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Scientific Article

Analysis of Chronic Kidney Disease After Radiation Therapy for Gastric/Duodenal Mucosa-Associated Lymphoid Tissue Lymphoma

Tsuyoshi Katsuta, MD,[a,1,*] Kanji Matsuura, MD, PhD,[b] and Kozo Kashiwado, MD, PhD[a]

[a]Department of Radiation Oncology, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Sendamachi, Naka-ku, Hiroshima City, Hiroshima, Japan; [b]Department of Radiation Oncology, Hiroshima City Hospital Organization, Hiroshima City Hiroshima Citizens Hospital, Motomachi, Naka-ku, Hiroshima City, Hiroshima, Japan

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Abstract

Purpose: This study aimed to evaluate the relationship between chronic kidney disease (CKD) after radiation therapy for gastric/duodenal mucosa-associated lymphoid tissue lymphoma and dose-volume histogram of the kidneys.

Methods and Materials: We retrospectively reviewed 40 patients who received 3-dimensional conformal radiation therapy. CKD was evaluated using the Common Terminology Criteria for Adverse Events version 5.0. The mean dose of bilateral kidneys/right kidney/left kidney ($D_{mean\ of\ b\text{-}kidneys}$) ($D_{mean\ of\ r\text{-}kidney}$) ($D_{mean\ of\ l\text{-}kidney}$), bilateral kidneys/right kidney/left kidney volume receiving ≥ x Gy ($V_{x\ of\ b\text{-}kidneys}$) ($V_{x\ of\ r\text{-}kidney}$) ($V_{x\ of\ l\text{-}kidney}$), and patients' baseline clinical characteristics were analyzed.

Results: The median radiation therapy dose was 28 (range, 24-44.8) Gy in 14 fractions. The median follow-up period was 63.1 months, and the 5-year cumulative incidence of grade 2 CKD rate was 14.8%. Among several factors, $V_{5\ of\ b\text{-}kidneys}$ was most strongly associated with grade 2 or worse CKD, with an area under the curve of 0.81 in the receiver operating characteristic curve. The 5-year incidence rate in patients with $V_{5\ of\ b\text{-}kidneys} \geq 58\%$ was significantly higher than that in other patients (24.5% and 9.8%, respectively; $P < .05$).

Conclusions: In this study using 3-dimensional conformal radiation therapy, the rate of adverse events at 5 years was low, many patients showed toxicity after 5 years; thus, continuous follow-up is necessary to detect potential nephrotoxicity. Our data demonstrate that $V_{5\ of\ b\text{-}kidneys}$ was most strongly associated with the risk of CKD. With lower doses and more advanced techniques in recent years, the incidence of CKD may be further reduced.

Introduction

"Mucosa-associated lymphoid tissue" (MALT) is a generic term for the lymphatic systems present in the mucosal membranes of the salivary glands, gastrointestinal tract, and bronchi. Isaacson and Wright[1] described MALT lymphoma as a low-grade malignant lymphoma that originates from MALT and is frequently associated with underlying inflammation. An association with *Helicobacter pylori* (*H. pylori*) infection has been noted, and

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*Corresponding author: Tsuyoshi Katsuta, MD; E-mail: stroke07makes.perfect@gmail.com

[1] Present address: Department of Radiation Oncology, Graduate School of Biomedical and Health Sciences, Hiroshima University.

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eradication therapy often results in resolution of the disease.[2,3] For *H. pylori*-negative patients or patients who have not responded to eradication therapy, the National Comprehensive Cancer Network guidelines recommend involved site radiation therapy (ISRT) as a local treatment for organ preservation,[4] and several studies have shown excellent clinical outcomes.[5-10]

Radiation-associated kidney disease is one of the late complications of radiation therapy (RT) to the abdominal region and is characterized by increased serum creatinine levels, proteinuria, anemia, and hypertension.[11,12] The incidence of the disease is not known owing to its high latency. There are also less data available on volumetric effects of more advanced irradiation techniques than on 3-dimensional conformal radiation therapy (3D-CRT).

Current recommendations for the treatment of localized MALT lymphoma suggest the use of ISRT alone,[4] as it is associated with excellent outcomes. Chemotherapy is typically not indicated because it could cause toxicities including renal damage. In addition, ISRT has a good prognosis and can be followed up for a long period, which enables us to gain more insight into the clinical data of chronic kidney disease (CKD).

This study does not represent the rate of CKD toxicity associated with current RT for gastric MALT, which is currently treated with lower doses and more sophisticated irradiation techniques. However, examining the relationship between factors related to previous irradiation and renal damage may be helpful for future treatment planning. Here, we report a retrospective analysis of CKD after 3D-CRT for gastric/duodenal MALT lymphoma.

Methods and Materials

Patients

A total of 65 patients with stage I to Ⅱ gastric/duodenal MALT lymphoma were treated with RT at our institution between January 2002 and December 2019. A retrospective study was conducted with data collected from the patients' medical records. The selection criteria were as follows: treatment with 3D-CRT, available analyzable dose-volume histogram (DVH) data, and follow-up period of at least 6 months. Patients with decreased renal function before RT were excluded from the study. Accordingly, 40 patients met the selection criteria and were included in the study. This study was approved by the independent local medical ethics committee and was designed in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice and the Declaration of Helsinki.

Treatment

All patients included in the study were treated with 3D-CRT, which was planned using a 3D radiation treatment planning system. We used the Cadplan (Varian Medical Systems, Palo Alto, CA) planning system before March 2013 and the Eclipse (Varian Medical Systems) system after March 2013. Patients underwent computed tomography (CT) for 3D-CRT after a minimum fasting period of 4 to 6 hours. The clinical target volume was defined as the entire stomach or duodenum, including the perigastric lymph nodes. The planning target volume (PTV) included the clinical target volume and additional margins to account for internal organ motion and set-up errors. Before April 2017, PTV margins were employed with approximately 1.5-cm superior and 2- to 3-cm inferior directions. After April 2017, we used 4-dimensional CT (4D-CT) to estimate the respiratory movement of the stomach, and a suitable PTV margin was set for each patient. RT was delivered on a linear accelerator using a 6- to 10-MV photon beam via noncoplanar static 3 or 4 fields to avoid the kidneys. A comparison of the dose distributions with a noncoplanar static 4 fields and anterior-posterior/posterior-anterior parallel-opposed fields is shown in Supplementary Materials Figure E1.

Before and after the introduction of 4D-CT, RT was planned on free breathing CT and the kidneys were contoured on it, without taking into account respiratory movement. The mean radiation doses of the bilateral kidneys ($D_{\text{mean of b-kidneys}}$), mean dose of the right/left kidney ($D_{\text{mean of r-kidney}}$) ($D_{\text{mean of l-kidney}}$), $V_{x\ Gy}$ of the bilateral kidneys ($V_{x\ \text{of b-kidneys}}$), and $V_{x\ Gy}$ of the right/left kidney ($V_{x\ \text{of r-kidney}}$) ($V_{x\ \text{of l-kidney}}$) were calculated using DVH analyses. $V_{x\ Gy}$ was defined as the percentage of the specified kidney portion irradiated with more than x Gy. $V_{5-25\ \text{of b-kidneys}}$, $V_{5-25\ \text{of r-kidney}}$, and $V_{5-25\ \text{of l-kidney}}$ were calculated.

Endpoints, follow-up, and statistics

Chronic RT-associated kidney disease was assessed using the rate of decline in the glomerular filtration rate (GFR). The GFR of each participant was calculated using serum creatinine (S-Cr) levels and age with the Japanese-coefficient-modified modification of diet in renal disease study equation as follows[13]:

$$\text{GFR}\left(\text{mL}/\text{min}/1.73\text{m}^2\right) = 0.881 \times 186 \times \text{age}^{-0.203} \times \text{S} - \text{Cr}^{-1.154}(\text{for females} \times 0.742)$$

The endpoint of the follow-up period was grade 2 (G2) or worse CKD (GFR < 60 mL/ min/1.73 m^2 for ≥ 3 months)[14] according to the Common Terminology Criteria for Adverse Events, version 5.0.

Patients underwent blood tests before RT to ensure that there was no decrease in renal function. They were

followed up regularly during treatment and at intervals of approximately 6 to 12 months after RT.

The following clinical factors were investigated for associations with the risk of CKD events: sex (male vs female), age (continuous), diabetes mellitus (DM) (yes vs no), hypertension (yes vs no), smoking (yes vs no), receiving chemotherapy after radiation therapy (yes vs no), $D_{mean\ of\ b\text{-}kidneys}$, $D_{mean\ of\ r\text{-}kidney}$, $D_{mean\ of\ l\text{-}kidney}$, $V_{5-25\ of\ b\text{-}kidneys}$, $V_{5-25\ of\ r\text{-}kidney}$, and $V_{5-25\ of\ l\text{-}kidney}$ were included in the statistical analysis.

The cumulative rate of each adverse event (AE) was calculated from the end of treatment to the date of G2 CKD using the Kaplan-Meier method. Univariate analysis using Cox proportional hazards model was performed to test the association between the different factors and AEs. For multivariate analysis, the forward Wald procedure was performed using Cox proportional hazards model, which contained all significant variables in the univariate analysis ($P < .10$). The correlations among the DVH parameters were assessed using Pearson's correlation coefficient test. The area under the curve (AUC) of the receiver operating characteristic (ROC) curves was used to identify the dose-volume parameters that were most strongly associated with AEs. To detect the optimal cut-off values from the ROC curves, the point on the curve closest to the upper left corner was determined. In the analysis of the data, statistical significance was set at $P < .05$. All statistical analyses were performed using the Excel statistical software package, version 3.21 (Bell-curve for Excel; Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

The characteristics of the 40 evaluable patients are summarized in Table 1. After a median follow-up period of 63.1 months (95% confidence interval, 44.0-68.5 months), 36 patients survived and 4 patients died of causes other than MALT lymphoma. Seven patients had DM requiring medication, and 11 patients underwent regular examinations for hypertension. Sixteen patients had a history of smoking, 17 had none, and 7 were unknown. Two patients received chemotherapy after RT; 1 had local and distant relapses 95 months after ISRT and received R-CHOP treatment (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone). G2 CKD was observed 106 months after initial treatment. The other patient developed intrahepatic bile duct cancer and received gemcitabine chemotherapy, without any treatment-induced decline in renal function.

During the observation period, the rate of GFR decline in all patients was 1.57 mL/min/1.73 m^2/year on average, which was higher than that of 0.36 mL/min/1.73 m^2/year on average in healthy Japanese individuals over 40 years of age.[15] Ten patients (25.0%) developed ≥ G2 CKD. Of the 10 patients, 2 (5.0%) developed G3 at 77 and 225 months after ISRT, respectively. None of the patients had a CKD higher than G4. After RT, 5 out of 10 patients showed G2 toxicity in 5 years, and the 5-year cumulative incidence rate was 14.8% (Fig 1). The median onset time of G2 CKD was 54.8 months (12.1-126.8 months). Among the 10 patients who developed ≥ G2 CKD, 1 patient had both DM and hypertension. None of the patients had DM only, and 3 had hypertension only. In contrast, in the 30 patients who did not develop CKD, 6 had DM only and 7 had hypertension only.

The results for the RT plans are shown in Table 2. The median total dose for PTV was 28 Gy (range, 24-44.8 Gy), $D_{mean\ of\ b\text{-}kidneys}$ was 9.0 Gy (range, 1.0-21.4 Gy), $D_{mean\ of\ r\text{-}kidney}$ was 5.5 Gy (range, 1.2-21.7 Gy), and $D_{mean\ of\ l\text{-}kidney}$ was 9.6 Gy (range, 0.9-25.5 Gy). $D_{mean\ of\ l\text{-}kidney}$ was higher than $D_{mean\ of\ r\text{-}kidney}$ in 34 of 40 cases.

Table 1 Patient and treatment characteristics and result of 3D-CRT for MALT lymphoma

Characteristic	No. of patients (N = 40)	(%)
Sex		
Male	19	48
Female	21	52
Age (years)		
Median	63	
Range	38-81	
Primary site		
Gastric	36	90
Duodenum	2	5
Gastric and duodenum	2	5
Lugano stage		
Ⅰ	35	88
Ⅱ1	3	7
Ⅱ2	2	5
DM		
Yes	7	17
No	33	83
Hypertension		
Yes	11	28
No	29	72
Smoking		
Yes	16	40
No	17	43
Unknown	7	7
Chemotherapy after radiation therapy		
Yes	2	5
No	38	95
Incidence of CKD		
Grade 0 or 1	30	75
Grade 2 or worse	10	25
Grade 3 or worse	2	5
Grade 4 or worse	None	

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; CKD = chronic kidney disease; DM = diabetes mellitus; MALT = mucosa-associated lymphoid tissue.

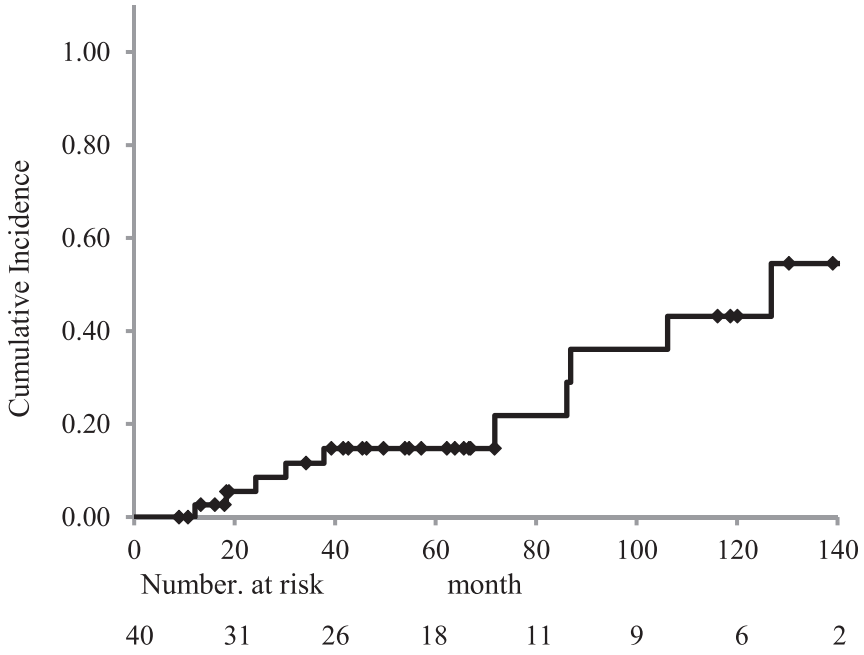

Fig. 1 Kaplan-Meier curves for the cumulative incidence rate of ≥ grade 2 (G2) chronic kidney disease (CKD). Censored case patients are shown as diamonds.

The results of univariate analysis are summarized in Table 3. As for the clinical characteristics, none of the factors were significant predictors of AEs. As for the DVH parameters, there were significant differences in $D_{mean\ of\ b\text{-}kidneys}$, $V_{5-10\ of\ b\text{-}kidneys}$, $V_{25\ of\ b\text{-}kidneys}$, $D_{mean\ of\ r\text{-}kidney}$, and $V_{5-25\ of\ r\text{-}kidney}$. These parameters closely correlated with each other when assessed using Pearson's correlation coefficient test (r: 0.536-0.970; $P < .001$); thus, we compared them using the AUC of the ROC curve (for the details of the ROC curve analysis of all DVH parameters, see Supplementary Materials). The parameter that was most strongly associated with AEs was $V_{5\ of\ b\text{-}kidneys}$, and the AUC was 0.810. The cut-off value was 58%, with sensitivity and specificity of 80% and 83.3%, respectively.

We performed the multivariate analysis including the following factors; gender, age, hypertension, and $V_{5\ of\ b\text{-}kidneys} \geq 58\%$, because gender and age were incorporated into the GFR formula,[13] and hypertension was marginally significant ($P = .071$; hazard ratio, 3.767) in the univariate analysis. The DVH parameters that were significant in univariate analysis strongly correlated with each other; therefore, $V_{5\ of\ b\text{-}kidneys} \geq 58\%$ was selected based on the ROC curve analysis. The results of multivariate analysis showed $V_{5\ of\ b\text{-}kidneys} \geq 58\%$ was a significant factor (hazard ratio, 4.96; 95% confidence interval, 1.0003-24.5712; $P = .04996$) (Table 4). The cumulative incidence rate of AEs according to the cut-off value of $V_{5\ of\ b\text{-}kidneys}$ is shown in Figure 2. The 5-year incidence rate in patients with $V_{5\ of\ b\text{-}kidneys} \geq 58\%$ was significantly higher than that in other patients (24.5% and 9.8%, respectively; $P < .05$).

The relationship between $V_{5\ of\ r\text{-}kidney}$ and $V_{5\ of\ l\text{-}kidney}$ to $V_{5\ of\ b\text{-}kidneys}$ was investigated. Among 10 patients

Table 2 Dose index and DVH parameters of 3D-CRT (n = 40)

Parameter	Median (range)		
The total dose for PTV (Gy)	28 (24-44.8)		
	b-kidneys	r-kidney	l-kidney
D_{mean} (Gy)	9.0 (1.0-21.4)	5.5 (1.2-21.7)	9.6 (0.9-25.5)
V_5 (%)	46.2 (1.8-97.0)	33.0 (0-96.0)	54.0 (1.6-100.0)
V_{10} (%)	34.5 (0-93.0)	24.9 (0-84.0)	38.5 (0-100.0)
V_{15} (%)	26.0 (0-87.0)	15.0 (0-73.0)	32.3 (0-100.0)
V_{20} (%)	14.3 (0-58.0)	5.5 (0-65.0)	18.3 (0-95.0)
V_{25} (%)	5.0 (0-32.5)	1.0 (0-52.0)	7.5 (0-45.0)

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; b-kidney = bilateral kidneys; D_{mean} = mean dose; DVH = dose-volume histogram; l-kidney = left kidney; PTV = planning target volume; r-kidney = right kidney; V_x = volume of the kidneys receiving a dose greater than x Gy.

Table 3 Univariate analysis of clinical and DVH factors influencing the incidence of ≥G2 CKD (N = 40)

Factor	HR (95% CI)	*P* value
Sex (male vs female)	1.858 (0.509-6.779)	.348
Age (continuous)	1.055 (0.984-1.131)	.135
DM (yes vs no)	0.489 (0.060-3.995)	.505
Hypertension (yes vs no)	3.767 (0.892-15.908)	.071
Smoking (yes vs no)	0.743 (0.193-2.863)	.667
Chemotherapy after RT (yes vs no)	1.487 (0.185-11.971)	.709
$D_{mean\ of\ b\text{-}kidneys}$	1.180 (1.002-1.390)	.047*
$V_{5\ of\ b\text{-}kidneys}$	1.053 (1.007-1.102)	.025*
$V_{10\ of\ b\text{-}kidneys}$	1.046 (1.004-1.090)	.033*
$V_{15\ of\ b\text{-}kidneys}$	1.037 (0.997-1.078)	.068
$V_{20\ of\ b\text{-}kidneys}$	1.035 (0.991-1.081)	.125
$V_{25\ of\ b\text{-}kidneys}$	1.068 (1.007-1.133)	.029*
$D_{mean\ of\ r\text{-}kidney}$	1.148 (1.031-1.277)	.012*
$V_{5\ of\ r\text{-}kidney}$	1.036 (1.008-1.064)	.011*
$V_{10\ of\ r\text{-}kidney}$	1.039 (1.009-1.068)	.009*
$V_{15\ of\ r\text{-}kidney}$	1.041 (1.009-1.073)	.011*
$V_{20\ of\ r\text{-}kidney}$	1.033 (1.001-1.066)	.043*
$V_{25\ of\ r\text{-}kidney}$	1.044 (1.006-1.085)	.025*
$D_{mean\ of\ l-kidney}$	1.043 (0.929-1.171)	.477
$V_{5\ of\ l\text{-}kidney}$	1.008 (0.980-1.038)	.582
$V_{10\ of\ l\text{-}kidney}$	1.006 (0.982-1.031)	.635
$V_{15\ of\ l\text{-}kidney}$	1.003 (0.979-1.027)	.833
$V_{20\ of\ l\text{-}kidney}$	1.005 (0.978-1.032)	.715
$V_{25\ of\ l\text{-}kidney}$	1.0037 (0.982-1.095)	.193

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; DM = diabetes mellitus; $D_{mean\ of\ b\text{-}kidneys}$ = mean dose of bilateral kidneys; $D_{mean\ of\ l\text{-}kidney}$ = mean dose of left kidney; $D_{mean\ of\ r\text{-}kidney}$ = mean dose of right kidney; DVH = dose-volume histogram; G2 = grade 2; HR = hazard ratio; RT = radiation therapy; $V_{x\ of\ b\text{-}kidneys}$ = volume of the bilateral kidneys receiving a dose greater than x Gy; $V_{x\ of\ l\text{-}kidney}$ = volume of the left kidney receiving a dose greater than x Gy; $V_{x\ of\ r\text{-}kidney}$ = volume of the right kidney receiving a dose greater than x Gy.
* $P < .05$.

with ≥ G2 CKD, the median values of $V_{5\ of\ r\text{-}kidney}$ and $V_{5\ of\ l\text{-}kidney}$ were 59.2% and 65%, respectively, which were both higher than the cut-off values obtained from the ROC curves (47% and 48%, respectively). However, among the 30 patients with < G2 CKD, the median value of $V_{5\ of\ l\text{-}kidney}$ was 48.9%, which was slightly higher than the respective cut-off value, whereas the median value of $V_{5\ of\ r\text{-}kidney}$ was 27.6%, which was lower than the respective cut-off value.

Table 4 Multivariate analysis of the incidence of ≥ G2 CKD (N = 40)

Factor	HR (95% CI)	*P* value
Sex (male vs female)	1.51 (0.347-6.539)	.5840
Age (continuous)	1.03 (0.942-1.116)	.5615
Hypertension (yes vs no)	2.24 (0.430-11.664)	.3386
$V_{5\ of\ b\text{-}kidneys} \geq 58\%$ (yes vs no)	4.96 (1.0003-24.5712)	.04996*

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; G2 = grade 2; HR = hazard ratio; $V_{x\ of\ b\text{-}kidneys}$ = volume of the bilateral kidneys receiving a dose greater than x Gy.
* $P < .05$.

Discussion

CKD is the main risk factor for end-stage renal disease, cardiovascular disease, and premature death.[16] The prevalence of CKD has increased in recent years[17] and has become a significant public health problem worldwide. DM, hypertension, metabolic syndrome, and radiation exposure of the kidneys is one of the risk factors for CKD.[18-21] In a study examining renal function among survivors of the Nagasaki atomic bomb blast, it was reported that higher radiation doses were likely to cause CKD, and the risk increased 1.29 times for every 1 Sv of additional exposure.[22]

In our study of CKD after ISRT for gastric/duodenal MALT lymphoma, G2 AEs were observed in 10 patients (25.0%) and G3 in only 2 patients (5.0%). There were low rates of serious AEs; however, 5 of 10 patients (50.0%) developed G2 after ≥5 years from RT. Radiation nephropathy is characterized by its development over an extended period, usually presenting months to years after radiation exposure. This latency is associated with slower cell turnover rates in renal tissues than in early responding tissues such as the gastrointestinal epithelium or bone marrow.[23] Thompson et al[24] reported that the frequency of renal dysfunction was higher after 5 years than within 5 years of RT, and a similar trend was observed in the current study. Therefore, long-term monitoring of renal function is essential.

Several reports have been published on the relationship between radiation dose and nephropathy. Regarding whole kidney irradiation, Cheng *et al.* performed a comprehensive review of 12 studies reporting on renal dysfunction after total body irradiation and found a 5% risk with an average dose of 10 Gy.[25] Regarding partial kidney irradiation, there were several reports on CT-based planning,[26,27,28,29,30] although the observation period for most of them was less than 5 years. The relationship between renal damage and the dose index over longer periods of time is not known. In this study, we found a 9.8% risk of injury at 5 years when $V_{5\ of\ b\text{-}kidneys}$ was < 58%. This dose index appeared to be more restrictive than the constraints reported by Enami et al.[31] Several causes may have led to this result. First, as we have been observing the patients for a long period of time (more than 5 years), we could detect potential renal dysfunction. Second, we used different endpoints from previous studies, which may have affected the results. In previous reports, various endpoints were applied,[30] including subclinical categories such as elevated serum β_2

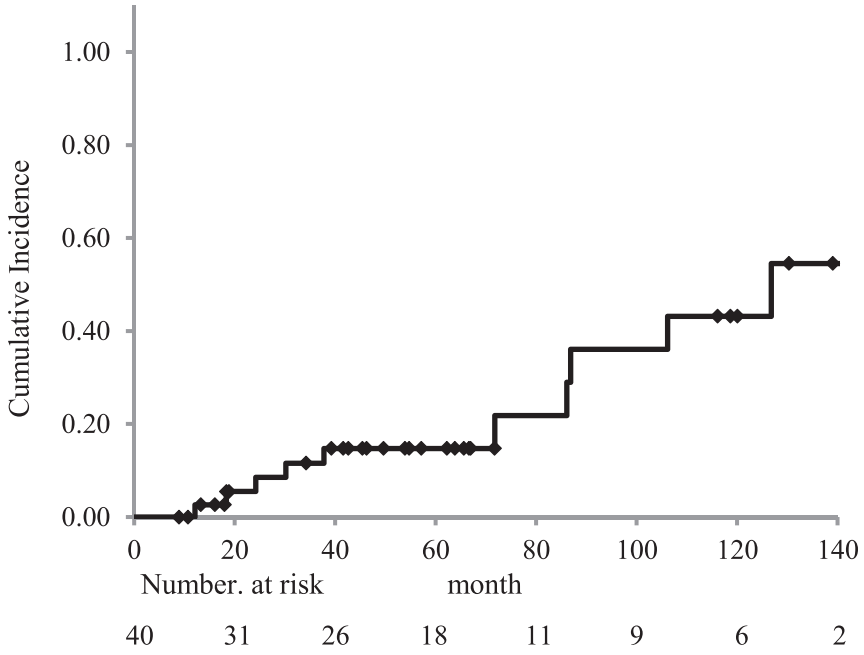

Fig. 2 Cumulative incidence of chronic kidney disease ($P = .018$). Dotted line: $V_{5\ of\ b\text{-}kidneys} \geq 58\%$ and solid line: $V_5 < 58\%$. Censored case patients are shown as diamonds.

macroglobulin, elevated serum creatinine levels, and scintigraphy-image changes and clinical categories such as malignant hypertension and edema. GFR-based grading has now been recommended,[16] which we have followed in our study. Finally, we did not examine the functional aspects of the kidneys using renal scintigraphy before RT; therefore, the results could have been different if the irradiation of the functional kidney was biased.

Our results suggest that it is necessary to assess not only the entire kidney dose but also the right and left kidneys separately. In most cases, the right kidney dose was lower than the left kidney dose, and reducing the right kidney as well as the bilateral kidney dose was effective in preventing CKD. Specifically, in the case of $V_{5\ of\ b\text{-}kidneys}$ exceeding 58%, it was suggested to maintain $V_{5\ of\ r\text{-}kidney}$ below 47%. 3D-CRT is superior to anterior-posterior-posterio-anterior parallel-opposed fields for sparing kidneys,[32] and we used noncoplanar static 3 or 4 fields to avoid the kidneys as much as possible. In the future, intensity modulated RT and volumetric modulated arc therapy are expected to create more accurate and flexible dose distribution. Compared with 3D-CRT, these recent techniques have the potential to reduce the kidney dose, especially in patients with anatomic overlap between their PTV and both kidneys.[32,33] In addition, other radiation techniques, such as breath-hold irradiation, are also useful. Because of the proximity of the stomach to the diaphragm, respiration can influence gastric motion.[34] Deep-inspiration breath-hold can limit respiratory-induced gastric motion and facilitate the use of smaller PTV margins.[35]

It is also effective to consider a reduction in the prescribed dose to reduce organ-at-risk dose exposure. Doses of 30 to 45 Gy have been used in the past to treat gastric MALT patients.[5] Given the highly favorable outcomes of ISRT with a dose < 30 Gy, dose de-escalation has been considered. Tsang et al[7] found that doses of 25 to 30 Gy yielded good local control, and Pinnix et al[36] reported no difference in the 2-year local control and overall survival between reduced dose groups of 24 Gy and dose groups of ≥ 30 Gy. Therefore, the National Comprehensive Cancer Network guidelines recommend ISRT at 24 Gy as well as 30 Gy in 20 fractions.[4] Furthermore, it has been reported that complete remission was observed in 61% of patients with low-grade lymphoma including MALT lymphoma, even at a low dose (2 × 2 Gy), and it might be possible to treat with even lower doses in some cases.[37] At our institution, some patients with gastric MALT lymphoma were treated with doses lower than 30 Gy, with good results. We would like to continue low-dose RT to reduce the renal dose in the future.

Aging is a confounding factor in long-term follow-up periods as it causes a physiological decline in GFR. It is known that renal function in people in their 80s can drop to 60% of that in people in their 30s,[38] with an average decrease in GFR of 0.36 mL/min/1.73 m^2/year.[15] Our study group showed an average decline in GFR of 1.57 mL/min/1.73 m^2/year, which was greater than the value of physiological decline, indicating an effect of RT.

The present study has some limitations. We hypothesized that RT caused a decline in GFR and renal function. However, there were many causes of CKD, such as

glomerulonephritis.[39] Information available in the medical records was added to adjust for confounding factors, but owing to the limited number of patients, it was not possible to account for all of them. Regarding DM and hypertension, we also lacked information on the degree of control by specific values such as hemoglobin A1c or blood pressure. Owing to the retrospective nature of the study, the possibility of bias could not be ruled out. However, because the cumulative incidence of long-term renal toxicity of ISRT for gastric/duodenal MALT lymphoma has not been well described, we believe that our study has value. Furthermore, the concept of avoiding low dose irradiation to the kidneys derived from this study could be applied, with a good prognosis, not only to gastric/duodenal MALT but also to other diseases such as indolent lymphoma or seminoma.

Conclusions

In this study using 3D-CRT, the rate of AEs at 5 years was low, many patients showed toxicity after 5 years; thus, continuous follow-up is necessary to detect potential nephrotoxicity. Our data demonstrate that V5 of b-kidneys was most strongly associated with the risk of CKD. To prevent CKD, it is also important to reduce the right kidney dose as well as the bilateral kidney dose. With lower doses and more advanced techniques developed in recent years, the incidence of CKD may be further reduced.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.adro.2021.100788.

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