation and Wilms. *Abbreviations:* GFR = Glomerular Filtration Rate, NKF = National Kidney Foundation, TD50, Total Dose in which 50% of patients experience toxicity. EQD2 = Equivalent Dose in 2 Gy per fraction.

Limitations

Given the differences in radiation exposure of 1 versus 2 kidneys and the different systemic therapies used in patients, we analyzed WAI-Wilms tumor and TBI separately, although they were modeled together because of insufficient data, especially for Wilms tumor. It should be noted that where 2 kidneys are present but only 1 is exposed to radiation, damage to that kidney can be obscured by the compensation afforded by the other without performing kidney function tests such as renal scintigraphy.

In our review, we were unable to model the data according to age, development status, sex, race, or comorbid medical conditions, as these data were not available in the majority of studies. We were also unable to gather sufficient accurate information to model the effect of nephrotoxic chemotherapy, except in the publication by Green et al,[41] from which we generated our partial kidney

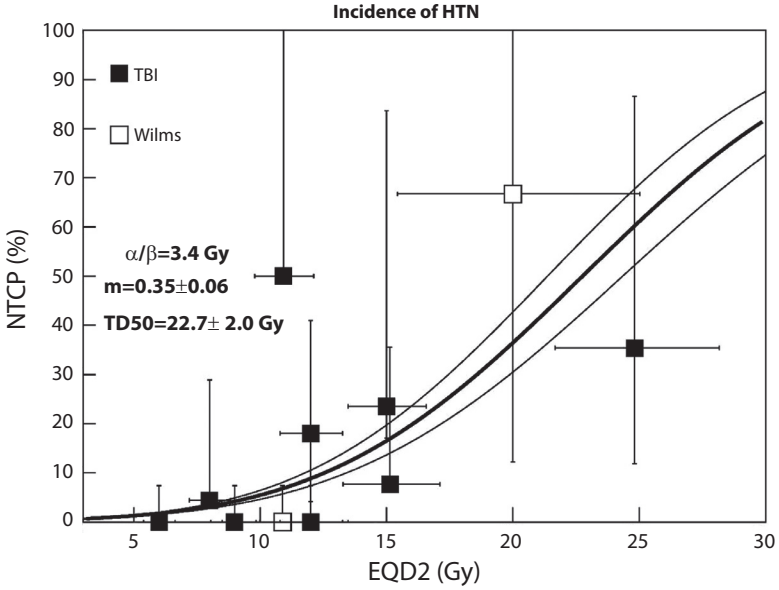

Fig. 4. Hypertension toxicity as a function of equivalent single daily dose of 2 Gy per fraction and model fitting results (thick lines) and 95% confidence levels (thin lines) for total body irradiation and Wilms. *Abbreviations:* GFR = Glomerular Filtration Rate, NKF = National Kidney Foundation, TD50, Total Dose in which 50% of patients experience toxicity. EQD2 = Equivalent Dose in 2 Gy per fraction.

Table 6 Total dose if given in 2 Gy per fx (95% CI) predicted to be associated with 5% rates of various levels of renal toxicity

Doses to whole kidney	
HTN	9.6 (9.1-10.3)
NKF grade ≥1	8.5 (7.1-10.2)
NKF grade ≥2	10.2 (9.3-11.2)
NKF grade ≥3	14.5 (12.2-19.0)

EQD2 (Gy) calculated via the linear quadratic model and an assumed $\alpha:\beta$ value of 3.4 Gy.[87] *Abbreviations:* CI = confidence interval; EQD2 = equivalent dose in 2 Gy/fx calculated assuming an $\alpha:\beta$ ratio of 3.4 Gy (see text for details and justification); HTN = hypertension; NKF = National Kidney Foundation.

tolerance model. We partially account for this by analyzing data from WAI-Wilms and TBI separately, because most patients with unilateral favorable histology Wilms do not receive nephrotoxic chemotherapy. This analysis was limited to whole kidney irradiation in the setting of WAI-Wilms tumor and TBI. Although we limited our analysis to pediatric data, we were unable to model specific effects by year of age. The timing to the development of renal dysfunction and HTN was not available in the majority of the publications we reviewed, which could be important given the large range of median follow-up years. It has been shown that GFR decreases postnephrectomy over time, regardless of radiation exposure.[5,6]

In our modeling, we included data from published reports in the years 1968 to 2011 with a range of short and long follow-up intervals. We were unable to account for toxicity based on follow-up duration or decade, as the majority of toxicity was not scored as such. The Wilms data comes from 4 sources with the periods 1975 to 2011, 1970 to 1980, 1968 to 1994, and 1981 to 2000.[6,13,16,18] Median follow-up in those 4 data sets was 8, 13, 15, and 15 years. For the TBI data, almost all come from the years 1980 to 2000. We have a total of 9 data sets with interval ranges of 1985 to 1994,[29] 1982 to 1993,[30] 1995 to 2003,[31] 1985 to 1997,[23] 1986 to 2003,[32] 1969 to 2004,[24] 1981 to 1988,[25] 1980 to 1987,[26] and 1989 to 2006.[33] There appears only 1 outlier, which includes data from the 1970s.[24] All data sets have a mean follow-up period of >3 years, except 2.[26,31] One publication described a median of only 4.5 months; however, patients in that data set had CKD at 2.4, 4, 4.2, 4.8, 5.7, 7.2, 9, 14.2, and 27 months after transplant.[31]

Although a comparison of adult and pediatric radiation effects on renal function would be of interest and the relevant QUANTEC report would offer the best opportunity for this, the differences in methodology and data precluded this.[3] QUANTEC data included a combination of pediatric and adult patients. QUANTEC non-TBI data are primarily from seminoma and gynecological (GYN) publications where both kidneys are intact, in contrast to patients with Wilms tumor where 1 kidney has been resected and the remaining kidney is irradiated. QUANTEC did not stratify toxicity by severity or report NCTP for different severity levels. Despite these caveats, the results from QUANTEC and PENTEC seem to be concordant.

Toxicity Scoring Recommendations

Similar to the NKF recommendations, we recommend future studies report estimated GFR as well as the need for dialysis or kidney transplant. In the setting of

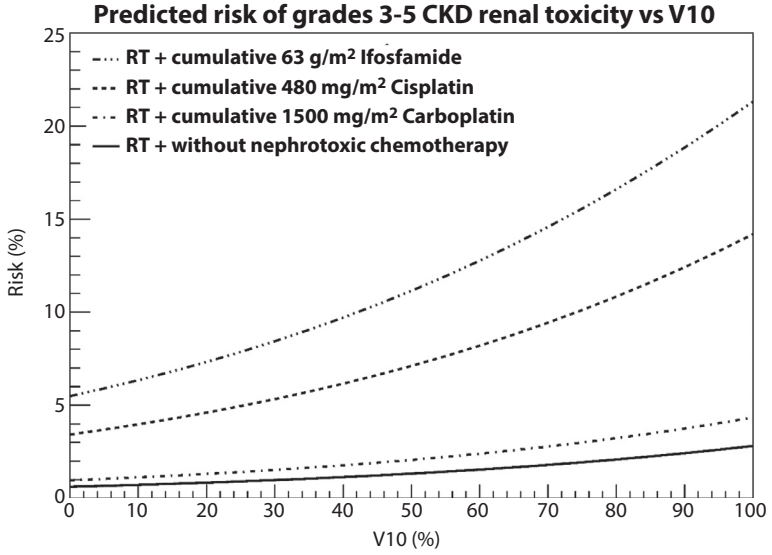

Fig. 5. Volume of kidney receiving ≥10 Gy of radiation partial kidney modeling, based on data from Green et al[41] based on chemo exposure. *Abbreviations:* GFR = Glomerular Filtration Rate, NKF = National Kidney Foundation, TD50, Total Dose in which 50% of patients experience toxicity. EQD2 = Equivalent Dose in 2 Gy per fraction.

Table 7 Predicted rates (%) of renal toxicity (NKF grading) for commonly prescribed radiation doses (95% CI)

Total dose and fractionation	NKF ≥3	NKF ≥2	NKF ≥1	HTN
WAI, 1.5 Gy × 7 fx = 10.5 Gy	1.2 (0.2-2.8)	4.2 (3.1-5.5)	7.5 (3.6-11.1)	4.9 (4.2-5.8)
TBI, 1.5 Gy × 8 fx = 12 Gy	1.8 (0.6-3.8)	6.4 (4.7-8.4)	11.9 (7.5-16.3)	7.0 (5.9-8.3)
TBI, 2 Gy × 6 fx = 12 Gy	2.5 (1.0-4.7)	8.4 (6.2-11.1)	16.1 (11.7-20.9)	8.8 (7.4-10.5)

Abbreviations: CI = confidence interval; HTN = hypertension; NKF = National Kidney Foundation; TBI = total body irradiation; WAI = whole abdominal irradiation.

partial kidney radiation, adding kidney perfusion scan results would allow reporting of ipsilateral versus contralateral kidney function based on which kidney was irradiated. Using CTCAE version 5 (or later equivalent) will help to ensure that toxicity grades reflect these endpoints.

We recommend evaluating for stage 1 and 2 HTN based on the American Heart Association scoring used in adults or established expected normal values in children, given that these values have been correlated with an increased risk of cardiovascular disease (CVD) and are universally accepted.[52] HTN criteria should be graded according to age and reproduced on at least 2 occasions.

Data Reporting Standards Specific to the Kidney

Most of these data come from Wilms and TBI reports in which 2D radiation planning with limited volumetric dosimetric details were available. The few studies reporting renal dosimetry describe few cases of moderate or severe renal injuries. Future publications should optimally conform to a uniform reporting standard to facilitate pooled analysis. Thus, we propose reporting the following information in future studies (on a per-patient basis, for those with and without toxicity):

- Patient sex and race
- Clinical indication for RT (ie, cancer diagnosis)
- Age at the start of RT
- Prescribed RT total dose and dose fractionation
- RT technique (ie, photon-based 2D, 3D, IMRT, volumetric-modulated arc therapy; proton therapy − passive scatter, spot scanning, intensity modulated proton therapy (IMPT))
- Kidney radiation exposure described by relevant normal organ dose volume histogram with 0.1 Gy dose resolution, including each kidney separately and combined volume
- Recommended dosimetry
  - Min, max, and mean dose to kidney
  - Volume of each kidney receiving >10, 15, 20, and 30 Gy
- Nephrotoxic chemotherapy use (if yes, timing with respect to RT and agents with dose given)
- Frequency of clinical follow-up for late complications of RT
- Frequency of laboratory and/or imaging follow-up
- Number of patients in the study and the number of those with or without toxicity
- Dosimetric data for patients, both those with and without toxicity
- Description of the toxicity endpoint(s) including how it is measured and what toxicity scoring system was used
- Patient-reported outcomes and symptoms (eg, HTN, renal impairment or failure)
- CTCAE late toxicity (>6 months from completion of radiation) with age and time from radiation
- Description of other possible factors contributing to CKD such as kidney infections, diabetes, renal calculi, nephrotoxic antibiotics, and so forth

Future Investigations

TBI

Although current doses used for TBI appear safe, clinical trials that investigate the efficacy and safety of lower renal doses during TBI may reduce the risk of chronic kidney problems. Newer technologies (eg, IMRT) afford the possibility of total marrow irradiation in lieu of TBI, thus lowering the dose of radiation delivered to the kidney and elsewhere.[84]

Wilms tumor

Intensity modulated volume-based WAI could be used to lower radiation dose to the remaining kidney.[85] Novel systemic therapies could be considered for patients with bilateral, unfavorable histology, and recurrent Wilms tumor that are less nephrotoxic than the current standard.

Partial kidney radiation

In the setting of partial kidney radiation, a better understanding of chemotherapy effects and dose-response curves for regional renal injury will allow us to make

optimal use of dose-steering tools such as IMRT and protons. Improved image guidance, intensity modulation, and proton radiation will likely be additional tools to further decrease dose to kidneys. Children's Oncology Group (COG) AREN1921 (NCT04322318) will be the first COG Wilms protocol that will allow IMRT and proton RT. In the setting of the oncologic target in close proximity to the kidney, motion management could decrease the risk of incidental radiation to the uninvolved kidney.[86] We also propose future studies define renal cortex and medulla separately to collect dosimetry data for future toxicity analysis.

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