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RADIATION-ASSOCIATED KIDNEY INJURY

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The kidneys are the dose-limiting organs for radiotherapy to upper abdominal cancers and during total body irradiation. The incidence of radiotherapy-associated kidney injury is likely underreported owing to its long latency and because the toxicity is often attributed to more common causes of kidney injury. The pathophysiology of radiation injury is poorly understood. Its presentation can be acute and irreversible or subtle, with a gradual progressive dysfunction over years. A variety of dose and volume parameters have been associated with renal toxicity and are reviewed to provide treatment guidelines. The available predictive models are suboptimal and require validation. Mitigation of radiation nephropathy with angiotensin-converting enzyme inhibitors and other compounds has been shown in animal models and, more recently, in patients. © **2010 Elsevier Inc.**

Kidney injury, Radiation toxicity, Radiotherapy.

1. CLINICAL SIGNIFICANCE

The kidneys are the dose-limiting organs for radiotherapy (RT) to gastrointestinal cancers, gynecologic cancers, lymphomas, and sarcomas of the upper abdomen and during total body irradiation (TBI). The kidneys are vitally important, responsible for filtering waste metabolites and electrolytes from the blood, producing erythropoietin to stimulate red blood cell production, and modulating blood pressure by fluid/electrolyte balance. The incidence of RT-associated kidney injury is likely underreported owing to its long latency and because dysfunction is likely often attributed to more common causes.

2. ENDPOINTS

The findings associated with RT-induced kidney injury can be segregated into subclinical and clinical (Table 1). After TBI, RT-induced kidney injury often includes features of hemolytic-uremic syndrome (*e.g.,* microangiopathic hemolytic anemia, and thrombocytopenia) (1).

Acute (within 3 months) RT-induced kidney injury is generally subclinical. The signs and symptoms (*e.g.,* decreased glomerular filtration rate [GFR], increased serum β_2-microglobulin) usually develop during the subacute period (3–18 months). Chronic injury (>18 months) is characterized by benign or malignant hypertension, elevated creatinine levels, anemia, and renal failure (2, 3). If no changes in renal blood perfusion or GFR are observed within 2 years after RT, subsequent chronic injury is unlikely (4). RT-induced kidney injury can also reduce a patient's reserve against future renal insults.

The long latency for clinical kidney toxicity was highlighted in a study of 67 patients with peptic ulcer disease, without pre-existing hypertension, who were treated with ~20 Gy within 3 weeks (encompassing the left kidney) (5). Of the 67 patients, 31 (46%) developed kidney toxicity within 8–19 years after RT, including 7 patients with fatal uremia (n = 5) or malignant hypertension (n = 2). At autopsy, atrophy of the left kidney with degenerative changes of the small and medium arteries were observed. The long latency for RT-induced kidney injury and the high prevalence of confounding non–RT-related factors (see the section ''Patient- and Treatment-Related Factors'') that can injury the kidneys have hindered our ability to understand the effects of partial kidney RT.

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Table 1. Radiation-associated kidney toxicity endpoints

Category	Physiologic	Biochemical	Imaging
Subclinical	Elevated blood pressure Increased weight	Elevated serum β_2-microglobulin Elevated urine beta2 microglobulin Elevated serum blood urea nitrogen Elevated serum creatinine Elevated serum renin Reduced glomerular filtration rate Decreased creatinine clearance* Proteinuria Urine casts Hematuria Anemia	Reduced glomerular function, GFR ^{99m}Tc-DTPA renography Reduced tubular function ^{99m}Tc-DMSA scintigraphy Perfusion deficits on scintigraphy ^{131}Iodine radiohippurate Asymmetric uptake of intraenous contrast on computed tomography Kidney atrophy
Clinical	Malignant hypertension Headache, Edema, Dyspnea Fatigue, Nausea, Vomiting Confusion, Coma, Death		

Abbreviations: ^{99m}Tc-DTPA = ^{99m}Technetium-diethylene-triamine-penta-acetic acid; GFR = glomerular filtration rate; ^{99m}Tc-DMSA = ^{99m}Technetium-dimercaptosuccinyl acid.
* Often used to estimate GFR.

3. DEFINING THE KIDNEYS

The kidneys are relatively easy to identify on the planning computed tomography (CT) scan, even without intravenous contrast. Typically, the doses delivered to each kidney alone and combined should be evaluated. Ideally, the kidney parenchyma should be segmented, because this is the ''functional'' component. The magnitude of errors introduced by including the collecting system in the ''kidney volume'' is unclear.

The existing published data were largely derived from patients treated without computed tomography-based planning, and with delivery techniques associated with substantial dosimetric uncertainty (*e.g.,* the moving strip technique). Even with modern planning, kidney breathing motion or shifts in kidney position are not usually accounted for, introducing uncertainty in the delivered vs. the planned kidney doses (6). The kidneys move inferiorly (by $\leq$7 cm) and change shape in the upright vs. supine position (7); thus, if kidney blocks were designed using supine CT scans for patients treated in the upright position (*e.g.,* with TBI), the actual kidney doses would be far greater than planned.

4. REVIEW OF DOSE–VOLUME DATA

The risk of RT-induced kidney injury largely depends on the use of whole-volume or partial-volume RT to one or both kidneys. In the present report, whole kidney tolerance refers to bilateral, uniform kidney RT, segregated by the use of TBI or not, and partial kidney tolerance includes any partial-volume RT experience, including uniform RT to one kidney.

Whole kidney tolerance

The dose–response data for whole kidney irradiation in patients undergoing TBI is summarized in Table 2 and Fig. 1. Patients undergoing TBI typically have substantial co-morbidities and also receive potentially nephrotoxic chemotherapy. Cheng *et al.* (8) conducted a comprehensive review of 12 studies reporting kidney toxicity (increased creatinine or hemolytic uremic syndrome) after TBI (Table 2 and Fig. 1). On multivariate analysis, for those reports describing adult-only experience (n = 479 patients), the dose was the only significant factor associated with increased kidney toxicity. Neither the dose rate nor the number of fractions were significant in their model. For the studies that included adult and pediatric populations (n = 437 patients), significant factors included the dose, dose rate ($\leq$6 vs. 6.1–9.9 vs. $\geq$10 cGy/min) and the use of fludarabine. Considering all the studies, except for those with pediatric populations only (n = 916 patients), the number of fractions became a significant factor, in addition to the total dose and dose rate. The dose associated with a 5% risk of kidney toxicity, without nephrotoxic drugs, was 9.8 Gy, regardless of the fractionation scheme used (median dose, 12 Gy; range, 7.5–14; median fractions, 6; range 1–11, delivered once or twice daily).

The whole kidney dose–response data, excluding TBI, is summarized in Table 3 and Figs. 2 and 3. The dose–response data are consistent with previous reviews (e.g., Emami *et al.* [9] in 1991 and Cassady [10] in 1995; Fig. 1) that suggested a total dose associated with a 5% and 50% risk of injury at 5 years of 18–23 Gy and 28 Gy, in 0.5–1.25 Gy/fraction, respectively. Increases in creatinine clearance have been observed after 10–20 Gy to both kidneys, at 0.8–1.25 Gy/fraction (11).

Partial kidney tolerance

Nephrectomy is more often associated with subclinical elevations in creatinine and late chronic kidney injury than is ''nephron-sparing'' partial nephrectomy (12). Thus, the global function/reserve appears related to the nephron volume, and tolerance to RT is likely reduced in patients with one (vs. two) kidneys.

Table 4 summarizes the key studies describing partial kidney tolerance to RT. Unilateral kidney RT is not risk free, as

Table 2. Selected studies of bilateral whole kidney toxicity after TBI and transplantation

Authors^	Patients (n)	Population	Total kidney dose (Gy)	Fractions (n)	Fractions/d (n)	Dose rate (cGy/min)	Renal toxicity (%)	Chemotherapy regimen*
Frisk 2002	22	P	7.5	1	1	15	27.3	1
Lawton 1997	72	A	14	9	3	14	18.1	2
	68	A	11.9	9	3	11.9	10.3	2
	17	A	9.8	9	3	9.8	0	2
Rabinowe 1991	112	A	12	6	2	7.5	9.8	3
Miralbell 1996	24	P/A	10	6	2	16	4.2	4
	32	P/A	12	6	2	16	28.1	4
	23	P/A	13.5	6	2	16	34.8	4
Chou 1996	58	P	12	6	2	15	3.4	5
Borg 2002	47	P/A	12	6	2	7.5	2.1	6
Bradley 1998	31	A	12	6	2	12	12.9	7
	36	P	13.2	11	3	12	0	7
	10	P	13.5	9	2	12	30	7
Tarbell 1990	12	P	14	8	2	10	33.3	8
	15	P	12	6	2	10	46.7	8, 9
Igaki 2005	70	P/A	12	6	2	10	20	10
	39	A	10	6	2	8.5	0	10
Delgado 2006	65	P/A	7.5	1	1	13	9.2	11
	46	P/A	7.5	1	1	13	2.2	12
	84	P/A	12	6	2	6	1.2	12
	26	P/A	14.4	8	2	6	3.8	11
	20	P/A	14.4	8	2	6	0	13
Moreau 2005	140	A	8	4	1	NA	3.6	14
Van Why 1991	39	P	13.2	8	2	14	23.1	15

Abbreviations: P = pediatric; A = adult; P/A = mixed; NA = not available.
Modified, with permission, from Cheng *et al*. (8).
^ All references in first column are included within the review by Cheng *et al*. (8).
* Chemotherapy regimens: 1, teniposide, daunorubicin, vincristine, cyclophosphamide, and cytarabine; 2, cytarabine and cyclophosphamide; 3, cyclophosphamide with or without cytarabine; 4, cyclophosphamide with or without thiotepa, daunorubicin, busulfan, or cytarabine; 5, cyclophosphamide, cytarabine, methotrexate, and etoposide; 6, cyclophosphamide with or without melphalan, busulphan, or etoposide; 7, cyclophosphamide or etoposide; 8, cyclophosphamide, teniposide, and cytarabine; 9, neuroblastoma—teniposide, cyclophosphamide, cisplatin, and melphalan with or without methotrexate; 10, cyclophosphamide and cytarabine or cyclophosphamide and busulfan; 11, cyclophosphamide and fludarabine with or without alemtuzumab; 12, cyclophosphamide with or without alemtuzumab, or melphalan, or etoposide; 13, cyclophosphamide with or without alemtuzumab; 14, vincristine, adriamycin, and melphalan; 15, Cyclosporin A and/or amphoterecin B.

shown by Thompson *et al*. (5), who observed a dose response for kidney atrophy and clinical kidney toxicity many years after unilateral kidney RT (13). Willett *et al*. (14) found a volume-dependent decrease in creatinine clearance after ≥26 Gy to ≥50% of one kidney. In gastric cancer patients treated primarily using anteroposterior beams with little dose to the right kidney, a progressive decrease in left (vs. right) renal function, as assessed by renography, was seen 12–18 months after chemoradiotherapy, with an associated increase in serum creatinine (15). The volume of the left kidney receiving >20 Gy and the mean left kidney dose were associated with increased risk of renal injury. Regional kidney injury has been detected using scintigraphy after low doses; 5% of the irradiated kidneys developed abnormalities after 3–6 Gy, in 15–30 fractions, independent of the irradiated volume. These findings improved with time, likely due to the reserve capacity of the spared kidney tissue (16).

Pediatric kidney tolerance

Neonates appear to have an increased sensitivity to RT. Doses of 12–14 Gy at 1.25–1.5 Gy/fraction to an entire neonate kidney have been associated with a decreased GFR (17) and subsequent abnormalities on bone scan and intravenous pyelography. Age less than 5 years was associated with increased risk of acute renal dysfunction post TBI in one study (new reference 'A') For older children, no convincing evidence has shown that the kidney tolerance is different from that of adults. A study of 108 children who underwent nephrectomy predominantly for Wilms tumor and RT to the contralateral remaining entire or partial kidney showed that abnormal creatinine clearance was dose dependent (18). Abnormal creatinine clearance, defined as <63 mL/min/m^2, was found in 29 (41%) of 70 children receiving <12 Gy, 15 (56%) of 27 children receiving 12–24 Gy, and 10 (91%) of 11 children receiving >24 Gy to the remaining kidney ($p < .05$). All 5 patients with clearance <24 mL/min/m^2 had hypertension and elevated blood urea nitrogen, and 4 died of kidney failure. In a different Wilms tumor study, nephropathy was seen in 0 of 17 children receiving 11–14 Gy to the remaining kidney and 1 (25%) of 4 receiving 14–15 Gy (fraction size not reported) (10). In another study, 1 of 38 children with bilateral Wilms tumors developed kidney failure after 27 Gy in 21 fractions to the lower half and 12 Gy in 11 fractions to

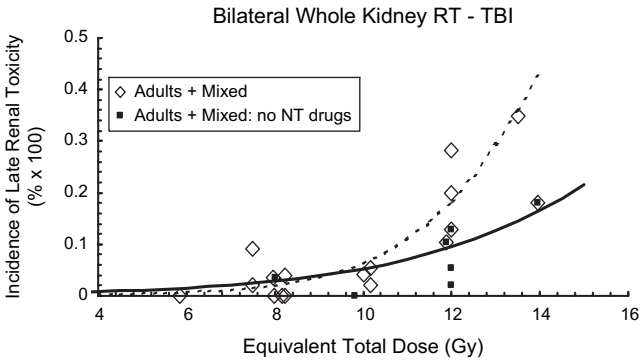

Fig. 1. Dose–response curve for increased creatinine or hemolytic uremic syndrome after total body irradiation (TBI). Open diamonds represent fitted data for studies that included adults alone or adult/pediatric mixed populations (with or without nephrotoxic drugs). Solid squares represent fitted data for same population excluding those treated without nephrotoxic (NT) drugs, cyclosporine, teniposide, or fludarabine. Fractionation schemes (listed in Table 3) were converted to ''equivalent'' doses delivered in six fractions at 10-cGy/min dose rate. Modified, with permission, from Cheng *et al.* (8).

the upper half of the remaining kidney (19). No kidney failure occurred in children receiving bilateral kidney doses of 10–12 Gy, in 1.5–2 Gy/fraction. In the National Wilms Tumor Study experience, kidney failure was more common in children with bilateral than unilateral Wilms tumor (20). For the 3 patients with unilateral tumors who developed kidney failure, the dose to the remaining kidney was 15, 18, and 20 Gy in 1.5–2 Gy/fraction.

In the review by Cheng *et al.* (8) of kidney toxicity after TBI, for pediatric patients (n = 192), the use of cyclosporine and teniposide was associated with an increased risk of kidney toxicity. When these drugs were excluded, no dose response was found, and, at doses ≤13 Gy, the incidence of kidney toxicity was <8% (8). Data on the pediatric kidney partial volume tolerance are not available.

RT-induced reduction in compensatory response

After injury to one kidney, a compensatory increase in kidney function of the spared kidney often occurs. Low-dose RT to the ''spared'' kidney can blunt this compensation. At 6–9 years after 40 Gy in 1.5-Gy fractions to the left kidney and 12–13 Gy in 1-Gy fractions to the right kidney, the left kidney glomerular and tubular function, as assessed by scintigraphy, had decreased to 21% and 31% of baseline, respectively, with an associated decline in creatinine clearance. The compensatory response was reduced compared with that in patients with complete sparing of ≥70% of one kidney (21).

5. PATIENT- AND TREATMENT-RELATED FACTORS

Chemotherapy can enhance RT-associated kidney injury in adults and pediatric populations treated with and without TBI (8, 22) (Fig. 1). The review by Cheng *et al.* (8) found that after TBI, the use of fludarabine, cyclosporine, or teniposide increased the risk of renal injury (odds ratio, 6.2, 5.9, and 10.5, respectively). A TBI dose rate of ≤6 cGy/min and 6.1–9.9 cGy/min was associated with an odds ratio of 0.0046 and

Table 3. Selected studies of bilateral whole kidney irradiation (non-TBI)

Investigator	Patients (n)	Disease	Chemotherapy	Dose (Gy)	Dose/fraction (Gy)	Incidence of injury	Endpoint
Kunkler 1952 (23)	55	Seminoma	None				
				23 or 28	0.9–1.12	22/55 (40%)	RF (sBP >160 mm Hg + albuminuria)
						7/55	Death
				23	0.92	2/18 (11%)*	RF (sBP >160 mm Hg + albuminuria)
				28	1.12	18/25 (51%)*	RF (sBP >160 mm Hg + albuminuria)
Avioli 1963 (24)	10		None				
		Gynecologic cancer (n = 8), Sarcoma (n = 1), Seminoma (n = 1)		7.5–16.5; 20–24	0.5–1.1; 1.0–1.2	0/5; 4/5	No change in GFR; no HTN or RF; Reduced GFR (75-83%), no HTN or RF
Keane 1976 (25)	2	Ovarian cancer	None	25, 27		2/2	Reduced CrCl (30 mL/min), ESRD
Churchill 1978 (26)	1	Seminoma	Bleomycine and vinblastin	26–38†	1.6	1/1	ARF at 5 wk
Irwin 1996 (27)	60	Ovarian cancer, NHL, carcinoid	None	7–23	1–1.25	5/60	New HTN, No change in CrCl
Schneider 1999 (11)	56	Ovarian cancer	Cisplatin (n = 25)	5–17	0.65–1.15	71–76%	Reduced CrCl by >2 mL/min, Reduced CrCl (84–66 mL/min)

Abbreviations: RF = renal failure; sBP = systolic blood pressure; GFR = glomerular filtration rate; HTN = hypertension; CrCl = creatinine clearance; ESRD = end-stage renal disease; ARF = acute (<1 y) RF; NHL = non-Hodgkin's lymphoma.

* Denominator estimated from text.

† Two-thirds of kidneys received 38 Gy.

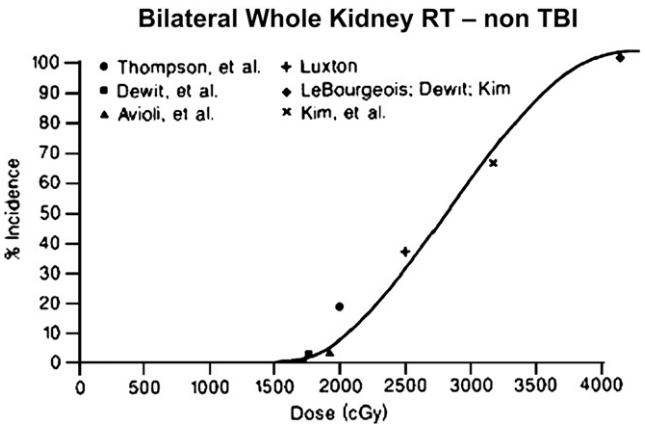

Fig. 2. Dose–response curve for symptomatic kidney injury after non–total body irradiation of bilateral kidneys. Note, y axis is different from than that in Fig. 1. Data from review from Cassady *et al.* (10).

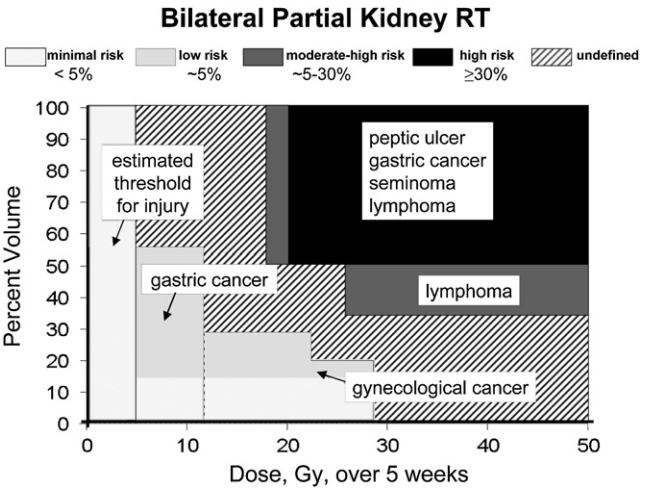

Fig. 3. Composite schematic of combined kidney dose–volume histogram of data from Tables 4 and 5, represented as regions associated with minimal (<5%), low (~5%), moderate-to-high (~5–30%), high (≥30%), or undocumented estimated toxicity risks. Clinical experience that yielded risk estimates for each region also indicated. Actual risks associated with using each region on its own or regions in combination are plan-specific and associated with substantial uncertainty.

0.083, respectively, compared with ≥10 cGy/min (8). Underlying renal insufficiency, diabetes, hypertension, liver disease, heart disease, and smoking can also reduce the kidney's tolerance to RT; however, the magnitude of these effects is unclear. Animal models have suggested that angiotensin-converting enzyme inhibitors, dexamethasone, and acetylsalicylic acid can prevent and treat RT-induced kidney injury (28–30). Angiotensin-converting enzyme inhibitors improve non–RT-associated kidney failure (31) and, recently, were suggested in a randomized trial to reduce the incidence of nephropathy or hemolytic uremic syndrome (3.7% vs. 15%, $p = .1$) after TBI (32).

6. PREDICTIVE MODELS

The Lyman-Burman-Kutcher normal tissue complication probability model parameters (median toxic dose, 28 Gy, $n = 0.70$, $m = 0.10$) (33) have been used to describe the tolerance estimates reported by Emami *et al.* (9). Cassady (10) pooled the data on bilateral whole kidney RT tolerance and confirmed a threshold dose for RT injury of 15 Gy with a 5% and 50% risk of injury at 5 years for whole-kidney RT of 18 Gy and 28 Gy, respectively, within 5 weeks (Fig. 2). It has been demonstrated that greater doses can be safely delivered to partial kidney volumes (9, 34). Quantitative data to support more refined models are not available.

Cheng *et al.* (8) found a less steep dose response ($m = 0.26$) after TBI (median dose, 12 Gy in six fractions twice daily). The dose associated with a 5% risk of kidney toxicity was 9.8 Gy. The addition of nephrotoxic drugs made the dose–response curve steeper (Fig. 1).

7. SPECIAL SITUATIONS

The response of the kidney is highly dependent on the fraction size; therefore, extrapolation of previous experience to different fraction sizes can be problematic (35–38). One hypothesis is that nearly complete sparing of a substantial volume of the kidney should be associated with compensatory effects and preservation of renal function, despite the delivery of focal high doses. Symptomatic kidney injury has not been reported after potent doses of stereotactic body radiotherapy; however, elevations in creatinine have been observed 52 months after renal stereotactic body radiotherapy (SBRT) (39). Follow-up of long-term survivors from these series is required to determine the kidney's and collecting system's tolerance to SBRT.

Few of the published reports on kidney tolerance have focused on intensity-modulated RT (IMRT), and the effects of different spatial dose distributions are not well established. IMRT often leads to a low dose delivered to a larger volume compared with simpler plans, which might reduce the possibility of a compensatory increase in kidney function.

8. DOSE–VOLUME RECOMMENDATIONS

All dose–volume recommendations are associated with substantial uncertainty, because few studies are available of patients who have been followed for ≥10 years. However, some broad guidelines can be useful and will hopefully be tested in future studies (Table 5 and Fig. 3).

9. AREAS FOR FUTURE STUDY

The kidney partial tolerance to RT is largely unknown and deserves more study. Collaborative prospective studies are needed, with collection of dose–volume histogram and spatial dose data, along with serial long-term objective outcome assessments. The baseline clinical kidney function and comorbidities need to be documented, along with the use of

Table 4. Selected studies addressing partial kidney irradiation

Investigator	Patients (*n*)	Disease	Chemotherapy	Dose/fraction (Gy)	Dose/volume	Incidence	Endpoint
Kunkler 1952 (23)	60	Seminoma	None	0.9–1.12	$D_{33\%}$ < 18 Gy (18–29 Gy to kidneys)	0/60	No RF (sBP >160 mm Hg + albuminuria
Thompson 1971 (5)	67	Peptic ulcer	None	1.0–1.3	$D_{50\%}$ = 15–35 Gy	31/67	RF or HTN (8–19 y)
					$D_{50\%}$ = 15 Gy	0/2	Kidney atrophy (I/S)
					$D_{50\%}$ = 20 Gy	6/6	Kidney atrophy (I/S)
					$D_{50\%}$ = 30–35 Gy	2/2	Marked kidney atrophy (I/S)
						2/2	Malignant HTN
Le Bourgeois 1978 (40)	74	Hodgkin's disease	None	1	$D_{15–40\%}$ = 20 Gy	74/74	70% Focal decrease in glomerular fn
						3/74	Proteinuria, no change in CrCl
Birkhead 1979 (41)	23	Hodgkin's disease	1 Patient	2	$D_{16\%}$ = 40 Gy	6/16	Focal scintigraphy changes; no RF
Kim 1980 (42)	18	NHL	None	1	$D_{25–50\%}$ = 25–44 Gy	3/18	Decreased CrCl
						5/18	HTN
Kim 1984 (43)	18	NHL	None	1	$D_{25–50\%}$ = 21– 33 Gy	2/9	Reduced blood flow or perfusion
					$D_{25–50\%}$ = 30–40 Gy	4/7	Reduced blood flow or perfusion
					$D_{25–50\%}$ > 40 Gy	3/3	Atrophy
Willett 1986 (14)	86	Mixed	Not stated	1.5–1.8	V_{26Gy} = 50%		10% Decrease in CrCl
					V_{26Gy} > 90%		24% Decrease in CrCl
					All patients	2/73	New HTN
						4/13	Increase in HTN medications
Flentje 1993 (44)	142	Seminoma	None	0.7–1	$D_{50\%}$ < 18 Gy	0/100	RF or HTN
					$D_{50\%}$ > 18–32 Gy	7/42	
Dewitt 1993 (22)	7	Seminoma	None	2	$V_{25–35Gy}$ = 20–30%	0/7	CrCl or SC
Dewitt 1993 (22)	7	NHL	None		V_{40Gy} = 50%		25% Decrease in glomerular fn Sc
					$V_{12–13Gy}$ = 100%		31% Decrease in tubular fn Sc
Kost 2002 (16)	91	Seminoma (*n* = 45), NHL (*n* = 42), RCC (*n* = 6), Sarcoma (*n* = 1)		1.8–2.0	$V_{3–6Gy}$ > 10%	5%	Decrease in fn Sc
					V_{27Gy} = 10%	50%	Decrease in fn Sc
					$V_{7.6Gy}$ = 100%	50%	Decrease in renal flow; no RF
Nevinny-Stickel 2007 (34)	19	Cervical cancer		0.4–1.8	V_{28Gy} < 25% V_{23Gy} < 33%	3/19	Decrease in renal flow; no RF
Jansen 2007 (15)	44	Gastric cancer	Capecitabine or cisplatin (*n* = 21)	0.4–1.8	V_{20Gy} (1 kidney) >64% vs. <64%		66% vs. 34% decrease in fn (I/S)
						1/15*	HTN
Welz 2007 (13)	27	Gastric cancer	5-FU, cisplatin, paclitaxel	0.4–1.8	V_{12Gy} < 62.5% functional kidneys		Trend toward increase Cr; no HTN

Abbreviations: $D_{y\%}$ = dose to y% of volume; I/S = irradiated vs. spared; fn = function; RCC = renal cell cancer; 5-FU = 5-fluoruracil; Sc = scintigraphy; $V_{x\ Gy}$ = volume receiving >x Gy; NHL = non-Hodgkin's lymphoma; other abbreviations as in Table 1.

* Among patients with follow-up ≥18 months.

nephrotoxic or antihypertensive medications. Differences in the dose per fraction should also be accounted for. Proposed research topics of importance include the following:

–Pathophysiology of RT-induced kidney injury
–Interaction between clinical factors and kidney tolerance to RT

Table 5. Suggested dose–volume constraints for estimated risk of <5%

Variable	Dose–volume metric	Investigator
Bilateral kidney irradiation		
TBI	Mean kidney dose <10 Gy	Cheng *et al.* (8)
Non-TBI	Mean kidney dose <18 Gy	Cassady (10)
Partial kidney irradiation		
Bilateral kidneys	Mean kidney dose <18 Gy	Nevinny-Stickel *et al.* (34)
Bilateral kidneys	$V_{28Gy} < 20\%$	Nevinny-Stickel *et al.* (34)
Bilateral kidneys	$V_{23Gy} < 30\%$	Nevinny-Stickel *et al.* (34)
Bilateral kidneys	$V_{20Gy} < 32\%$	Jansen *et al.* (15)
Bilateral kidneys	$V_{12Gy} < 55\%$	Welz *et al.* (13)*
If mean kidney dose to 1 kidney >18 Gy	V_{6Gy} (remaining kidney) <30%	

Abbreviations: $V_{x\ Gy}$ = volume of bilateral kidneys receiving >x Gy; TBI = total body irradiation.

* Estimated from Welz *et al.* (13); 62.5% reduced to 55% because 62.5% was functional volume.

–Mitigating factors and radioprotectors
–Renal compensatory effects and how low-dose RT alters the compensatory capacity
–Spatial variation in radiation sensitivity (e.g. with functional imaging)
–Surrogates for risk of clinical toxicity (*e.g.,* cytokines, proteonomics)

Table 6. K/DOQI stages of chronic kidney disease (kidney disease occurring for > 3 mo)

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or GFR	≥90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 (or dialysis)

Abbreviations: K/DOQI = Kidney/Dialysis Outcomes Quality Initiative; GFR = glomerular filtration rate.

Kidney damage defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

Data from National Kidney Foundation (available from: www.kidney.org).

10. SCORING TOXICITY

Studies of RT-induced kidney injury have been confounded by the use of variable, most often asymptomatic, endpoints, largely because the symptoms usually occur many years after RT. Because early changes in renal flow and GFR correlate with an increased risk of subsequent symptomatic toxicity, these endpoints should be considered in future studies. The severity of injury should be graded according to the GFR, as has been recommended for all chronic kidney disease (Table 6) (45). Serial urine protein, serum blood urea nitrogen, creatinine clearance, blood pressure measurements, and symptoms of renal failure can also been used to grade the severity of RT-induced injury (46).

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