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ORIGINAL ARTICLE

Long-term Changes in Creatinine Clearance and Renal Parenchymal Volume with Dosimetric Parameters in Gastric Cancer Patients with Treated Chemoradiotherapy

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OBJECTIVE

The objective of the study was to evaluate the long-term impact of adjuvant chemoradiotherapy (CRT) on renal function through the creatinine clearance (Ccr) and renal parenchymal (RPR) volume and to compare the results with dose-volume histogram parameters in gastric cancer patients.

METHODS

This retrospective study was carried out from 2013 to 2014 in the Department of Radiation Oncology, Faculty of Medicine, Bulent Ecevit University, Zonguldak. Thirty-four patients who underwent post-operative CRT and were followed at least four years with Stage 1-3 gastric cancer were included in the study.

RESULTS

The median Ccr significantly decreased from 82.8 mL/min to 78.4 mL/min at 24 months and to 75.3 mL/min at 48 months after radiotherapy (RT) (p=0.034). Both RPR were significantly decreased 4 years after RT (p=0.001). Ccr reductions were >10 mL/min in 16 (47%) patients. The total kidney dose, bilateral kidney V20, bilateral kidney V25, and right kidney V20 doses were significantly higher in patients with decreased Ccr more than 10 mL/min at 48 months after RT than those who did not decrease (p=0.003, p=0.037, p=0.029, and p=0.013, respectively).

CONCLUSION

Long-term progressive renal toxicity with both functional and imaging tests was found after adjuvant CRT in gastric cancer. Decline in renal function was associated with bilateral and compensatory kidney radiation dose and volume. For RT planning, bilateral and compensatory kidney radiation dose and volume might be evaluated for safe dose constraints and may be useful for predicting late kidney toxicity.

Keywords: Creatinine clearance; gastric cancer; late renal toxicity; radiotherapy; Renal Parenchymal Volume.
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Introduction

Gastric cancer is one of common and lethal cancer worldwide, with more than 1 million people new cases reported each year.[1] Despite the global decline in incidence and mortality and also recent development in treatment of gastric cancer in the past five decades, the prognosis is still poor, and it remains the third leading cause of cancer-related death.[2] The curative management of gastric cancer is difficult unless it is found at an early stage. Primary curative therapy for gastric cancer is surgical intervention with lymph node dis-

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section, but overall 5-year survival rates remain low after resection, particularly in patients with T3-T4 or metastasis.[3] After the intergroup-0116 trial, adjuvant chemoradiation (chemoradiotherapy [CRT]) has become the standard of care for high-risk patients with gastric cancer as an additional treatment that prolongs survival and reduces local recurrence rates.[4] However, long-term toxicity associated with treatment with CRT still remains a significant problem. The kidneys are radiosensitive organs and thus are dose-limiting structures for abdominal radiotherapy (RT) in gastrointestinal cancers; late effects of renal irritation may develop depending on dose and volume.[5] The incidence of RT-related kidney damage may probably not be reported due to the long delay time, and late renal dysfunction due to RT may often be attributed to other more common causes.[6] Despite advances in RT techniques, dose-related reductions in renal function have been reported in patients with abdominal malignancies from 6 months up to 10 years after irradiation.[7] However, the pathophysiology of radiation-related nephropathy in gastric cancer is poorly understood. To date, few studies have been conducted the effects of RT on renal function through creatinine clearance (Ccr) and renal parenchymal (RPR) volume, which are used as an indicator of impaired renal function overtime, and the relationship between these parameters and the dose-volume histogram (DVH).[5,6,8] However, their results were inconclusive. Besides, some studies examined radiation-induced renal damage have short follow-up times and use of nephrotoxic chemotherapy regimens.

The aim of this study is to evaluate the long-term impact of adjuvant CRT on renal function through the Ccr and RPR volume and to compare the results with DVH parameters in gastric cancer patients treated with CRT using a non-nephrotoxic chemotherapy agent.

Materials and Methods

The study was designed as a single-center retrospective study and was carried out from 2013 to 2014 in the Department of Radiation Oncology, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey. A total of 34 patients diagnosed with Stage 2-3 gastric cancer (T2-4, N0-3, and M0) who received post-operative CRT were included the study. All patients underwent D2 dissection and were histologically proven to have gastric adenocarcinoma. Patients were included in this study if they received RCT and three-dimensional conformal abdominal RT (3D-CRT) or intensity-modulated RT (IMRT); had laboratory data, imaging studies, and dosimetric parameters available for evaluation; had no history kidney disease before RCT; and had at least one kidney included in the RT treatment fields. At least 4 years of follow-up were required for eligibility. Patients with systemic diseases which could have influenced renal function, metastasis, a history of kidney disease (glomerular filtration rate [GFR] <55 mL/min/1.73 m^2), and positive surgical margin were excluded from the study. All research procedures were evaluated and accepted by the Clinical Research Ethics Committee of Bulent Ecevit University (No: 2018-118-11/04) and were conducted in agreement with the ethical standards specified in the Declaration of Helsinki. As a retrospective design, written informed consent from patients was disclaimed.

RT and Chemotherapy

All patients were treated according to the INT-0116 trial and received concurrent CRT.[4] One cycle of 425 mg/m^2 per day of 5-fluorouracil (FU) and 20 mg/m^2 per day folinic acid (FA) chemotherapy was given for 5 days before CRT. A second course of chemotherapy comprised 5-FU (400 mg/m^2/day) and FA (20 mg/m^2/day) during the first 4 and last 3 days of RT. After completion of RT, two additional cycles of chemotherapy were administered. Patients received RT by 3D-CRT or IMRT with linear accelerators using 6 or 15 MV photon beams in a total dose of 45 Gy in 25 fractions of 1.8 Gy in 5 weeks. Computed tomography-based treatment planning was managed using Eclipse treatment planning system (Varian Medical Services, CA, USA). 3D-CRT plans were generated in seven patients with three (gantry angels: 0°, 90°, and 270°) or four fields (gantry angels: 0°, 90°, 180°, and 270°), whereas IMRT plans were designed in 27 patients with seven fields (gantry angels: 25°, 75°, 135°, 180°, 225°, 280°, and 325°). The design of the radiation treatment field was individualized depending on the extent and location of the primary tumor and involved lymph nodes.[9] DVHs were generated for kidneys, planning target volume (PTV), and liver in all patients. During planning and evaluation of DVHs, the dose delivered to target volume was intended to cover at least 95% of PTV in 3D-CRT plans and also to achieve D2 and D98 values as recommended in ICRU-83 in IMRT plans.[10] In addition, mean kidney dose (MKD) and also the renal volume that received more than 10 Gy (V10), 15 Gy (V15), 20 Gy (V20), 25 Gy (V25), 28 Gy (V28), and 30 Gy (V30) were calculated for the left, right, and both kidneys.

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Follow-up

Patients were followed every 3 months after CRT during the first 2 years and at 6 months intervals thereafter. During the follow-up period, demographic and clinical parameters including age, gender, height, weight, body mass index, comorbidities, treatment features, and results of basal, the 2nd and 4th year biochemical parameters were obtained. To evaluate renal function, Ccr was calculated using the Cockcroft-Gault formula before RT (but after CT), 24 and 48 months after RT.[11]

Ccr= ((140-age) * body weight in kilograms)/72 * serum creatinine

This value was adjusted for females by multiplying by 0.85.[11] The ratio of Ccr was calculated by the formula: Post-RT Ccr divided by pre-RT Ccr. In addition, RPR volume was calculated by contouring the kidneys except the calyx in each tomographic slice, and the results were evaluated by computed tomography before and 48 months after RT. Volumes were expressed as a percentage of the volume in CT before RT.

Statistical Analysis

All statistical analyses were performed using the SPSS software version 16.0 (SPSS Inc., Chicago, IL). Patients and treatment characteristics were given as percentage. Kidney parenchymal volume, kidney dose, and DVH values were reported as mean and standard deviation. Ccr was demonstrated as median and range. The categorical data were compared by means of Chi-square test. The comparisons of the groups were assessed using the Student's t-test for normally distributed continuous variables. The Mann-Whitney U-test was utilized for non-normally distributed continuous variables. Statistical significance was defined as $p<0.05$.

Results

A total of 34 patients with gastric cancer who received CRT were included retrospectively in the study. The median of the patients was 60 years (range: 42-79) and most of them were male (n=26; 76.5%). In pathological examinations, all patients were diagnosed with gastric adenocarcinoma. Fifteen patients (44.1%) had Stage 2 and 19 had (55.9%) Stage 3. Because of the stomach position, the irradiation doses of the left kidneys were higher than the right kidney doses (10.2 vs. 15.58 Gy, respectively). During the follow-up period, Grade 2 renal toxicity was observed in five patients, while none of the patients had Grade 3 toxicity. However, no patients had renal failure or requiring hemodialysis. Demographic and treatment characteristics of patients are shown in Table 1.

Table 1 Demographic and treatment characteristics of patients (n=34)

Characteristics	n	%
Age (years)	60	42-79
Gender		
Male	26	76.5
Female	8	23.5
Stage		
2A	5	14.7
2B	10	29.4
3A	11	32.4
3B	5	14.7
3C	3	8.8
Radiotherapy planning		
3D-CRT	7	20.6
IMRT	27	79.4
Irradiation dose		
Left kidney (Gy)	15.8	
Right kidney (Gy)	10.2	

3-D-CRT: Three-dimensional conformal radiotherapy; CRT: Chemoradiotherapy; IMRT: Intensity-modulated radiotherapy. Values are given as median (range) or, for categorical data, number (percentage)

Median of Ccr before RT was 82.8 mL/min (range: 41-130). Following RT, Ccr decreased to 78.4 mL/min (range: 39-130) 24 months after RT and to 75.3 mL/min (38-123) 48 months after completion of treatment (Table 2). There was statistically significant difference in terms of Ccr before and 48 months after RT (p=0.034). The number of patients with a Ccr value >90 mL/min decreased from 14 to 10 at the 24th month and to 8 at the 48th month. In addition, the number of patients with Ccr 60-89 mL/min increased from 18 to 21 at 24 months and increased to 23 at 48 months. The left and right RPR volumes were significantly decreased in 4 years after RT (from 143.4 to 126.1 cm^3 and 141.9-126.9 cm^3, respectively, both p=0.001) (Table 2).

Radiation therapy was given as a MKD of 13.5±4.3 Gy. We found that the mean left kidney dose was

Table 2 Changes in Ccr and kidney parenchymal volume after radiotherapy overtime

Parameter	Pre-RT	24 months	48 months	p
Ccr (mL/min)	82.8 (41-130)	78.4 (39-130)	75.3 (38-123)	0.034
MLKV (cm^3)	143.4±39.4		126.1±32.7	0.001
MRKV (cm^3)	141.9±41.2		126.9±31.7	0.001

Pre-RT: Before radiotherapy; Ccr: Creatinine clearance; MLKV: Mean left kidney parenchymal volume; MRKV: Mean right kidney parenchymal volume. Values for Ccr are given as median (range). Values for kidney parenchymal volume are given as mean (SD)

15.5±8.1 Gy, and also the mean right kidney dose was 10.2±6.7 Gy (Table 3). While 13 of 17 patients (76.5%) with a MKD >14 Gy had decreased Ccr, only three of 19 patients (19.8%) with a MKD of ≤14 Gy showed Ccr reduction, and this difference was statistically significant (p=0.001). The Ccr reduction percentage at 48 months after RT was 9%, which showed a significant correlation with the total dose of renal radiation (p=0.008) (data not shown). The total kidney dose, bilateral kidney V20, bilateral kidney V25, and right kidney V20 doses were significantly higher in patients with decreased Ccr more than 10 mL/min at 48 months after RT than those who did not decrease (p=0.003, p=0.037, p=0.029, and p=0.013, respectively) (Table 3). In correlation analysis, we found no correlation between not only the changes in RPR volume and Ccr but also the changes in RPR volume and renal mean doses in the study group (data not shown).

Table 3 Radiation treatment characteristics

Parameter	All patients (n=36)	Ccr reduction >10 mL/min (n=16)	Ccr reduction <10 mL/min (n=18)	p
MKD (Gy)	13.5±4.3	15.3±3.3	11.1±4.2	0.003
MLKD (Gy)	15.5±8.1	16.1±9.6	14.8±6.5	>0.05
MRKD (Gy)	10.2±6.7	11.4±6.5	9.8±6.6	>0.05
V20 (bilateral)	31.7±12.6	36.2±12.5	27.3±11.4	0.037
V25 (bilateral)	25.1±11.5	29.2±10.9	20.7±11.1	0.029
V20 (left)	37.7±18.5	41.3±16.1	33.6±20.5	>0.05
V20 (right)	21.7±11.6	26.3±10.7	16.5±10.5	0.013

Values for dose-volume parameters (mean Vn) represent percentage of kidney volume receiving at least n dose in Gy. Ccr: Creatinine clearance; MKD: Mean kidney dose; MLKD: Mean left kidney dose; MRKD: Mean right kidney dose; V20 (bilateral): Mean bilateral kidney V20; V25 (bilateral): Mean bilateral kidney V25; V20 (left): Mean left kidney V20; V20 (right): Mean right kidney V20

Discussion

The study was aimed to assess the prolonged effects of adjuvant CRT on renal function and to compare the results with DVH parameters in gastric cancer patients treated with CRT. We found decreased Ccr and kidney parenchymal volume in follow-up period after treatment. These changes demonstrate that parameters associated with renal functions tended to decrease with CRT overtime. We showed a correlation between Ccr reduction and the renal radiation dose in the follow-up period. We also revealed the relationships decreased Ccr and bilateral kidney V20, bilateral kidney V25, and right kidney V20.

Adjuvant post-operative chemotherapy and abdominal RT have been used in the management of locally advanced gastric cancer to improve local control and survival rates. Radiation-associated renal toxicity has been recognized as one of the most important dose-limiting factors in abdominal RT.[12] Acute toxicity may occur between 6 and 12 months after RT and is usually subclinical.[13] The late kidney damage emerges after 18 months, with a longer period may be required for the development of symptomatic nephropathy. In our study, Grade 2 renal toxicity was developed in five patients, during the 48 months follow-up period, while none of the patients had renal failure or requiring hemodialysis. Human studies on kidney toxicity of adjuvant CRT in gastric cancer are limited and these studies also have relatively short follow-up period. Yavas et al.[6] demonstrated in 12 months of follow-up period that MKD >1500 cGy and basal GFR <90 mL/min/1.73 m^2 were associated with an increased risk of decreased GFR at 12 months in 59 gastric cancer patients who underwent post-operative CRT. Inaba et al.[8] showed in 38 patients with primary gastric diffuse large B-cell lymphoma treated with CRT that Ccr and kidney parenchymal volumes decreased 4 years after CRT. They found the mean Ccr values to be 82.7 mL/min before treatment and 70.4 mL/min 4 years after CRT. They also demonstrated 12% reduction of RPR volumes in the same period. These results were consistent with our study. To show the possible toxicity, we followed all patients for at least 4 years in our study. We found similar reduction of Ccr and RPR volume in our patient group. This indicates that a progressive decline in renal function may occur in gastric cancer patients after adjuvant post-operative CRT. However, we could not observe these declines in clinically. None of the patients had symptomatic nephropathy. It may have been due to the compensatory response of the other kidney or asymptomatic course of renal damage. Other cofactors and comorbidities including diabetes and hypertension may also complicate the course of renal failure of RT. However, none of the patients had diabetes and hypertension in our study.

The use of nephrotoxic chemotherapeutic agents, such as cisplatin, with abdominal RT in the adjuvant treatment of gastric cancer can reduce renal tolerance and lead to renal toxicity. Welz et al.[14] showed in 27 gastric cancer patients with treated cisplatin before and after simultaneous FU and RT in 26 months of follow-up period that Ccr tended to worsen overtime. Therefore, all patients in our study received only 5-FU-based chemotherapy, which was safer and had fewer renal side effects.

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Total renal radiation dose has an important impact on renal function, and several studies have shown a relationship between renal radiation dose and renal function. A comprehensive review of 12 studies revealed that the total dose was the only significant variable associated with increased renal toxicity after total body irradiation in adults.[15] Inaba et al.[8] showed that kidney $D_{30\%}$ <19 Gy and V_{20Gy} <26.6% should be obtained to achieve safe dose constraints for a lower Ccr reduction. May et al.[16] showed in 164 patients with gastrointestinal malignancies who were treated with CRT that V10 and mean kidney radiation dose were found to be related to Ccr reduction 1 year after treatment. Jansen et al.[17] demonstrated renal function by renography in 44 gastric cancer patients treated with post-operative CRT and observed a progressive decrease in left kidney function during the 18-28 month follow-up, as well as a relationship between the mean left kidney dose and left kidney V20 and decreased kidney function. Kaydihan et al.[18] revealed in 22 gastric cancer patients that V5 and V10 of the left and bilateral kidneys were related with GFR decline. Diavolitsis et al.[19] observed a significant correlation between decreased Ccr and all DVH parameters including V5, V10, V20, and absolute volume of kidney in 125 patients with gastrointestinal malignancies treated with RT, with a median follow-up of 2.4 years and MKD of 16.2 Gy. In our study, we examined Ccr, kidney parenchymal volume, and DVH to demonstrate the late effects of adjuvant CRT. We showed a relationship between total renal dose and reductions of Ccr. This indicates that the onset and extent of renal failure are dose dependent in gastric cancer patients after CRT. We also found that the patients with Ccr reduction of >10% had significantly higher total renal dose, higher V20, V25, and right kidney V20 values. Although no statistically significant difference was found except V20 in our study, the right kidney DVH parameters tended to be higher in patients with >10% Ccr reduction. Therefore, it can postulate that the right kidney's V20 value may affect the compensatory response of the right kidney. It also indicates that the irradiated or low dose irradiated kidney has an important, compensatory response feature after contralateral, whole volume, and high-dose irradiation.

Abdominal RT is commonly delivered using CT-based treatment planning including 3D-CRT or IMRT. The standard target dose of 45 Gy limits the ability to deliver higher doses, exceeding the tolerance of some critical normal tissues. Studies have shown that fewer side effects can be achieved with IMRT due to lower kidney and other surrounding tissue doses.[20] IMRT may allow higher doses to increase control and reduce acute toxicity by limiting the dose to normal structures.[20] Wieland et al.[21] showed that median renal dose can be reduced by >50% with IMRT compared with 3D planning. Minn et al.[20] demonstrated a comparison of IMRT and 3D-CRT as adjuvant therapy for gastric cancer and found similar survival rates and Grade >2 acute gastrointestinal toxicity, indifferent serum creatinine levels between two groups. In addition, Chopra et al.[22] compared 3D-CRT and IMRT in 51 patients with gastric cancer patients and found no difference between 3D-CRT and IMRT in terms of gastrointestinal, hematological or renal toxicity, as well as local relapse and overall survival. In our study, 3D-CRT was generated in seven patients and IMRT was designed in 27 patients. Since the number of patients treated with 3D-CRT is low, we did not compare the effect of 3D-CRT and IMRT on kidney function.

The study has some limitations. First, because of the nature of retrospective study design, our analyses did not include the homogeneous data. Second, the study involved the small patient numbers and relatively short follow-up. Third, we did not compare 3D-RT and IMRT in our study group. Third, we examined on the patients with similar ethnicity (Turkish population). Thus, the results may not be representative of the general population of gastric cancer treated with post-operative CRT.

Conclusion

We observed long-term progressive renal toxicity with both functional and imaging tests after post-operative adjuvant CRT in locally advanced gastric cancer. We also demonstrated that decline in renal function was associated with bilateral and compensatory kidney radiation dose and volume. For RT planning, bilateral and compensatory kidney radiation dose and volume might be evaluated for safe dose constraints and may be useful for predicting late kidney toxicity.

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Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Bulent Ecevit University Clinical Research Ethics Committee and were conducted in agreement with the ethical standards specified in the Declaration of Helsinki (No: 2018-118-11/04, Date: 11/04/2018).

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