Radiotherapy and Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Long-term observations of radiation-induced creatinine clearance reduction and renal parenchymal volume atrophy

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ARTICLE INFO

Article history:
Received 13 June 2015
Received in revised form 6 April 2016
Accepted 16 April 2016

Keywords:
Renal volume change
Creatinine clearance
Dose constraint

ABSTRACT

Purpose: The kidney is a dose-limiting organ for upper abdominal radiotherapy. In this study, radiation-induced kidney injury represented by changes of creatinine clearance (Ccr) and renal parenchymal volume measured by computed tomography (CT) were evaluated by analysing dose–volume histograms (DVHs) in patients with primary gastric diffuse large B-cell lymphoma (PGDLBCL) treated with chemoradiotherapy.

Materials and methods: Thirty-eight PGDLBCL patients (seventy-six kidneys) treated with chemoradiotherapy were included in this study. At least 4 years of follow-up was required for eligibility. Patients underwent (immuno-) chemotherapy followed by radiotherapy with approximately 40 Gy to the whole stomach and perigastric lymph nodes. Ccr and CT were obtained at least annually. Changes of Ccr and renal parenchymal volume before and 4 years after radiotherapy were compared using DVH parameters.

Results: Mean Ccr decreased significantly from 82.7 mL/min (range, 39–124 mL/min) before radiotherapy to 70.4 mL/min (range, 35–109 mL/min) ($p = 0.01$) 4 years after radiotherapy. Mean reduction of bilateral renal parenchymal volume was 12% (range, −5–37%) in the same time period. Ccr and renal parenchymal volume tended to lower over time more than 4 years after radiotherapy. Concerning DVH analysis, $V_{20Gy} \geqslant 26.6\%$ and $D_{30\%} \geqslant 19$ Gy had a significant risk of bilateral renal atrophy of $\geqslant 14\%$ and reduction of the Ccr $\geqslant 20$ mL/min.

Conclusion: This study revealed that there was a definite relationship between DVH, renal atrophy and Ccr reduction. $V_{20Gy} < 26.6\%$ and $D_{30\%} < 19$ Gy appeared to be safe dose constraints for a Ccr reduction of <20 mL/min 4 years after radiotherapy.

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Kidneys are dose-limiting organs for radiotherapy, and there are many reports of radiation-induced kidney injury [1–9]. TD5/5 (the tolerance dose that produces a 5% incidence of complications in 5 years) and TD50/5 (the tolerance dose that produces a 50% incidence of complications in 5 years) are frequently used indicators of kidney radiation tolerance [1]. Due to recent advances in radiotherapy techniques that reduce the renal radiation dose, renal injury with apparent clinical symptoms of renal failure is rarely encountered. Although there have been studies analysing changes of renal function and size by nuclear medicine imaging and computed tomography (CT) [2,3,6,8,9], few studies dealing with dose–volume histogram (DVH) analysis of kidney radiotherapy and its correlation with kidney parenchymal volume change (as measured by CT) have been performed. Additionally, most studies of radiation-induced renal injury have short follow-up period [2,5–7] and use of chemotherapy regimens that are nephrotoxic [2,3,5–7].

In this study, patients with primary gastric diffuse large B-cell lymphoma (PGDLBCL) were selected as subjects. Because the prognosis of PGDLBCL is excellent and abdominal CT is performed regularly during follow-up examinations at our institution, a study of the long-term effect of radiotherapy on the kidneys was possible. Additionally, the CHOP chemotherapy regimen (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone) with or without rituximab employed in the management of PGDLBCL appears to be less nephrotoxic than the CDDP. In this study, we evaluated creatinine clearance (Ccr) reduction as an indicator of impaired renal function, as well as renal parenchymal volume change 4 years after radiotherapy. Furthermore, we

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http://dx.doi.org/10.1016/j.radonc.2016.04.022
0167-8140/

explored the interrelationships between Ccr reduction, renal atrophy and DVH parameters.

Materials and methods

Seventy-six kidneys of 38 patients with PGDLBCL treated by (immuno-) chemotherapy and ensuing radiotherapy between January 2000 and July 2011 were included in this study. At least 4 years of follow-up was required for eligibility. Most patients underwent 3 courses of triweekly CHOP chemotherapy: cyclophosphamide (750 mg/m^2 on day 1), hydroxydaunorubicin (50 mg/m^2 on day 1), vincristine (1.4 mg/m^2 on day 1), and prednisolone (100 mg/body on days 1–5) with or without rituximab; and radiotherapy of 40.5 Gy/27 fractions (fr) or 40 Gy/20 fr. Radiotherapy was performed using 2 fields in 8 patients, 3 fields in 6 patients and 4 fields in 24 patients (Table 1). The clinical target volume (CTV) was the whole stomach and perigastric lymph nodes; if the tumour invaded adjacent organs such as the pancreas, the CTV was expanded to cover the invasive tumour. Radiotherapy beam arrangement was planned to cover the CTV while avoiding the kidney and liver as much as possible. After completing treatment, CT, endoscopic, and blood examinations were performed at least annually. Although six patients had hypertension or diabetes mellitus, which could have influenced renal function, their diseases were controlled. For evaluating renal injuries induced by the (immuno-) chemotherapy, Ccr before and after chemotherapy (but before radiotherapy) were compared. Similarly, for obtaining Ccr changes due to radiotherapy, Ccr before radiotherapy (but after chemotherapy) and 4 years after radiotherapy were compared. Ccr was calculated by the Cockcroft–Gault formula:

$$\mathrm{Ccr} = \{(140\text{-age}) \times \text{body weight}\}/72 \times \mathrm{sCr}.$$

This value was adjusted for females by multiplying the Ccr × 0.85 [10]. Renal volume was defined as the renal parenchymal volume contoured excluding the calyces. For delineation of the renal parenchyma, CT before radiotherapy and follow-up CTs were used, and volumes were expressed as a percentage of the volume at the CT before radiotherapy. In this study, the renal parenchymal volumes 4 years after radiotherapy were compared to the volumes before radiotherapy. The calculated DVH parameters were mean dose; fractional volumes of the renal parenchyma receiving more than 5 Gy (V_{5Gy}), 10 Gy (V_{10Gy}), 15 Gy (V_{15Gy}), 20 Gy (V_{20Gy}), 25 Gy (V_{25Gy}), 30 Gy (V_{30Gy}), 35 Gy (V_{35Gy}), and 40 Gy (V_{40Gy}); and minimum doses covering 90% ($D_{90\%}$), 80% ($D_{80\%}$), 70% ($D_{70\%}$), 60% ($D_{60\%}$), 50% ($D_{50\%}$), 40% ($D_{40\%}$), 30% ($D_{30\%}$), 20% ($D_{20\%}$), and 10% ($D_{10\%}$) of the renal parenchymal volumes.

Correlations between Ccr reduction of ⩾20 mL/min and DVH parameters of both kidneys were investigated as a continuous variable. The cut-off points of the DVH parameters of both kidneys were estimated using receiver operating characteristic (ROC) curve, and chi-square tests were performed to examine whether the selected cut-off point correlated significantly with the decrease of Ccr. Additionally, the cut-off points of the DVHs were also investigated for any correlation with bilateral renal parenchymal volume changes. The institutional review board at our institution approved this study. Treatment was conducted with informed consent.

Table 1
Patient and treatment characteristics.

			n
Age			Median 62 years (37–81)
Sex			Male: 22, Female: 16
Chemotherapy	CHOP and CHOP-like	3 cycles	34
		6 cycles	3
		8 cycles	1
	Rituximab	0 cycle	14
		1 cycle	1
		2 cycles	1
		3 cycles	2
		4 cycles	3
		6 cycles	2
		7 cycles	1
		8 cycles	14
Radiotherapy	40 Gy/20 fractions		28
	40.5 Gy/27 fractions		10
Radiation plan	2 fields		8
	3 fields		6
	4 fields		24
Stage (Lugano)	Stage I		21
	Stage II1		15
	Stage II2		1
	Stage IIE		1
Comorbidity	Hypertension		4
	Diabetes Mellitus		2

CHOP: cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone.

Results

The characteristics and treatments undergone by the 38 patients included in this study are shown in Table 1. Mean values and ranges of mean dose, $D_{30\%}$, and V_{20Gy} of the left kidneys were 16.9 Gy (0.6–38 Gy), 19.7 Gy (0.3–42.3 Gy), and 44.3% (0–100%), respectively. Mean values and ranges of mean dose, $D_{30\%}$, and V_{20Gy} of the right kidney were 5.0 Gy (0.2–16.5 Gy), 6.1 Gy (0.2–29.3 Gy), and 9.7% (0–49.3%), respectively. The left kidneys were irradiated with higher doses than the right kidneys because the stomach lies anterior to the left kidney.

Fig. 1 shows changes of Ccr and kidney parenchymal volumes with time, and demonstrates that Ccr tended to decrease over time after radiotherapy. Total parenchymal volumes of both kidneys showed a similar tendency of a reduction in volume as time elapsed after radiotherapy despite compensatory hypertrophy of the right kidney in some patients. Ccr and bilateral kidney volume apparently continued to decrease even more than 4 years after radiotherapy (Fig. 1).

Mean Ccr before and after (immuno-)chemotherapy were 81.8 (range: 44–110) mL/min and 82.7 (range: 39–124) mL/min, respectively. Because no statistically significant difference was observed between the Ccr before and after the (immuno-) chemotherapy, the (immuno-)chemotherapy regimen employed in PGDLBCL patients did not appear to affect kidney function significantly at an early phase. In contrast, mean Ccr was reduced significantly from 82.7 (range: 39–124) mL/min before radiotherapy to 70.4 (range: 35–109) mL/min 4 years after radiotherapy ($p = 0.01$) (Fig. 1 and Table 2). Notably, Ccr reduction 1 year after radiotherapy appeared to predict further Ccr reduction 4 years after radiotherapy. Seven of 9 patients (78%) with a Ccr reduction of >10 mL/min 1 year after radiotherapy had a Ccr reduction of >20 mL/min 4 years after the treatment. In contrast, only 3 of 28 patients (11%) with a Ccr reduction of <10 mL/min 1 year after radiotherapy had a Ccr reduction of >20 mL/min 4 years after radiotherapy ($p < 0.0001$, chi-square test).

To obtain the dose parameters that would produce a Ccr reduction of ⩾20 mL/min, DVH parameters were analysed to determine a cut-off point by using ROC curves. $D_{30\%} \geqslant 19$ Gy and $V_{20Gy} \geqslant 26.6\%$ to both kidneys had an increased risk of Ccr reduction of ⩾20 mL/min. (Table 3). Eight of 20 patients (40%) with $D_{30\%} \geqslant 19$ Gy to both kidneys had a Ccr reduction of ⩾20 mL/min. In contrast, there were 2 of 18 patients (11%) of those with $D_{30\%} < 19$ Gy to both kidneys who showed a Ccr reduction ⩾20 mL/min; the difference was statistically significant ($p = 0.04$,

Please cite this article in press as: Inaba K et al. Long-term observations of radiation-induced creatinine clearance reduction and renal parenchymal volume atrophy. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.04.022