Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–8, 2010

0360-3016/09/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.07.1744

CLINICAL INVESTIGATION

RENAL ATROPHY SECONDARY TO CHEMORADIOTHERAPY OF ABDOMINAL MALIGNANCIES

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Purpose: To identify factors predictive of renal atrophy after chemoradiotherapy of gastrointestinal malignancies.
Methods and Materials: Patients who received chemotherapy and abdominal radiotherapy (RT) between 2002 and 2008 were identified for this study evaluating change in kidney size and function after RT. Imaging and biochemical data were obtained before and after RT in 6-month intervals. Kidney size was defined by craniocaudal measurement on CT images. The primarily irradiated kidney (PK) was defined as the kidney that received the greater mean kidney dose. Receiver operating characteristic (ROC) curves were generated to predict risk for renal atrophy.
Results: Of 130 patients, median age was 64 years, and 51.5% were male. Most primary disease sites were pancreas and periampullary tumors (77.7%). Median follow-up was 9.4 months. Creatinine clearance declined 20.89%, and size of the PK decreased 4.67% 1 year after completion of chemoradiation. Compensatory hypertrophy of the non-PK was not seen. Percentage volumes of the PK receiving ≥10 Gy (V_{10}), 15 Gy (V_{15}), and 20 Gy (V_{20}) were significantly associated with renal atrophy 1 year after RT ($p = 0.0030$, 0.0029, and 0.0028, respectively). Areas under the ROC curves for V_{10}, V_{15}, and V_{20} to predict >5% decrease in PK size were 0.760, 0.760, and 0.762, respectively.
Conclusions: Significant detriments in PK size and renal function were seen after abdominal RT. The V_{10}, V_{15}, and V_{20} were predictive of risk for PK atrophy 1 year after RT. Analyses suggest the association of lower-dose renal irradiation with subsequent development of renal atrophy. © 2010 Elsevier Inc.

Renal atrophy, Kidney tolerance, Chemoradiation, Complications, Dose–volume histogram.

INTRODUCTION

Chemotherapy and abdominal radiotherapy (RT) are used in the management of gastrointestinal (GI) malignancies. The kidneys are inherently radiosensitive organs and thus are major dose-limiting structures in abdominal RT treatment fields. Development of late effects of renal irradiation is both dose and volume dependent (1–5).

The pathophysiology of radiation-induced renal dysfunction involves both tubular and glomerular effects resulting in fibrosis (5). The clinical presentation of renal dysfunction includes radiation nephropathy and hypertension (2, 5–7). Subclinical complications have a shorter latency period than clinical presentation of symptomatic nephropathy (1–3). Presymptomatic toxicity can be detected by renal functional decline, measured by biochemical endpoints such as creatinine and creatinine clearance (CrCl), and decrease in kidney size (KS) (4, 8–10). Much of the data from which renal tolerances have been based comes from bilateral kidney irradiation in the setting of total-body and whole-abdominal irradiation (6, 7). There are limited data available on late renal effects using modern CT-based RT planning and treatment techniques.

As a result, predicting renal toxicity after RT to the abdomen using current techniques is difficult. This study evaluated patients who received chemotherapy and three-dimensional (3D) conformal RT to the abdomen in the treatment of GI malignancies for subsequent change in KS. Renal atrophy was defined as decrease in craniocaudal length of the primarily irradiated kidney (PK) as measured on serial CT scans. This analysis was conducted to identify clinical and dosimetric parameters predictive of renal atrophy after abdominal RT.

METHODS AND MATERIALS

Patient selection

A retrospective review with institutional review board approval was conducted to evaluate change in renal size after abdominal

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Conflict of interest: none.
Received March 8, 2009, and in revised form July 22, 2009. Accepted for publication July 23, 2009.

chemoradiotherapy. Patients with GI malignancies treated between 2002 and 2008 were identified and included in this study if they received concurrent chemotherapy and 3D conformal abdominal RT; had laboratory data, imaging studies, and dosimetric parameters available for review; and had at least one kidney included in the RT treatment fields.

Radiotherapy and chemotherapy

All patients underwent CT simulation for treatment planning and received 3D conformal external beam RT to the abdomen. Computed tomographic simulation scans were obtained using ≤5-mm slice thickness. No respiratory gating or breath hold techniques were used; all patients were simulated and treated using free breathing. Patients who received intensity-modulated radiotherapy (IMRT) were excluded. Radiotherapy was delivered on linear accelerators using 6–23-MV photons. Computed tomography based treatment planning was done using the Theraplan Plus treatment planning system (MDS Nordion, Ottawa, Ontario, Canada) and Eclipse Treatment Planning System (Varian Medical Services, Palo Alto, CA). Targets and organs at risk were contoured. Treatment field arrangements were designed to encompass targets and areas at risk with margin while sparing organs at risk. Prescribed dose to targets varied by primary disease sites. Planning dose constraints used were consistent with Emami *et al*. (11); specific renal constraints were one third of the volume not to exceed 50 Gy and two thirds of the volume not to exceed 30 Gy.

All patients received concurrent chemoradiotherapy. Few patients received chemotherapy before RT, and most patients had further chemotherapy after RT. Specific chemotherapy regimens used varied given the different primary sites included in this study and individual patient circumstances.

Endpoints

Change in KS was assessed using craniocaudal length on CT imaging. Change in renal function was assessed using creatinine and CrCl. Creatinine clearance was calculated using the Cockcroft-Gault formula (12): [(140 − age) × (weight in kilograms)]/(72 × serum creatinine). This value was adjusted for female gender by multiplying the CrCl × 0.85. Imaging and laboratory data were determined before RT and after RT in 6-month intervals.

Statistical analysis

Statistical analyses for comparing groups with regard to categoric variables were performed using Fisher's exact test. Similar comparisons for continuous variables were done using the Wilcoxon nonparametric test with exact p values. A logarithmic transformation was applied to variables creatinine and CrCl to satisfy statistical assumptions of normality. Change in outcome variables over time was assessed using a repeated measures linear model. To account for missing data, a pattern mixture model was used (13). The Spearman correlation was used to determine the relationship between continuous variables. Logistic regression was used to model >5% decrease in PK size after RT as a function of patient and treatment factors. Covariates considered for multivariate analyses included pre-RT CrCl, age (<65 or ≥65 years), gender, V_{10}, V_{15}, V_{20}, and mean kidney dose (MKD). Because individual dose–volume parameters were of interest yet highly correlated, separate multivariate models were fit for each individual parameter with the others excluded. The initial models consisted of all the main effects and two-way interactions, and the final models were obtained using backward elimination of the interactions using the criteria of $p < 0.05$. When considering predicting a binary response as a function of a numeric predictor, the predictor is often dichotomized for clinical use. Receiver operating characteristic (ROC) curves are plots of sensitivity (true-positive rate) vs. 1 − specificity (false-positive rate) for a collection of cutpoints. The ROC curves were generated using dosimetric parameters as predictors for decrease in size of the PK. The approximate area under the curve (AUC) for each ROC plot was estimated to assess the predictive ability of each individual parameter. Areas under the correlated ROC curves were compared using the nonparametric approach proposed by DeLong *et al*. (14). Values for continuous variables are given as mean (standard deviation). Values for categoric data are specified as number (percentage). Statistical analysis was performed using SAS statistical analysis software, version 9.1.3 (SAS Institute, Cary, NC). A nominal significance level of 0.05 was used.

Table 1. Patient characteristics (n = 130)

Age (y)	64 (31–87)
Gender	
Male	67 (51.5)
Female	63 (48.5)
Follow-up (mo)	9.4 (0–55.5)
Primary sites	
Pancreas	80 (61.5)
Periampullary	21 (16.2)
Gastric	14 (10.8)
Gastroesophageal junction	13 (10)
Retroperitoneum	2 (1.5)
Hypertension	63 (48.5)
Diabetes	30 (23.1)
Current smoking	17 (13.1)
Renal insufficiency	6 (4.6)

Values are given as median (range) or, for categoric data, number (percentage).

RESULTS

Patients were identified who received concurrent chemoradiotherapy to the abdomen during the period 2002–2008. Median age of the 130 patients included in this study was 64 years. Sixty-seven patients were male (51.5%). Median follow-up was 9.4 months. The majority of primary disease sites were pancreas and periampullary tumors (77.7%). Patient characteristics are presented in Table 1.

The PK was defined as the kidney that received the greater MKD. The non-primarily irradiated kidney (non-PK) was defined as the kidney that received the lesser MKD. Bilateral MKD was defined as the average of individual right and left kidney mean doses. Median delivered RT dose to target was 50.4 Gy (range, 12.6–55.8 Gy).

Eighteen patients received chemotherapy before RT, most with gemcitabine-, 5-fluoruracil-, and/or capecitabine-containing regimens. All 130 patients received concurrent chemotherapy; 52.3% of patients received concurrent 5-fluorouracil–based regimens, 39.2% capecitabine-based regimens, 6.2% cisplatin-containing regimens, and 5.4% gemcitabine-based regimens. One hundred four patients received additional chemotherapy 0–6 months after RT, the majority with gemcitabine-containing (75%), capecitabine-containing (17.3%), and/or 5-fluorouracil–containing (14.4%) regimens. Twenty patients received chemotherapy 6–12 months after RT, and

Table 2. Radiation treatment characteristics

Characteristic	PK	Non-PK	Bilateral kidneys
V_{10}	58.02 (22.06)	21.40 (17.95)	38.96 (14.82)
V_{15}	50.84 (22.17)	14.12 (13.57)	32.46 (13.70)
V_{20}	43.77 (21.71)	10.84 (12.09)	27.39 (13.43)
V_{25}	33.76 (19.29)	7.41 (9.09)	20.60 (12.36)
V_{30}	24.25 (18.30)	4.10 (5.70)	14.18 (10.68)
V_{35}	19.48 (17.54)	2.55 (4.18)	11.17 (10.31)
V_{40}	15.97 (16.11)	1.76 (3.23)	8.80 (9.32)
MKD	18.62 (6.63)	7.06 (4.01)	12.84 (3.96)

Abbreviations: PK = the primarily irradiated kidney; non-PK = the non-primarily irradiated kidney; V_n = percentage volume of the kidney(s) receiving at least n dose in Gray (Gy); MKD = mean kidney dose.

Values for dose volume parameters (mean Vn) are given as percentage (SD). Values for MKD are given as dose in Gy (SD).

Table 3. Chemotherapy treatment characteristics

Characteristic	Before radiation	Concurrent chemoradiation	After radiation
Any chemotherapy	18 (13.9)	130 (100)	0–6 mo: 104 (80) 6–12 mo: 20 (15.4) 12–18 mo: 3 (2.3)

Values are given as number (percentage).

3 patients received further chemotherapy 12–18 months after RT; the majority of regimens included gemcitabine, capecitabine, and/or 5-fluorouracil. Thirteen patients (10%) received chemotherapy regimens including cisplatin at 14 time points. One patient received cisplatin-based chemotherapy both concurrently and during the initial 6 months after RT. One patient received cisplatin before RT, 8 patients received cisplatin-based regimens concurrently (6.2% of patients), 3 patients received cisplatin-containing regimens 0–6 months after RT and 2 patients 6–12 months after RT. Radiotherapy and chemotherapy characteristics are summarized in Tables 2 and 3.

Progressive change in KS and function was assessed by craniocaudal length on serial CT images and biochemical endpoints before RT and then in 6-month intervals after completion of RT (Table 4). Size of the PK and CrCl changed significantly over time, as shown in Fig. 1 ($p < 0.0001$). Change in size of the PK and non-PK over time is presented in Fig. 2. Compensatory hypertrophy of the non-PK was not seen ($p = 0.7814$). Mean decrease in PK size and CrCl were 4.67% and 20.89%, respectively, one year after completion of chemoradiation.

Univariate analysis of patient and treatment factors associated with decrease in size of the PK at 12 months after chemoradiation was conducted ($n = 48$). Evaluation of patient factors did not show age, gender, hypertension, diabetes, smoking, pre-RT CrCl, or pre-RT KS to be associated with >5% decrease in PK size. Three patients received cisplatin-containing regimens, all with decrease in KS ≤5%. Cisplatin was not a significant predictor for decrease in KS ($p = 0.5430$). Analysis of dose–volume parameters showed percentages of PK volume receiving ≥10 Gy (V_{10}), 15 Gy (V_{15}), and 20 Gy(V_{20}) to be associated with >5% decrease in PK size ($p = 0.0030$, 0.0029, and 0.0028, respectively) (Table 5).

Spearman correlation was used to determine the relationship between relative percentage decrease in size of the PK and V_{10}, V_{15}, and V_{20}. Spearman correlation coefficients for V_{10}, V_{15}, and V_{20} were −0.41458 ($p = 0.0034$), −0.43434 ($p = 0.0020$), and −0.39103 ($p = 0.0060$), respectively.

Multivariate logistic regression analyses were performed using patient and treatment covariates with V_{10}, V_{15}, V_{20}, and MKD separately because they were highly correlated. Spearman correlation coefficients for V_{10} and V_{15}, V_{10} and V_{20}, V_{15} and V_{20}, V_{10} and MKD, V_{15} and MKD, and V_{20} and MKD were 0.96474, 0.82423, 0.88589, 0.61705, 0.60998, and 0.59103, respectively ($p < 0.0001$). On the final model using covariates pre-RT CrCl, age, gender, and V_{10}, multivariate analysis showed V_{10} to be significant ($p = 0.0246$). The multivariate analysis conducted with covariates pre-RT CrCl, age, gender, and V_{15} showed V_{15} to be significant ($p = 0.0284$). On the final model using pre-RT CrCl, age, gender, and V_{20}, V_{20} was significant ($p = 0.0258$). On analysis with covariates pre-RT CrCl, age, gender, and MKD, no factor remained significant ($p = 0.0815$).

Receiver operating characteristic plots for V_{10}, V_{15}, V_{20}, V_{25}, V_{30}, V_{35}, V_{40}, and MKD were generated to assess the predictability of dosimetric parameters for decrease in the size of the PK after RT (Fig. 3a–h). Because V_{10}, V_{15}, and

Table 4. Change in mean kidney size and creatinine clearance after abdominal chemoradiation

Parameter	Before RT ($n = 130$)	6 mo ($n = 94$)	12 mo ($n = 51$)	18 mo ($n = 29$)	p
Mean KS of PK (mm)	105.02 (12.04)	102.39 (13.03)	100.88 (12.87)	97.76 (15.33)	<0.0001
Mean KS of non-PK (mm)	108.05 (12.66)	106.97 (12.89)	108.82 (12.51)	108.97 (12.28)	0.7814
KS ratio (PK/non-PK)	0.98 (0.12)	0.97 (0.13)	0.94 (0.15)	0.90 (0.11)	0.0002
Creatinine (mg/dL)	0.90 (0.34)	0.88 (0.28) ($n = 82$)	0.96 (0.23) ($n = 48$)	1.05 (0.25) ($n = 27$)	0.0015*
CrCl (mL/min)	91.09 (34.99)	83.18 (30.00) ($n = 81$)	77.61 (25.76) ($n = 48$)	80.51 (23.37) ($n = 26$)	<0.0001*

Abbreviations: KS = kidney size; PK = the primarily irradiated kidney; non-PK = the non-primarily irradiated kidney; CrCl = creatinine clearance; mo = months after radiation.

Values are given as mean (SD).

* p values obtained using log-transformed values.

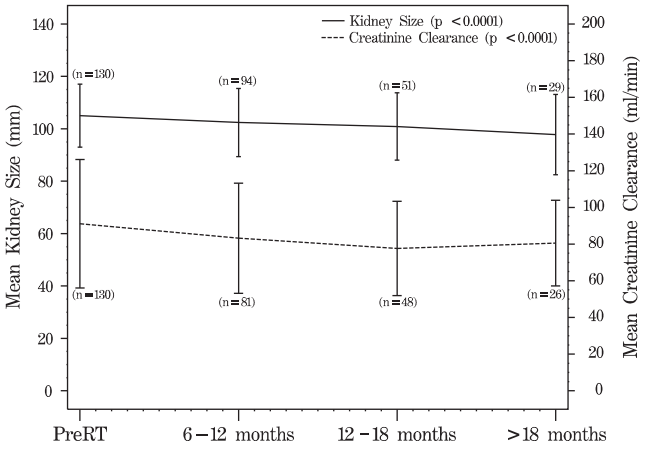

Fig. 1. Progressive change in mean kidney size of the primarily irradiated kidney and creatinine clearance over time after abdominal radiation. The vertical bars represent standard deviation.

V_{20} were significant on univariate and multivariate analyses, further investigation of the predictive ability of these parameters was conducted. The approximate AUC results from the ROC plots for V_{10}, V_{15}, and V_{20} were 0.760, 0.760, and 0.762, respectively. The test for equal areas under the correlated ROC curves was conducted, and no significant difference in AUC for V_{10}, V_{15}, and V_{20} was seen ($p = 0.9993$). The comparison plot is shown in Fig. 4.

DISCUSSION

Significant decline in PK size and renal function were seen after chemoradiotherapy to the abdomen in the treatment of abdominal malignancies. The PK size decreased 4.67% one year after RT. Compensatory hypertrophy of the non-PK was not seen. Patient factors associated with subsequent renal atrophy after RT were not identified. This study did find significant correlation between V_{10}, V_{15}, and V_{20} and >5% decrease in the PK size 1 year after chemotherapy and 3D conformal RT to the abdomen. Multivariate analyses showed V_{10}, V_{15}, and V_{20} to be associated with renal atrophy of the PK and highlight the importance of low dose volumes of irradiated kidney to subsequent late effects.

The kidneys are sensitive to the effects of RT and are major dose-limiting structures in RT to the abdomen. The dose tolerance limits for the kidneys are lower than other surrounding organs in the abdomen (11, 15). The literature available on renal tolerance and late toxicity has focused primarily on biochemical endpoints of renal function, such as creatinine and CrCl (4, 7, 8, 10). Publications on renal atrophy after chemoradiotherapy for GI malignancies are scarce.

Kidney length and volume have been used in evaluation of progressive renal dysfunction secondary to non–radiation-related kidney disease (16–19). Kidney length is clinically relevant and has been used as a surrogate for renal function (17–22). Kidney length has also been shown to correlate with histopathologic changes of renal disease and renal atrophy (23).

In their study investigating outcomes in 27 patients after high-dose unilateral kidney irradiation for gastric lymphoma,

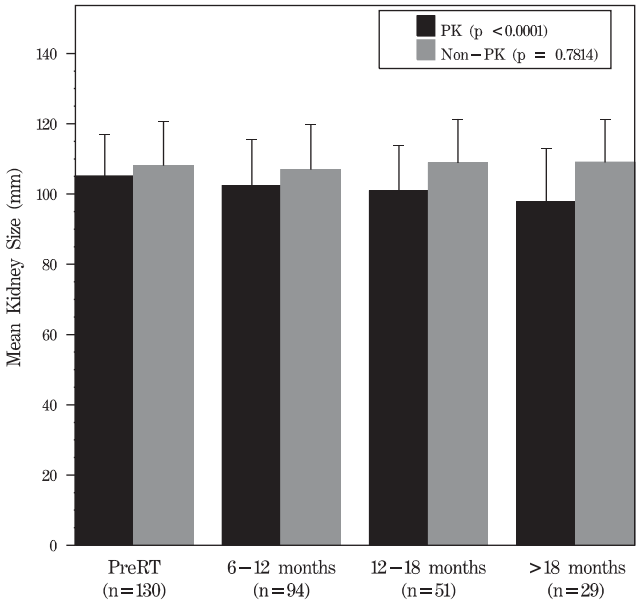

Fig. 2. Progressive change in size of the primarily irradiated kidney (PK) and non-primarily irradiated kidney (non-PK) over time after abdominal radiation. The vertical bars represent standard deviation.

Maor *et al.* (9) found that the degree of renal atrophy correlated with the volume of kidney irradiated, most significantly with irradiation of the entire kidney. Most patients had shrinkage in craniocaudal kidney length; 19 patients had ≥1.6-cm decrease.

In the present study, KS was similarly assessed using craniocaudal length. Such measurements are often available for patients with GI malignancies because pretreatment and follow-up CT imaging is commonly obtained as a part of evaluation. Additionally, because all patients in this study underwent CT simulation, these scans were also available as pre-RT baselines for comparison. All CT scans used in this analysis were acquired with slice thickness ≤5 mm. Scans were obtained using free breathing; no respiratory gating or breath-hold techniques were used. The CT acquisition protocols used for initial and follow-up diagnostic studies varied; most were fast spiral scans. Over the time period during which patients were included, 2002–2008, some early scans were slow spiral; more recent scans were fast spiral studies.

Renal length is known to vary by laterality (right vs. left), age, gender, height, weight, and comorbidities, including hypertension and diabetes (21, 24–26). To account for variability in KS of the PK based on laterality and individual patient differences, relative percentage change in KS rather than absolute change was investigated in this study.

Compensatory hypertrophy of the contralateral kidney after unilateral high-dose kidney irradiation has been reported (27, 28). Dewit *et al.* (29) described radiation-induced changes of the non- or minimally irradiated contralateral kidney in 5 patients receiving whole-abdominal RT followed by gastric boost for gastric non-Hodgkin's lymphoma. Relative renal volume of the irradiated kidney decreased to 30% of pre-RT volume ($p < 0.005$), and the other kidney increased

Table 5. Univariate analysis of patient and treatment factors related to decrease in size of primarily irradiated kidney at 12 months after radiotherapy

Factor	Decrease in KS ≤5% (n = 31)	Decrease in KS >5% (n = 17)	p
Age (y)			0.7566
<65	20 (64.52)	12 (70.59)	
≥65	11 (35.48)	5 (29.41)	
Gender			0.7646
Male	15 (48.39)	7 (41.18)	
Female	16 (51.61)	10 (58.82)	
HTN			1.0000
Yes	16 (51.61)	9 (52.94)	
No	15 (48.39)	8 (47.06)	
DM			0.3296
Yes	10 (32.26)	3 (17.65)	
No	21 (67.74)	14 (82.35)	
Smoking			0.3306
Yes	2 (6.45)	3 (17.65)	
No	29 (93.55)	14 (82.35)	
Pre-RT CrCl (mL/min)	98.81 (35.00)	109.61 (42.67)	0.3320
Pre-RT KS (mm)	106.45 (10.97)	105.59 (12.98)	0.8695
V_{10}	52.65 (25.71)	69.51 (13.13)	0.0030
V_{15}	46.85 (24.41)	62.98 (14.61)	0.0029
V_{20}	39.58 (23.32)	55.65 (14.28)	0.0028
V_{25}	30.41 (18.12)	39.09 (19.93)	0.1958
V_{30}	24.37 (18.41)	25.99 (20.16)	0.8546
V_{35}	21.31 (18.08)	17.84 (16.73)	0.5318
V_{40}	18.00 (16.58)	15.02 (15.10)	0.5605
MKD (Gy)	17.85 (6.92)	21.40 (4.44)	0.0846

Abbreviations: KS = kidney size; HTN = hypertension; DM = diabetes mellitus; Pre-RT = before radiation; CrCl = creatinine clearance; V_n = percentage volume of the kidney receiving at least n dose in Gray (Gy); MKD = mean kidney dose.

Values for categoric data are given as number (percentage). Values for continuous variables are given as mean (SD). Values for dose volume parameters (mean V_n) are given as percentage (SD). Values for MKD are given as dose in Gy (SD).

119% ($p < 0.005$). The CrCl for these patients decreased significantly, from 110 mL/min before RT to 75 mL/min. These changes were observed at 6–9 years after RT. In our study, size of the PK and CrCl did decline significantly over time ($p < 0.0001$). We did not observe compensatory hypertrophy of the non-PK kidney in the initial 18 months after chemoradiation. With lower dose and less volume irradiated in the non-PK, consequent effects may be reduced, and thus our study would have less power to detect a smaller difference. Likely the response to radiation in the non-PK involves complex pathophysiologic mechanisms causing a combination of atrophy in some functional subunits and hypertrophy and compensation in others. It is unclear what the dominant underlying process is in our study.

Current dose tolerance limits are useful for assessment of normal tissue complication probability based on dose and volume irradiated (11, 15). These data are less helpful for late toxicity risk estimation in the setting of modern RT planning and treatment. In a prior investigation of this patient cohort, significant decline in CrCl and increase in creatinine was seen after chemoradiotherapy for abdominal malignancies (10). Correlation was observed between pre-RT CrCl, V_{10}, and MKD and subsequent development of grade ≥2 renal toxicity, as defined by the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring schema (30). Analyses suggested an association between lower-dose renal irradiation and subsequent renal toxicity. This study sought to evaluate patient and treatment factors related to decrease in size of the PK. Our results on univariate and multivariate analyses similarly suggest that renal volumes receiving lower doses than current renal tolerance limits contribute to renal atrophy. We found V_{10}, V_{15}, and V_{20} to be significantly associated with >5% decrease in size of the PK.

We calculated ROC plots and AUCs to evaluate the utility of dose–volume parameters to predict risk for >5% decrease in size of the PK. Lind *et al.* and others have used similar techniques to predict risk of radiation-induced toxicity (31–34). To our knowledge, this is the first report applying ROC curve analyses to predict radiation-induced kidney complications. In this study, the ROC plots and AUCs for dose–volume parameters V_{10}, V_{15}, and V_{20} show the correlation between the volume of kidney receiving lower doses of RT and subsequent renal atrophy. The AUCs for each parameter did not significantly differ, as shown in Fig. 4. As such, one was not better than the others in predicting decrease in KS. All three parameters, V_{10}, V_{15}, and V_{20}, were highly correlated. These data suggest that there is an association between lower-dose irradiation of the kidney and development of renal atrophy.

A benefit of using ROC plots to assess the predictability of a given parameter is that all potential cut-points are displayed (31). A minimum sensitivity (true-positive rate) for a dosimetric predictor can be selected that is clinically relevant. Then a minimum false-positive rate (1 − specificity) can be chosen. The minimum specificity should not be so strict such that dosimetric constraints are too restrictive for treatment planning, potentially jeopardizing coverage of the clinical targets to spare organs at risk. A cutoff value for the given parameter can then be determined from the ROC plot. Using the ROC plot for V_{15} (Fig. 3b) as an example and selecting a minimum sensitivity of 80% and specificity of 70%, a cutoff for V_{15} of 50% was predictive for risk of developing renal atrophy.

There are several limitations to this study. We did not control for renal mobility. Renal mobility has been shown to be greatest in the craniocaudal direction (35). Use of breath-hold and other respiratory gating techniques may obviate some renal movement; however, patients in this study were simulated and treated using free breathing. We evaluated change in KS, using craniocaudal distance on CT images, and not a direct clinical endpoint for radiation-induced nephropathy. Because CT acquisition protocols varied over the time period of this retrospective study, the inclusion of slow and fast spiral scans may have resulted in observation bias within the analyses. Although our study was not able to identify patient, clinical, or other treatment factors associated with decrease in

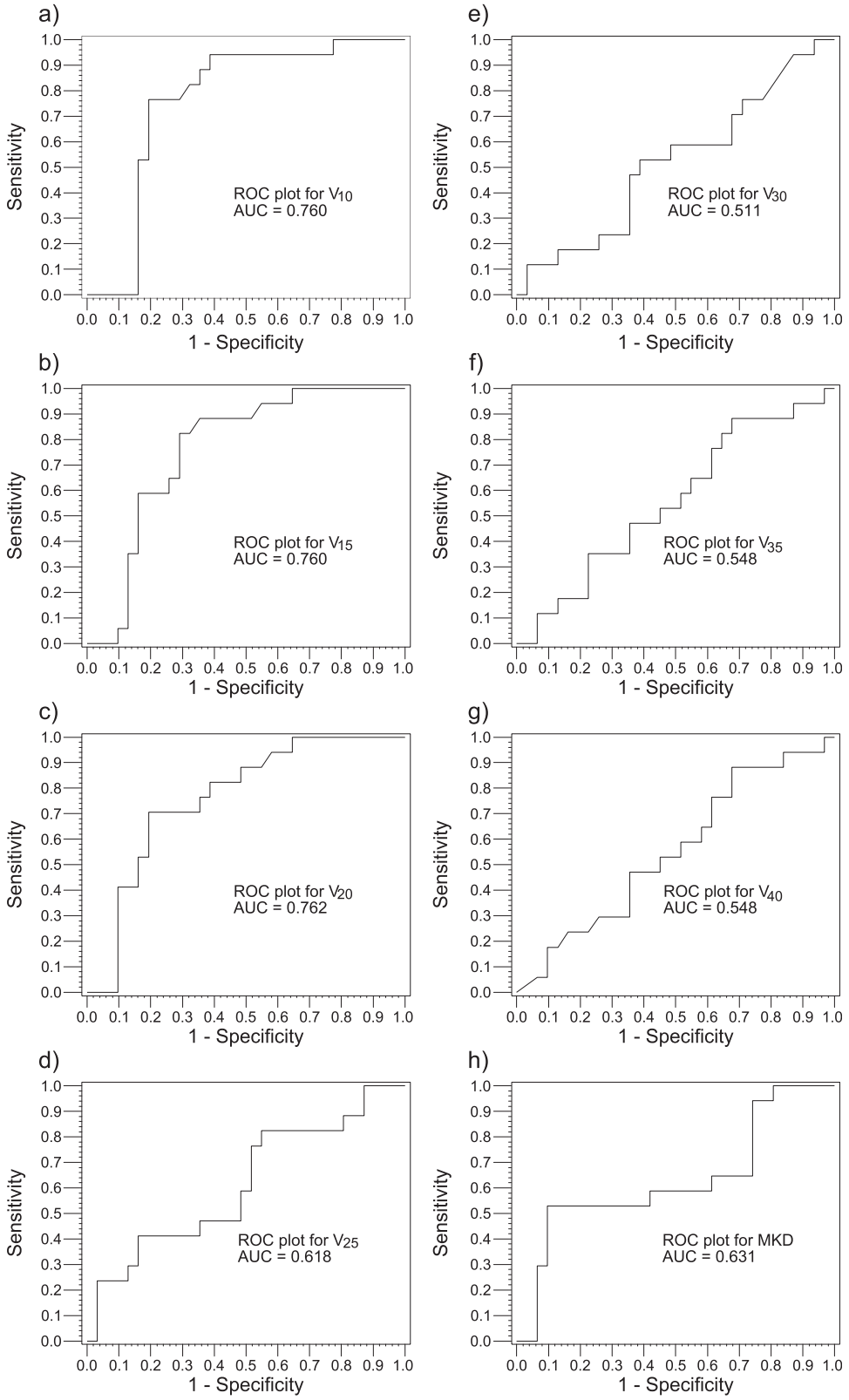

Fig. 3. Receiver operating characteristic (ROC) curves for V_{10}, V_{15}, V_{20}, V_{25}, V_{30}, V_{35}, V_{40}, and mean kidney dose (MKD) (a–h, respectively) to assess the predictability of each dose–volume parameter for >5% decrease in size of the primarily irradiated kidney. The approximate area under the curve (AUC) for each dose volume parameter is shown.

size of the PK, it is likely that multiple other parameters are involved in radiation-induced renal complications. Use of nephrotoxic chemotherapy such as cisplatin has the potential to compound renal toxicity secondary to RT, although our sample size did not permit further investigation of this association. Nor could the influence of other chemotherapeutic

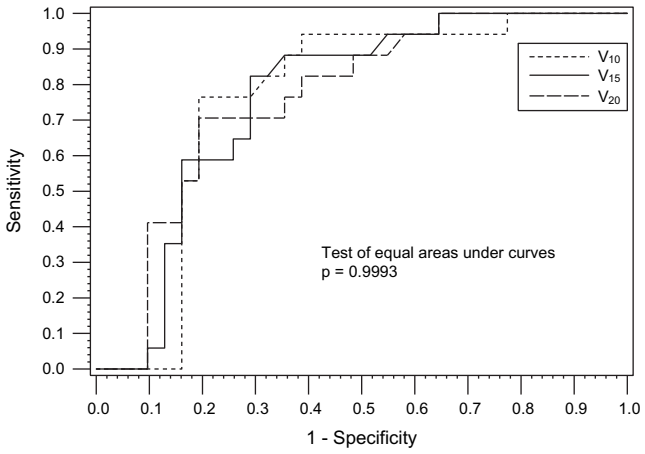

Fig. 4. The receiver operating characteristic curves for V_{10}, V_{15}, and V_{20} with the approximate area under the curve (AUC) for each parameter are shown. The comparison plot for test of equal AUCs for V_{10}, V_{15}, and V_{20} demonstrates that the AUCs for each parameter did not significantly differ.

agents be assessed because of the multiple agents and combinations of systemic therapies included in this study. Because radiation-induced renal toxicity is progressive, additional contributing factors may be identified with longer follow-up.

Larger renal volumes receiving lower doses may impact renal function and subsequent late toxicity. Our study showed that V_{10}, V_{15}, and V_{20} are predictive of risk for renal atrophy after abdominal chemoradiation. The ROC plots provided may be used to inform treatment planning decisions. Under certain circumstances, modification of treatment fields and/or shielding may be preferable. The significance of lower-dose renal irradiation on late effects may have potential implications for RT delivery techniques such as IMRT and arc therapy in the abdomen. Further investigation is needed to validate the preliminary findings of this study; specifically, evaluation of late renal effects in patients treated using these treatment modalities.

CONCLUSIONS

Significant detriments in PK size and renal function were seen after abdominal chemoradiotherapy. The parameters V_{10}, V_{15}, and V_{20} were associated with >5 % decrease in size of the PK 1 year after RT. Analyses suggest the association of larger kidney volumes receiving lower doses and subsequent development of renal atrophy. Receiver operating characteristic plots are useful models to predict risk of renal atrophy on the basis of dosimetric parameters. These observations can assist with renal dose constraints in RT treatment planning. Further studies and longer follow-up are necessary to evaluate renal dose parameters for long-term toxicity.

REFERENCES

1. Kunkler PB, Farr R, Luxton RW. The limit of renal tolerance to xrays. *Br J Radiol* 1952;25:190–201.
2. Luxton RW. Radiation nephritis. *Q J Med* 1953;22:215–242.
3. Thompson PL, Mackay IR, Robson GSM, *et al*. Late radiation nephritis after gastric x-irradiation for peptic ulcer. *Q J Med* 1971;40:145–157.
4. Dewit L, Anninga JK, Hoefnagel CA, *et al*. Radiation injury in the human kidney: A prospective analysis using specific scintigraphic and biochemical endpoints. *Int J Radiat Oncol Biol Phys* 1990;19:977–983.
5. Krochak RJ, Baker DG. Radiation nephritis: Clinical manifestations and pathophysiologic mechanisms. *Urology* 1986;27: 389–393.
6. Cohen EP, Robbins MEC. Radiation nephropathy. *Semin Nephrol* 2003;23:486–499.
7. Cassady JR. Clinical radiation nephropathy. *Int J Radiat Oncol Biol Phys* 1995;31:1249–1256.
8. Willett CG, Tepper JE, Orlow EL, *et al*. Renal complications secondary to radiation treatment of upper abdominal malignancies. *Int J Radiat Oncol Biol Phys* 1986;12:1601–1604.
9. Maor MH, North LB, Cabanillas FF, *et al*. Outcomes of high-dose unilateral kidney irradiation in patients with gastric lymphoma. *Int J Radiat Oncol Biol Phys* 1998;41:647–650.
10. May KS, Khushalani NI, Chandrasekhar R, *et al*. Analysis of clinical and dosimetric factors associated with change in renal function in patients with gastrointestinal malignancies after chemoradiation to the abdomen. *Int J Radiat Oncol Biol Phys*. In press.
11. Emami B, Lyman J, Brown A, *et al*. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21: 109–122.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
13. Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychol Methods* 1997;2:64–78.
14. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* 1988;44: 837–845.
15. Milano MT, Constine LS. P Okunieff. Normal tissue tolerance dose metrics for radiation therapy of major organs. *Semin Radiat Oncol* 2007;17:131–140.
16. Sustic A, Mavric Z, Fuckar Z, *et al*. Kidney length in postoperative acute renal failure. *J Clin Ultrasound* 1998;26:251–255.
17. D'Souza RCM, Kotre CJ, Owen JP, *et al*. Computed tomography evaluation of renal parenchymal volume in patients with chronic pyelonephritis and its relationship to glomerular filtration rate. *Br J Radiol* 1995;68:130–133.
18. Sharma N, O'Hara J, Novick AC, *et al*. Correlation between loss of renal function and loss of renal volume after partial nephrectomy for tumor in a solitary kidney. *J Urol* 2008;179: 1284–1288.
19. Gandy SJ, Armoogum K, Nicholas RS, *et al*. A clinical MRI investigation of the relationship between kidney volume measurements and renal function in patients with renovascular disease. *Br J Radiol* 2007;80:12–20.
20. Burkhardt H, Hahn T, Gladisch R. Is kidney size a useful predictor of renal function in the elderly? *Clin Nephrol* 2003;59: 415–422.
21. Cheong B, Muthupillai R, Rubin MF, *et al*. Normal values for renal length and volume as measured by magnetic resonance imaging. *Clin J Am Soc Nephrol* 2007;2:38–45.
22. Adibi A, Adibi I, Khosravi P. Do kidney sizes in ultrasonography correlate to glomerular filtration rate in healthy children? *Australas Radiol* 2007;51:555–559.

23. Moghazi S, Jones E, Schroepple J, *et al*. Correlation of renal histopathology with sonographic findings. *Kidney Int* 2005;67: 1515–1520.
24. Emamian SA, Nielsen MB, Pedersen JF, *et al*. Kidney dimensions at sonography: Correlation with age, sex, habitus in 665 adult volunteers. *AJR Am J Roentgenol* 1993;160:83–86.
25. Miletic D, Fuckar Z, Sustic A, *et al*. Sonographic measurement of absolute and relative renal length in adults. *J Clin Ultrasound* 1998;26:185–189.
26. Paivansalo MJ, Merikanto J, Savolainen MJ, *et al*. Effect of hypertension, diabetes, and other cardiovascular risk factors on kidney size in middle-aged adults. *Clin Nephrol* 1998;50:161–168.
27. Kim TH, Somerville PJ, Freeman CR. Unilateral radiation nephropathy—the long-term significance. *Int J Radiat Oncol Biol Phys* 1984;10:2053–2059.
28. Michalowski A, Cullen BM, Burgin J, *et al*. Development of structural renal damage and its quantitation. *Br J Cancer* 1986;53(Suppl. VII):295–297.
29. Dewit L, Verheij M, Valdes Olmos RA, *et al*. Compensatory renal response after unilateral partial and whole volume high-dose irradiation of the human kidney. *Eur J Cancer* 1993;29A: 2239–2243.
30. Cox JD, Stetz J, Pajak TK. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–1346.
31. Lind PA, Marks LB, Hollis D, *et al*. Receiver operating characteristic curves to assess predictors of radiation-induced symptomatic lung injury. *Int J Radiat Oncol Biol Phys* 2002;54: 340–347.
32. Zapatero A, Garcia-Vicente F, Modolell I, *et al*. Impact of mean rectal dose on late rectal bleeding after conformal radiotherapy for prostate cancer: Dose-volume effect. *Int J Radiat Oncol Biol Phys* 2004;59:1343–1351.
33. Lind PA, Wennberg B, Gagliardi G, *et al*. ROC curves and evaluation of radiation-induced pulmonary toxicity in breast cancer. *Int J Radiat Oncol Biol Phys* 2006;64:765–770.
34. Schallenkamp JM, Miller RC, Brinkmann DH, *et al*. Incidence of radiation pneumonitis after thoracic irradiation: Dose-volume correlates. *Int J Radiat Oncol Biol Phys* 2007;67: 410–416.
35. van Sornsen de Koste JR, Senan S, Kleyman CE, *et al*. Renal mobility during uncoached quiet respiration: An analysis of 4DCT scans. *Int J Radiat Oncol Biol Phys* 2006;64:799–803.