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Radiotherapy plus cetuximab for locally advanced squamous cell head and neck cancer in patients with cisplatin-ineligible renal dysfunction: A retrospective study

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Abstract. Clinical trials have not fully demonstrated the efficacy and safety of radiotherapy plus cetuximab for locally advanced squamous cell head and neck cancer (LA-SCCHN) in patients with cisplatin-ineligible renal dysfunction. Patients who received radiotherapy plus cetuximab for LA-SCCHN at Chiba University Hospital (Chiba, Japan) between July 2013 and October 2018 were retrospectively reviewed. Background characteristics and locoregional control and overall survival rates were compared between patients with and without renal dysfunction. Survival was examined using Kaplan-Meier analysis and an adjusted Cox proportional hazards model. Kaplan-Meier analysis demonstrated that overall survival was shorter in patients with creatinine clearance of <45 ml/min (P=0.041; log-rank test). However, there was no difference in the locoregional control rate (P=0.477; log-rank test). Adjusted Cox analysis revealed that the risk of death was increased by 2.52-fold (hazard ratio, 2.52; 95% confidence interval, 1.01-6.30; P=0.048) if creatinine clearance was <45 ml/min. Moderate to severe renal dysfunction did not affect the locoregional control rate in patients with LA-SCCHN treated with radiotherapy plus cetuximab but was an adverse prognostic factor.

Introduction

Definitive radiotherapy combined with cisplatin is widely used for locally advanced squamous cell cancer of the head and neck (LA-SCCHN) based on Phase III trials showing better survival compared with radiotherapy alone (1-5). However, cisplatin is highly nephrotoxic and difficult to administer in patients with impaired renal function (6). The standard, primary curative treatment for LA-SCCHN is radiotherapy plus cisplatin, which must be administered at high doses (100 mg/m^2 at 3-week intervals, a total dosage ≥200 mg/m^2) (7,8). However, in patients with reduced renal function, alternative drugs may be required. In a randomized Phase III trial evaluating primary treatment of LA-SCCHN (9), locoregional control and overall survival were better in patients who received the combination of radiotherapy and cetuximab compared with radiotherapy alone. Also, a subsequent analysis found that quality of life scores were not significantly lower in the group that received cetuximab plus radiotherapy compared with the group that received radiotherapy alone (10). Another study found that the 5-year survival rate was approximately 9% higher in patients with LA-SCCHN who received radiotherapy plus cetuximab than in those who received radiotherapy alone (45.6% vs. 36.4%) (11).

Cetuximab is an immunoglobulin-based monoclonal antibody that is not metabolized or excreted via the kidney. There are two routes via which antibody preparations can be eliminated from the body. In the first, antibodies are taken up by reticuloendothelial cells in the liver and spleen, where some of the preparation is degraded and the rest becomes bound to the neonatal Fc receptor and recycled into plasma. In the second, antibodies can be taken up by cells expressing the target molecule and phagocytosed by immune cells (12). These elimination routes do not affect renal function, meaning that dose adjustment according to renal function is unnecessary. According to some case reports, the pharmacokinetics of cetuximab do not differ between patients with renal dysfunction and those with normal renal function. Similar results were reported from population pharmacokinetics analyses (13-15). In phase III clinical trials for LA-SCCHN, the only treatment other than platinum-based chemotherapy (3,16,17) to be compared with radiation alone was a cetuximab-based

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regimen (9). Thus, cetuximab may be considered in patients with LA-SCCHN who have renal dysfunction and cannot tolerate administration of cisplatin. However, there is still no detailed information on the efficacy and safety of cetuximab when used in combination with radiotherapy in these patients.

Cetuximab is classified as a biologic agent and has a radiosensitizing effect (18-20). It is approved for the treatment of squamous cell carcinoma of the head and neck and has a toxicity profile different from that of cytotoxic agents (21-25). Therefore, if radiotherapy and cisplatin cannot be administered because of renal dysfunction, we may choose to use radiotherapy plus cetuximab. However, there are reports indicating that radiotherapy plus cetuximab is not as effective as radiotherapy plus cisplatin in LA-SCCHN (21,23-29). Furthermore, a Phase II clinical study found that acute toxicity was increased and adherence was reduced in patients who received radiotherapy plus cetuximab (22). The toxicity of cetuximab is generally manageable (30-32), but severe toxicity has been observed (33,34). Therefore, guidelines recommend that the use of cetuximab instead of cisplatin must be carefully considered (35).

The randomized Phase III trials to date have excluded patients with renal dysfunction and have not confirmed the efficacy or safety of radiotherapy plus cetuximab in these patients (9). Unlike the populations typically enrolled in clinical trials, patients with LA-SCCHN encountered in actual clinical practice often have multiple comorbidities and adverse prognostic factors. Accordingly, in this study, we investigated the effects of renal dysfunction on locoregional control and overall survival in patients with LA-SCCHN who were treated with the combination of radiotherapy and cetuximab. Our aim was to determine whether this combination is safe and effective in these patients.

Patients and methods

Patients. Patients eligible for inclusion in this single-center retrospective study were those with stage III-IVB LA-SCCHN with primary sites in the hypopharynx, larynx, and oropharynx who received radiotherapy plus cetuximab at primary treatment between July 2013 and October 2018. Patients with cancer in the nasal cavity, oral cancer, and salivary gland cancer were excluded. Stage I-II and metastatic or recurrent cases were also excluded. Patients were also ineligible if they had undergone surgery or had previously received radiotherapy for head and neck cancer. The maximum follow-up period was 5 years. Data on the following patient characteristics were collected: age, sex, performance status, comorbidities, primary site, human papillomavirus (HPV) status in cases of oropharynx carcinoma, clinical stage, tumor stage, lymph node stage, laboratory data, creatinine clearance (CrCl, calculated by the Cockcroft-Gault formula), treatment after disease progression, smoking history (Brinkman index), and history of alcohol consumption. Comorbidities were quantified using the Charlson Comorbidity Index (CCI) (36). Details of the cetuximab and radiation doses used were collected from medical records.

Definition of moderate to severe renal dysfunction. We compared the prognosis after radiotherapy plus cetuximab between patients with moderate to severe renal dysfunction (CrCl <45 ml/min), in whom cisplatin is generally avoided or a significant dose reduction (50% reduction) is required (37), and those with normal renal function.

Treatment plan. All patients received concurrent radiotherapy plus cetuximab. Cetuximab was administered at a loading dose of 400 mg/m^2 followed by 250 mg/m^2 starting the following week. The planned total radiation dose was 70 Gy (2 Gy/day, 5 days/week). Radiotherapy was delivered using intensity-modulated radiotherapy or three-dimensional conformal radiotherapy. If chemoradiation enabled removal of residual disease, salvage surgery was performed.

Assessment of safety and efficacy. We collected data on the reasons for postponing or discontinuing radiotherapy and/or cetuximab as an indicator of safety. We also compared the degree of change in clinical laboratory values before and during treatment. Toxicities during treatment as confirmed by laboratory data were defined according to the Common Terminology Criteria for Adverse Events, version 5.0. Locoregional control and overall survival were compared between patients with CrCl <45 ml/min (moderate to severe renal dysfunction) and those with CrCl ≥45 ml/min to evaluate effectiveness. The maximum observation period was 5 years. Patients for whom treatment details could not be obtained because of transfer to another hospital and those who continued treatment after the end of the observation period were censored. Locoregional control was defined as no progression of local disease during the follow-up period. Overall survival was calculated from the first day of treatment to death or to censoring for any reason. Overall survival time and locoregional control were compared between patients with and without renal dysfunction using the Kaplan-Meier method and the log-rank test. Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for background factors contributing to overall survival identified in univariate and multivariate analyses. Subgroup analyses were performed in patients aged ≥70 years. Data were also collected on the response rate to treatment as evaluated by imaging studies as well as on recurrence or metastasis after treatment and subsequent treatment after disease progression. Treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (38). Categorical data were compared between groups using Fisher's exact test. Pre-treatment laboratory values and maximum values during treatment were compared using the paired *t*-test or the Wilcoxon rank-sum test. The degree of variation in laboratory values among patients with CrCl <45 ml/min and those with CrCl ≥45 ml/min was compared using the two-sample *t*-test or the Mann-Whitney *U* test. All statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp, Armonk, NY). Two-sided P-values of less than 0.05 were considered statistically significant.

This study was approved by the Ethical Committee of the Graduate School of Medicine, Chiba University (accession number 3419) and conducted in accordance with the ethical guidelines for medical research in humans in Japan. All patients provided written informed consent to receive radiotherapy plus cetuximab.

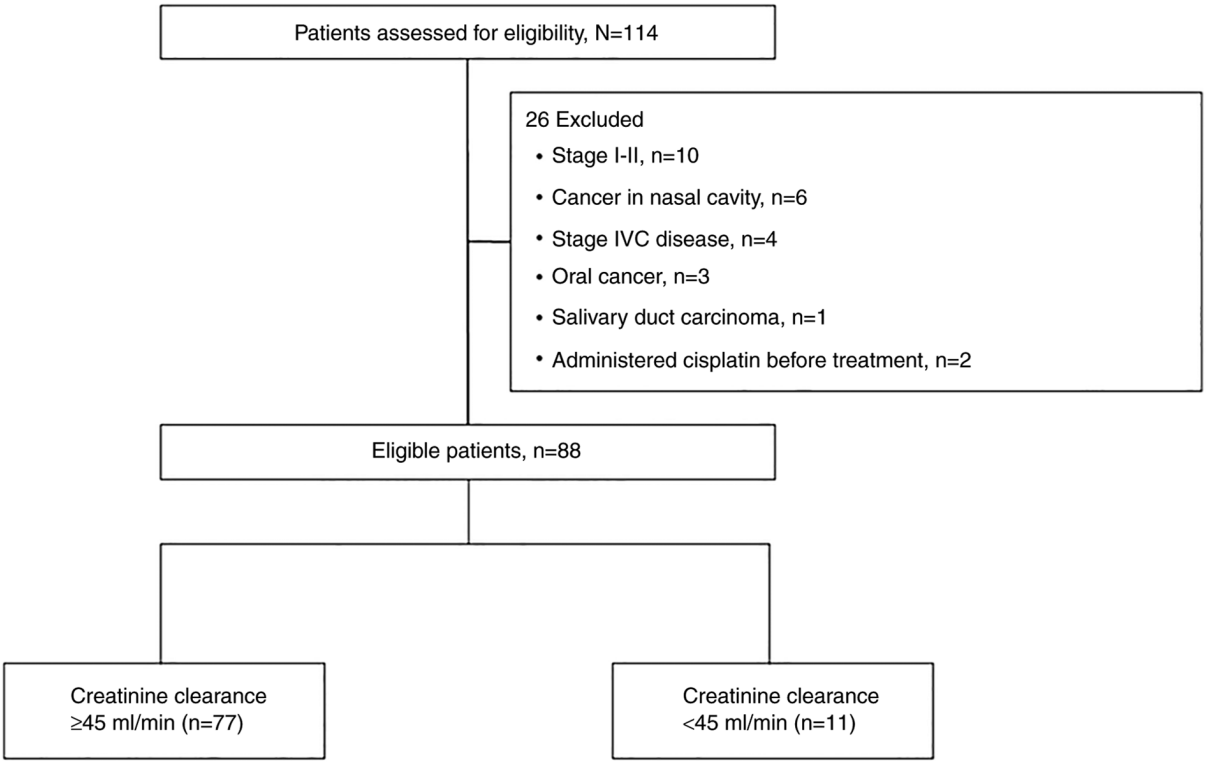

Figure 1. CONSORT flow diagram.

Results

Patient characteristics. The flow diagram of the study is shown in Fig. 1. The characteristics of the 88 patients included in the study are shown in Table I. Median age was 69 (range 48-84) years. CrCl was <45 ml/min in 11 patients. The group with CrCl <45 ml/min was significantly older than the group with CrCl ≥45 ml/min (median age 75 [range 71-84] years vs. 69 [range 48-81] years; P<0.0001). The proportion of patients with performance status of ≥2 tended to be higher in the group with CrCl <45 ml/min (18% vs. 4%, P=0.116). Mean CCI (± standard deviation) also tended to be higher in patients with CrCl <45 ml/min (1.82±1.54 vs. 1.08±1.19; P=0.066). There was no significant difference in patient background characteristics between the two groups or in primary site, clinical stage, T classification, N classification, Brinkman index, or alcohol use, which are generally regarded as prognostic factors for head and neck cancer.

Safety. The median number of cetuximab doses administered was significantly lower in the group with CrCl <45 ml/min (P=0.010). The reasons for discontinuing cetuximab in this group were deterioration of general condition (n=2), infection (n=2), fever (n=1), and infusion reaction (n=1). The median radiation dose was 70 Gy in both groups (Table I).

Reasons for postponing or discontinuing radiotherapy and/or cetuximab are shown in Table II. The incidence of fever tended to be higher in patients with CrCl ≥45 ml/min (P=0.259). Patients with CrCl <45 ml/min tended to be more likely to discontinue treatment because of worsening general condition (P=0.116). The incidence of oral mucositis was similar between the two groups (P=0.681). There was no significant difference between the groups in any of the items.

Fig. 2 shows a box-and-whisker plot of the changes in laboratory values (serum creatinine, hemoglobin, and albumin) from baseline. The degree of change in hemoglobin and albumin tended to be greater in patients with CrCl <45 ml/min, but the difference was not significant. However, the degree of change in serum creatinine was significantly greater in patients with CrCl <45 ml/min (median 0.19 [IQR 0.06-0.48] vs. 0.04 [−0.03-0.12]; P=0.006).

Association of response to treatment, locoregional control, and overall survival with CrCl. Assessment of post-treatment responses based on imaging studies evaluated according to the RECIST guidelines, there was no difference in the disease control rate between CrCl <45 ml/min and CrCl ≥45 ml/min (72% vs. 91%; P=0.107). There was no difference in the proportion of patients with metastasis or recurrence after treatment between the two groups (46% vs. 43%; P=0.406).

The data cutoff date for the final analysis of overall survival was December 10, 2019. The median follow-up period was 35.9 months. As of the cutoff date, 18.2% of patients with CrCl <45 ml/min and 20.8% of those with CrCl ≥45 ml/min were still under observation.

There was no difference in the locoregional control rate between patients with CrCl <45 ml/min and those with CrCl ≥45 ml/min (Fig. 3A). However, overall survival was significantly shorter in the group with CrCl <45 ml/min (Fig. 3B). Patients with moderate to severe renal dysfunction had median survival of 25.6 months when treated with radiotherapy plus cetuximab. Table III shows the HR for each patient characteristic identified as contributing to survival by univariate and multivariate analyses using a Cox proportional hazards model in all patients. Univariate analysis confirmed that CrCl <45 ml/min was a significant

Table I. Patient characteristics.

Variables	Total (n=88)	CrCl	
		<45 ml/min (n=11)	≥45 ml/min (n=77)
Median age, years (range)	69 (48-84)	75 (71-84)	69 (48-81)
Median CrCl, ml/min (range)[a]	72.4 (15.1-134.7)	38.8 (15.1-44.2)	75.9 (45.4-134.7)
Sex, n (%)			
Male	78 (89)	11 (100)	67 (87)
Female	10 (11)	0 (0)	10 (13)
Performance status, n (%)			
0-1	84 (96)	9 (82)	75 (96)
≥2	4 (4)	2 (18)	2 (4)
CCI, n (%)			
0	38 (43)	3 (27)	35 (45)
≥1	50 (57)	8 (73)	42 (55)
Primary site, n (%)			
Oropharynx	37 (42)	5 (45)	32 (42)
HPV-positive	10	2	8
HPV-negative	11	2	9
Unknown	16	1	15
Larynx or hypopharynx	51 (58)	6 (55)	45 (58)
T classification, n (%)			
T1	3 (3)	0 (0)	3 (4)
T2	32 (36)	3 (27)	29 (38)
T3	26 (30)	1 (9)	25 (32)
T4	27 (31)	7 (64)	20 (26)
N classification, n (%)			
N0	20 (23)	3 (27)	17 (22)
N1	6 (7)	1 (9)	5 (6)
N2	59 (67)	7 (64)	52 (68)
N3	3 (3)	0 (0)	3 (4)
Clinical stage, n (%)			
III	17 (19)	0 (0)	17 (22)
IVA-B	71 (81)	11 (100)	60 (78)
Treatment after disease progression, n (%)			
Yes	23 (26)	1 (9)	22 (29)
No	65 (74)	10 (91)	55 (71)
Brinkman index, n (%)			
<400	31 (35)	3 (27)	28 (36)
≥400	56 (64)	8 (73)	48 (62)
Unknown	1 (1)	0 (0)	1 (1)
Alcohol use, n (%)			
Yes	72 (82)	10 (91)	62 (80.5)
No	16 (18)	1 (9)	15 (19.5)
Median number of cetuximab cycles (range)	7 (1-9)	5 (1-8)	7 (1-9)
Median radiation dose, Gy (range)	70 (16-70)	70 (42-70)	70 (16-70)

[a]CrCl was calculated using the Cockcroft-Gault formula. CrCl, creatinine clearance; CCI, Charlson Comorbidity Index; HPV, human papillomavirus.

adverse prognostic factor (HR 2.48, 95% CI 1.01-6.12; P=0.048), as was CCI of ≥1 (HR 2.25, 95% CI 1.00-5.06; P=0.050). There was no statistically significant difference in prognosis between the two groups of patients over 70 years of age and under 70 years

Table II. Reasons for postponing or discontinuing radiation therapy or cetuximab.

Characteristics	Total, n (%) (n=88)	CrCl[a] <45 ml/min, n (%) (n=11)	CrCl[a] ≥45 ml/min, n (%) (n=77)
Fever	19 (21.6)	1 (9.1)	18 (23.4)
Oral mucositis	9 (10.2)	1 (9.1)	8 (10.4)
Pneumonia	6 (6.8)	0 (0.0.)	6 (8.8)
Aspiration pneumonia	4 (4.6)	0 (0.0)	4 (5.2)
Interstitial or aspiration pneumonia	1 (1.1)	0 (0.0)	1 (1.3)
Drug-induced neutrophil pneumonia	1 (1.1)	0 (0.0)	1 (1.3)
Deterioration of general condition	5 (5.7)	2 (18.2)	3 (3.9)
Salvage surgery	4 (4.6)	0 (0.0)	4 (5.2)
Dermatitis	3 (3.4)	1 (9.1)	2 (2.6)
Infusion reaction	2 (2.3)	1 (9.1)	1 (1.3)
Ileus or sub-ileus	2 (2.3)	2 (18.2)	0 (0.0)
Cardiac and vascular disorder	2 (2.3)	0 (0.0)	2 (2.6)
Neutropenia	1 (1.1)	0 (0.0)	1 (1.3)
Heart failure triggered by infection	1 (1.1)	1 (9.1)	0 (0.0)
Elevated hepatobiliary system enzymes	1 (1.1)	1 (9.1)	0 (0.0)
Urinary tract infection	1 (1.1)	0 (0.0)	1 (1.3)
Gastrointestinal bleeding	1 (1.1)	0 (0.0)	1 (1.3)

[a]CrCl was calculated using the Cockcroft-Gault formula. CrCl, creatinine clearance.

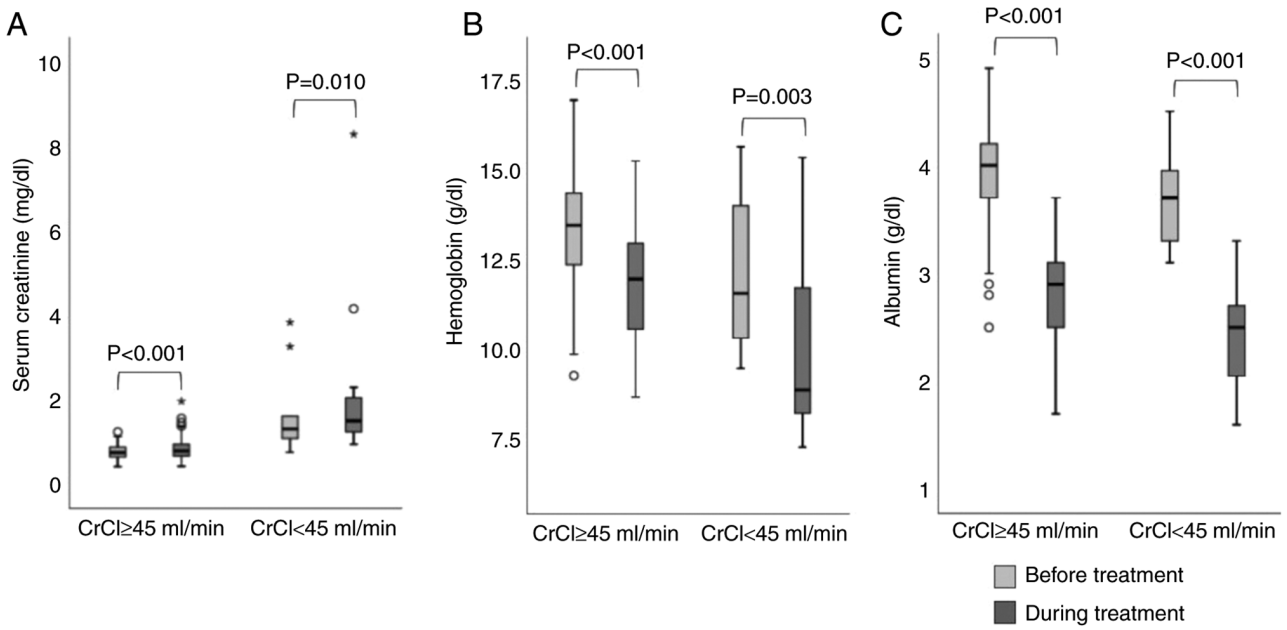

Figure 2. Box-and-whisker plots of change from baseline laboratory values. Levels of (A) serum creatinine, (B) hemoglobin and (C) albumin. Light colored boxes are values before treatment. Dark-colored boxes are maximum values during treatment. The divider in the box represents the median, the lower end of the box represents the lower quartile, the upper end of the box represents the upper quartile, and the ends of the whiskers represent the maximum and minimum values. Outliers are indicated by circles and asterisks. Circles indicate mild outliers (1.5-3 times the IQR). Asterisks indicate extreme outliers (>3 times the IQR). CrCl, creatinine clearance; IQR, interquartile range.

of age (HR 1.407, 95% CI 0.686-2.886; P=0.351). Multivariate analysis was performed by incorporating up to three variables into the Cox regression model based on the number of mortality events. Given that calculation of CrCl includes age, we performed the multivariate analysis without incorporating age and CrCl into one model. CCI includes items for moderate to severe renal dysfunction, but the definition is strict, with serum creatinine set as >3 mg/dl. Only two patients with CrCl <45 ml/min had a

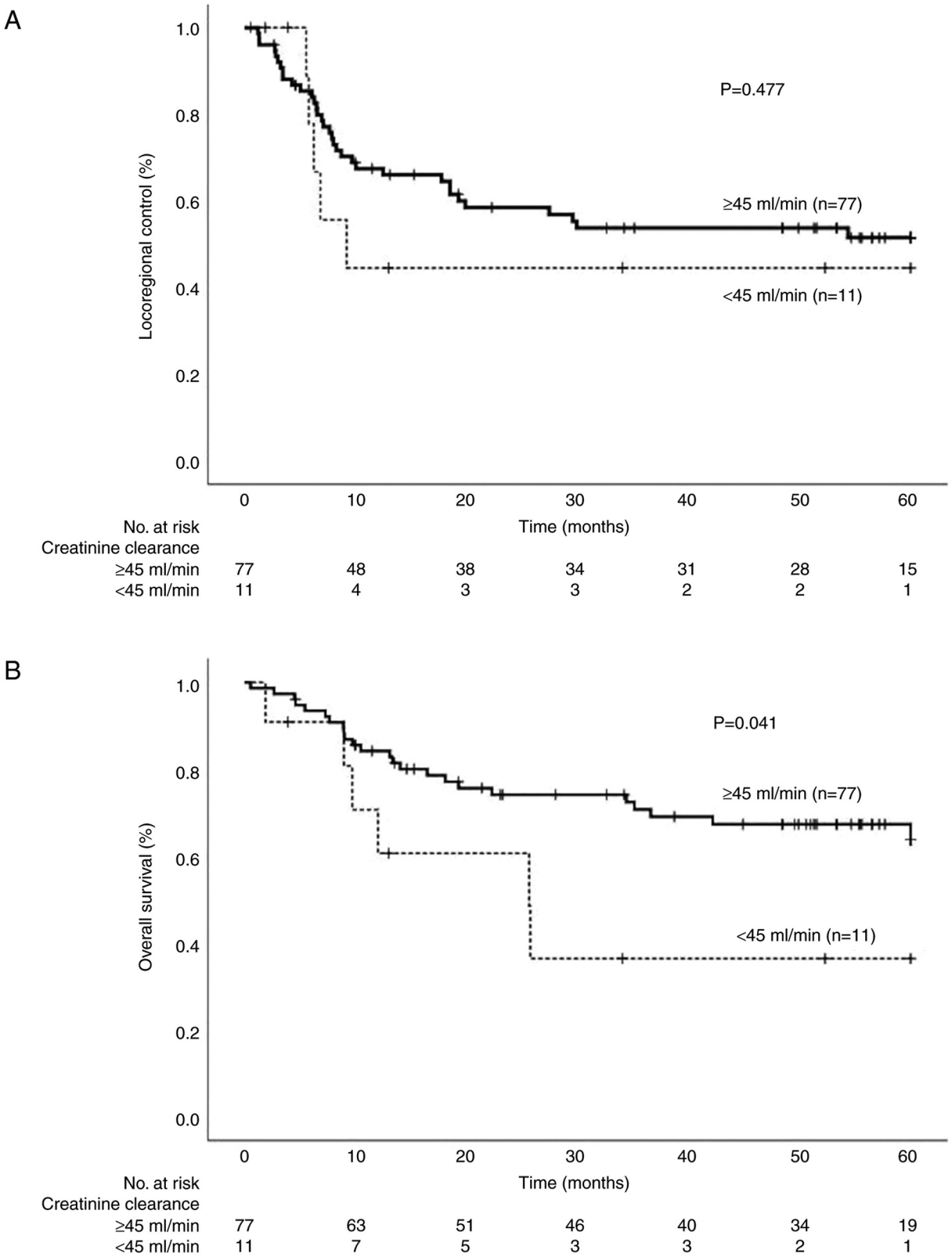

Figure 3. Kaplan-Meier curves for (A) locoregional control and (B) overall survival according to the presence or absence of renal dysfunction in patients with stage III-IVB locally advanced squamous cell head and neck cancer. The solid line indicates patients with CrCl ≥45 ml/min and the dotted line indicates those with CrCl <45 ml/min. P-values were calculated using the log-rank test. Cross marks on the solid and dotted lines represent censored patients (end of follow-up). CrCl, creatinine clearance.

serum creatinine level of >3 mg/dl. Furthermore, there was no correlation between CCI and whether CrCl was <45 ml/min. We added the primary site to the covariates because it is known to affect prognosis. For these reasons, we used the following three covariates in the multivariate analysis: whether the CCI score was ≥1, the primary site, and whether the CrCl was <45 ml/min.

Table III. Univariate and multivariate analyses of prognostic factors using a Cox proportional hazards regression model for overall survival in all patients.

	Univariate analysis		Multivariate analysis	
Variable	P-value	HR	P-value	HR
Age (years)	0.351			
<70		1		
≥70		1.41		
Sex	0.401			
Male		1		
Female		0.54		
Performance status	0.300			
0-1		1		
≥2		2.17		
CCI	0.050[a]		0.120	
0		1		1
≥1		2.25		1.93
Primary site	0.083		0.115	
Oropharynx		1		1
Larynx or hypopharynx		2.05		1.94
Clinical stage	0.389			
III		1		
IVA-B		1.53		
CrCl	0.048[a]		0.048[a]	
≥45 ml/min		1		1
<45 ml/min		2.48		2.52
Treatment after disease progression	0.123			
No		1		
Yes		2.48		
Brinkman index	0.602			
<400		1		
≥400		1.23		
Alcohol use	0.984			
No		1		
Yes		1.01		

[a]P<0.05 was considered to indicate a statistically significant difference. CrCl was calculated using the Cockcroft-Gault formula. CrCl, creatinine clearance; HR, hazard ratio; CCI, Charlson Comorbidity Index.

In the multivariate analysis, the significant association remained between shorter overall survival and CrCl <45 ml/min (adjusted HR 2.52, 95% CI 1.01-6.30; P=0.048).

Subgroup analysis in patients aged 70 years or older. As shown in Table III, age tended to affect prognosis, so we could not rule out the possibility that age was a confounding factor in the poorer prognosis seen in patients with CrCl <45 ml/min. Therefore, a subgroup analysis was performed in patients aged ≥70 years (Table IV). This cutoff was set because it was the median age in the full sample, meaning that about half the patients could be included in the subgroup analysis. In univariate analysis, the primary site was a significant prognostic factor (HR 9.37, 95% CI 1.24-71.03; P=0.03). CrCl <45 ml/min tended to be a marginally significant adverse prognostic factor (HR 2.45, 95% CI 0.88-6.83; P=0.086). In multivariate analysis, the primary site remained a significant prognostic factor (adjusted HR 13.56, 95% CI 1.73-106.67; P=0.013). After adjustment for primary site, CrCl <45 ml/min was a significant adverse prognostic factor (adjusted HR 4.16, 95% CI 1.39-12.46; P=0.011). There was no significant difference in mean CCI between patients with CrCl ≥45 ml/min and those with CrCl <45 ml/min (1.57±1.31 vs. 1.82±1.54; P=0.51).

Discussion

In this study, renal dysfunction did not affect locoregional control but had a significant effect on overall survival in

Table IV. Univariate and multivariate analyses of prognostic factors using a Cox proportional hazards regression model for overall survival in a subgroup of patients aged 70 years or older.

		Univariate analysis		Multivariate analysis	
Variables	Total, n (%) (n=41)	P-value	HR	P-value	HR
Sex		0.625			
Male	40 (98)		1		
Female	1 (2)		0.05		
Performance status		0.631			
0-1	38 (93)		1		
≥2	3 (7)		1.67		
CCI		0.184			
0	11 (27)		1		
≥1	30 (73)		2.74		
Primary site		0.030[a]		0.013[a]	
Oropharynx	14 (34)		1		1
Larynx or hypopharynx	27 (66)		9.37		13.67
Clinical stage		0.532			
III	9 (22)		1		
IVA-B	32 (78)		1.50		
CrCl		0.086		0.011[a]	
≥45 ml/min	30 (73)		1		1
<45 ml/min	11 (27)		2.45		4.16
Treatment after disease progression		0.558			
No	32 (78)		1		
Yes	9 (22)		1.41		
Brinkman index		0.287			
<400	14 (34)		1		
≥400	27 (66)		1.85		
Alcohol use		0.418			
No	5 (12)		1		
Yes	36 (88)		2.32		

[a]P<0.05 was considered to indicate a statistically significant difference. CrCl was calculated using the Cockcroft-Gault formula. CrCl, creatinine clearance; HR, hazard ratio; CCI, Charlson Comorbidity Index.

patients with LA-SCCHN treated with radiotherapy plus cetuximab. This finding may be a statistical artifact but could also reflect the impact of differences in patient characteristics. Patients with CrCl <45 ml/min tended to discontinue or postpone cetuximab or radiotherapy because of worsening general condition. These patients may have had background factors that affected their ability to tolerate this treatment. In general, this treatment may lead to feeding problems due to damage to the oral mucosa and dehydration due to the inability to drink water. Patients with impaired kidney function are more susceptible to the effects of dehydration. In our study, the magnitude of the change in serum creatinine during treatment in these patients was severe and treatment was poorly tolerated in most patients. Deterioration of renal function and general condition due to dehydration may lessen the feasibility of additional treatments if the disease progresses after treatment. In our study, only 9% of patients with CrCl <45 ml/min received therapy after disease progression. In contrast, 29% of patients with CrCl ≥45 ml/min received additional treatment. Furthermore, the fact that cisplatin can be used to treat disease progression in patients with CrCl ≥45 ml/min may have had a positive impact on prognosis. The combination of poor prognostic factors in the original renal dysfunction (39) and the abovementioned negative influencing factors may have had a significant negative impact on overall survival in patients with CrCl <45 ml/min. There may not be a single factor; rather, the additive involvement of multiple factors may be responsible for the significantly shorter overall survival in patients with CrCl <45 ml/min, even though the locoregional control rate and disease control rate were comparable.

A subgroup analysis of patients aged ≥70 years was performed to investigate the possibility of age as a confounding factor and also showed that decreased renal function was an adverse prognostic factor for overall survival. These findings

suggest that prognosis is poor in patients with comorbidities that reduce CrCl even when they are treated with radiotherapy plus cetuximab. However, in this study, 82% of these patients had a performance status of 0-1 and were deemed suitable for this treatment. Given the subjective nature of clinicians' judgment when evaluating performance status, objective indicators such as CrCl may be more useful when considering the treatment options.

Patients with head and neck squamous cell carcinoma, especially those with involvement of the oropharynx, have better prognosis if their tumors are HPV-positive than if they are HPV-negative (40,41). In our study, about 40% of patients in both groups had oropharyngeal carcinoma. However, HPV status was unknown in many cases because the study included patients who were treated at a time when it was not yet common practice to routinely test for HPV, even in patients with oropharyngeal carcinoma. Therefore, we did not include HPV status in our analysis. However, despite these missing data, about 50% of patients with oropharynx carcinoma in both groups were positive for HPV. We addressed this problem by adjusting the prognostic risk using the difference in the primary site as a covariate in multivariate analysis because about 40% of patients in both groups had oropharyngeal cancer.

The results of a randomized Phase III trial by Bonner *et al* (9) led to the approval of cetuximab for LA-SCCHN by the US Food and Drug Administration in 2006. Thereafter, there was an increase in use of cetuximab instead of cisplatin for LA-SCCHN (9). However, a later report suggested that the therapeutic effect of radiotherapy plus cetuximab in LA-SCCHN was not as good as that of chemoradiotherapy combined with cisplatin (21,23,26-29). RTOG 1016, a non-inferiority trial of radiotherapy plus cetuximab vs. radiotherapy plus cisplatin in patients with HPV-positive oropharyngeal cancer conducted by NRG Oncology, found that prognosis was significantly worse after radiotherapy plus cetuximab (24). The results of the De-ESCALaTE HPV trial in low-risk HPV-positive oropharyngeal cancer were similar (25). In these studies, there was a difference in the profile of moderate to severe acute and late toxicities between cetuximab and cisplatin but the proportion of patients experiencing at least one such event was similar. However, despite these problems, cetuximab remains an alternative for patients with renal dysfunction who cannot tolerate cisplatin because of its toxicity profile. Because adverse events associated with cetuximab are mainly reversible side effects such as dermatitis, it is less likely than cisplatin to cause irreversible renal dysfunction (24,25). In our study, serum creatinine was transiently elevated but reversible even in patients with CrCl <45 ml/min, except in those whose general condition deteriorated during treatment with radiation plus cetuximab. Disease control was also achieved in patients with CrCl <45 ml/min as effectively as in those with CrCl ≥45 ml/min. The results suggest that it may be possible to reduce symptoms caused by head and neck cancer (e.g., pain, dysphagia) even in situations where treatment options are limited by renal dysfunction. These data can be shown as an advantage of using radiotherapy plus cetuximab in patients with renal dysfunction. However, serum creatinine was greatly elevated in patients with CrCl <45 ml/min, likely as a result of dehydration caused by poor feeding and drinking due to stomatitis. Although cetuximab does not directly damage the kidneys, dehydration-which can also occur with radiation plus cetuximab-does affect kidney function and this should be considered when choosing a treatment for patients with impaired kidney function. This worsening of the patient's general condition will further limit the treatment options for patients with renal dysfunction in the event of disease progression or recurrence.

The MACH-NC (Meta-Analyses of Chemotherapy in Head and Neck Cancer) Study Group showed a modest but significant survival benefit from addition of chemotherapy to radiotherapy in patients with head and neck squamous cell carcinoma, except in those aged ≥70 years (42). A subgroup analysis of the 5-year follow-up study by Bonner *et al* (11) showed that the combination of radiotherapy and cetuximab was less beneficial in patients aged ≥65 years. However, the eligibility criteria in the above-mentioned studies only referred to normal renal function. If judged based solely on the serum creatinine level, renal function might have been overestimated in the elderly patients in those studies, which could have affected prognosis. Another report published before cetuximab was commonly used to treat head and neck cancer suggested that comorbidities are a poor prognostic factor in older patients with head and neck cancer (43). The authors of that report concluded that comorbidity status, but not age, was an independent prognostic factor. Our findings support this view. In general, elderly patients with head and neck cancer are a group with many comorbidities, and the same was true in our study. The CCI value could not predict the prognosis because comorbidities are so common in the population over 70 years of age. However, CrCl could predict the prognosis, suggesting that a decrease in overall organ function affects renal function, which in turn affects the prognosis.

Honma *et al* (44) found that renal function was a prognostic factor in oropharyngeal squamous cell carcinoma. They speculated that renal dysfunction could have attenuated the outcomes of chemoradiotherapy by making it more difficult to administer cisplatin. They also suggested that cetuximab could be an alternative treatment in the presence of renal dysfunction, pointing out that their data were collected before cetuximab was available. However, in our study, which also included patients with non-oropharyngeal cancers, prognosis was poor even with the use of cetuximab. Therefore, based solely on pharmacokinetic considerations, cetuximab should not be used in place of cisplatin in patients with renal dysfunction. Consideration should be given to the patient's general condition and the tolerability of treatment.

We defined a cutoff value of CrCl <45 ml/min as moderate to severe renal dysfunction. We had originally intended this to be CrCl <30 ml/min, which is the level at which cisplatin should be avoided (37), but this would have limited the number of cases for analysis. Even for patients with 30 ml/min ≤ CrCl <45 ml/min, a reduction of cisplatin to 50% is recommended (37). The standard, primary curative treatment for LA-SCCHN is radiotherapy plus cisplatin, which must be administered at high doses (100 mg/m^2 at 3-week intervals, total dosage ≥200 mg/m^2) (7,8). When clinicians consider reducing the dose of cisplatin from 100 mg/m^2 to 50 mg/m^2, they will likely be concerned about a decrease in therapeutic

effect. In such cases, many clinicians may use cetuximab as an alternative with the hope of maintaining the therapeutic effect. Considering this, we believe that a cutoff value of CrCl <45 ml/min is not an obstacle to resolving clinical questions in actual practice.

The regimens used for primary curative treatment of LA-SCCHN are platinum-based regimens and cetuximab. The recommendation for radiotherapy plus cetuximab has been lowered because of recent clinical studies showing that it is less effective compared with cisplatin (21,23-29). A cisplatin-based regimen requires high doses (100 mg/m^2 per dose) (7,8). For postoperative chemotherapy, cisplatin administered in weekly fractions at a single dose of 40 mg/m^2 was non-inferior to the high-dose regimen (45). However, this is not evidence for the primary curative treatment of LA-SCCHN and thus cannot be applied as such. Guidelines on primary curative treatment for LA-SCCHN suggest that high-dose cisplatin may be more effective than weekly cisplatin, although there has been no direct comparison (35). A carboplatin-based regimen is also recommended as primary curative treatment for LA-SCCHN (17). However, it is difficult to use in patients with renal dysfunction because the dosage is not based on renal function calculated using Calvert's formula. To determine the optimal primary curative treatment for LA-SCCHN, further studies are needed in special populations such as patients with renal dysfunction.

Although we found that radiotherapy plus cetuximab has a poor prognosis in patients with CrCl <45 ml/min, this does not mean the treatment itself is ineffective. Radiotherapy plus cetuximab may still achieve a better prognosis than radiation alone even if CrCl is <45 ml/min. However, the prognosis is worse overall, so patients should be selected for treatment very carefully. Particular caution is advised in elderly patients with renal dysfunction who are ineligible for treatment with cisplatin and have multiple comorbidities, even if there are no pharmacokinetic problems. However, the opposite line of thinking may be possible; that is, radiotherapy plus cetuximab may improve prognosis in elderly patients without comorbidities that cause renal dysfunction. However, cisplatin would still be considered the best option for these patients.

Our analysis of data from actual clinical practice found that patients with LA-SCCHN who had renal dysfunction due to aging or complications had poor prognosis when treated with radiotherapy plus cetuximab. This information was not available from clinical trials and should be useful when treating elderly patients with LA-SCCHN in routine clinical practice.

The main limitations of this study are that it had a single-center retrospective design and included a small number of cases, which meant that it was not possible to plan the statistical analysis in advance. Therefore, our finding of a significant reduction in overall survival despite no difference in locoregional control may have been a statistical artifact. In addition, we did not compare local control and overall survival between radiotherapy plus cetuximab and radiotherapy alone in a population with renal dysfunction, so we cannot use the results of our study to recommend radiotherapy alone for patients with renal dysfunction. The results only showed that patients with renal dysfunction who received radiotherapy plus cetuximab had a worse prognosis than patients without renal dysfunction. Therefore, the data may only indicate that patients with renal dysfunction have a poor prognosis.

In conclusion, this study found that patients with LA-SCCHN and renal dysfunction who were treated with radiotherapy plus cetuximab had a poor prognosis. The possibility that the prognosis may be poor even if this treatment is administered should be borne in mind when considering the treatment strategy for these patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CI conceived and designed the study. CI wrote the paper. CI, YT, TS and II analyzed the data and critically revised the manuscript. CI and TS confirm the authenticity of all the raw data. CI, HS, KY, AI, MA, AT, TS, YT, TH and II were involved in the interpretation of the data and preparation of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective study was approved by the Ethical Committee of the Graduate School of Medicine, Chiba University (approval number 3419; Chiba, Japan) and conducted in accordance with the ethical guidelines for medical research in humans in Japan. All patients provided written informed consent to receive radiotherapy plus cetuximab.

Patient consent for publication

Not applicable.

Competing interests

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