HOKKAIDO UNIVERSITY

Title	Association of impaired renal function and poor prognosis in oropharyngeal squamous cell carcinoma
Author(s)	Homma, Akihiro; Hayashi, Ryuichi; Kawabata, Kazuyoshi; Fujii, Takashi; Iwae, Shigemichi; Hasegawa, Yasuhisa; Nibu, Kenichi; Kato, Takakuni; Shiga, Kiyoto; Matsuura, Kazuto; Monden, Nobuya; Fujii, Masato
Citation	Head & neck, 38(10), 1495-1500 https://doi.org/10.1002/hed.24467
Issue Date	2016-10
Doc URL	http://hdl.handle.net/2115/67223
Rights	This is the peer reviewed version of the following article: Homma, A., Hayashi, R., Kawabata, K., Fujii, T., Iwae, S., Hasegawa, Y., Nibu, K., Kato, T., Shiga, K., Matsuura, K., Monden, N. and Fujii, M. (2016), Association of impaired renal function and poor prognosis in oropharyngeal squamous cell carcinoma. Head Neck, 38: 1495–1500, which has been published in final form at http://dx.doi.org/10.1002/hed.24467. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.
Type	article (author version)
File Information	HeadNeck38_1495.pdf

Instructions for use

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

Association of impaired renal function and poor prognosis in oropharyngeal squamous cell carcinoma

Akihiro Homma, M.D.[1], Ryuichi Hayashi, M.D.[2], Kazuyoshi Kawabata, M.D. [3], Takashi Fujii, M.D.[4], Shigemichi Iwae, M.D.[5], Yasuhisa Hasegawa, M.D.[6], Kenichi Nibu, M.D.[7], Takakuni Kato, M.D.[8], Kiyoto Shiga, M.D.[9,10], Kazuto Matsuura, M.D.[11], Nobuya Monden, M.D.[12], Masato Fujii, M.D.[13]

1 Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan

2 Head and Neck Surgery Division, National Cancer Center Hospital East, Kashiwa, Japan

3 Department of Head and Neck Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

4 Department of Otolaryngology, Head and Neck Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

5 Department of Head and Neck Surgery, Hyogo Cancer Center, Kobe, Japan

6 Department of Head and Neck Surgery, Aichi Cancer Center, Nagoya, Japan

7 Department of Otolaryngology-Head and Neck Surgery, Kobe University Graduate School of Medicine, Kobe, Japan

8 Department of Oto-Rhino-Laryngology, Jikei University School of Medicine, Tokyo, Japan

9 Department of Otolaryngology-Head and Neck Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan

10Department of Otolaryngology-Head and Neck Surgery, Iwate Medical University School of Medicine, Morioka, Japan

11 Division of Head and Neck Surgery, Miyagi Cancer Center, Sendai, Japan

12 Department of Otorhinolaryngology-Head and Neck Surgery, National Shikoku Cancer Center,

Matsuyama, Japan

13 Department of Otorhinolaryngology, National Tokyo Medical Center, Tokyo, Japan

Acknowledgments

This study was supported in part by Health and Labour Sciences Research Grants for Clinical Cancer Research (H22-017 and H26-141) from the Ministry of Health, and Labour and Welfare of Japan, the National Cancer Center Research and Development Fund (23-A-21 and 26-A-4) of Japan.

Corresponding author: Akihiro Homma, M.D.

Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan.

E-mail: ak-homma@med.hokudai.ac.jp

Running title: Renal function and oropharyngeal cancer

Keywords: oropharyngeal cancer, squamous cell carcinoma, prognosis, renal function, comorbidity

ABSTRACT

BACKGROUND: Renal function influences decisions regarding treatment for patients with squamous cell carcinoma of the oropharynx (SCC-OP). However, the importance of renal function in SCC-OP has not yet been reported.

METHODS: Four hundred and sixty patients with SCC-OP treated with curative intent between April 2005 and March 2007 in 12 institutions in Japan were analyzed retrospectively.

RESULTS: Four hundred and three patients (87.6%) showed a Ccr ≥50 mL/min and 57 (12.4%) a Ccr <50 mL/min. Age was associated with worse overall survival (OS), while stage IVB, radiotherapy, and Ccr<50 were associated with worse OS on univariate analyses. Surgery and hypertension were associated with better OS on univariate analyses. On multivariate analysis, age, stage, hypertension, and Ccr were also found to be significantly associated with OS.

CONCLUSIONS: Based on this retrospective study, impaired renal function is an independent predictor of increased risk of death in patients with SCC-OP.

Oropharyngeal cancer accounts for 10-20% of all head and neck malignancies; however, its incidence is now increasing due to increases in HPV-related squamous cell carcinoma of the oropharynx (SCC-OP) globally as well as in Japan [1-3]. SCC-OP is considered to be highly sensitive to chemotherapy and radiotherapy compared with other head and neck cancers such as cancers of the oral cavity, hypopharynx, and larynx. Therefore, chemotherapy is mostly used for advanced cases as part of a multidisciplinary approach, although monotherapies such as surgery or radiotherapy are applied to early cases. According to the 2005 National Comprehensive Cancer Network (NCCN) guidelines (Version 1), patients with T1-2, N0-1 disease were recommended to receive definitive radiotherapy, chemoradiotherapy (T1-2, N1 only), or surgery. Patients with more advanced stages were recommended to receive chemoradiotherapy or surgery. Postoperative radiotherapy or chemoradiotherapy was recommended if adverse pathologic features were present. Cisplatin has been the most important key drug in the treatment of SCC-OP as well as other head and neck cancers, although molecular-targeted agents have recently been applied to head and neck cancers. However, cisplatin has renal toxicity, so it is not indicated for patients with impaired renal function. Therefore, renal function influences decisions regarding treatment for patients in daily practice. However, the importance of renal dysfunction has not yet been reported, although comorbidity is known to have an impact on survival in cancers originating in certain sites [4-7].

In this study, we analyzed whether renal function is a prognostic factor in SCC-OP using data obtained from twelve institutions across Japan [8-10].

MATERIALS AND METHODS

Patients

The data for 523 patients with previously untreated oropharyngeal cancer between April 2005 and March 2007 were gathered from 12 institutions belonging to the Head and Neck Cancer Study Group in the Japan Clinical Oncology Group (JCOG). Overall, 37 patients who received palliative therapy, 16 patients with non-SCC, and 10 patients for whom complete data could not be obtained were excluded from further analysis, and the data for the remaining 460 patients were analyzed retrospectively. The general rule of treatment was decided on the basis of the above-mentioned NCCN guidelines at that time. However, the treatment for each patient was sometimes modified according to the patients' wishes and/or clinicians' preferences.

This multi-institutional joint research was representatively approved by the appropriate ethical committees of the National Hospital Organization Tokyo Medical Center, Tokyo, Japan.

Study variables

Clinical data including age, sex, stage, primary tumor subsite, treatment, alcohol consumption, smoking status, hypertension, and diabetes mellitus were recorded. Alcohol consumption, smoking status, hypertension, and diabetes mellitus were self-reported. Alcohol consumption was stratified as patients who never drank (never), those who quit drinking at any time prior to diagnosis (former), or those who drank at the time of diagnosis (current). Similarly, smoking status was also stratified as never, former, and current.

The initial main treatment was classified as the treatment for the primary tumor. A

classification of surgery included all cases undergoing surgery as the main treatment for primary disease even if patients received radiotherapy and/or chemotherapy before or after surgery. Similarly, a classification of radiotherapy or chemoradiotherapy included all cases receiving radiotherapy alone or radiotherapy with concomitant chemotherapy, respectively, as the main treatments for primary disease even if patients received chemotherapy before or after radiotherapy. The presence of surgery, radiotherapy, and chemotherapy were also classified as the initial therapy for the primary and/or neck disease.

Creatinine clearance (Ccr) was calculated using the Cockcroft-Gault formula. Patients were divided into those with a Ccr ≥50 mL/min and those with a Ccr <50 mL/min.

Statistical Analysis

All patients were closely observed during follow-up. The median follow-up period was 4 years (average 3.5years, range 0.1-6.3 years).

Contingency table analyses based on the unpaired student's t- test or the chi-square test were used to determine the statistical significance of associations between categorical variables. The nonparametric Kruskal-Wallis test was used for comparison of Ccr with age. Probabilities of overall survival (OS), which included death from any cause computed from the beginning of treatment to the time of death, was calculated by the Kaplan-Meier method and compared using the log-rank test. Disease-specific survival (DSS) was defined as the interval between the start of treatment to the time of death by SCC-OP. For determination of factors related to OS and DSS, a Cox proportional hazards model was used. The level of statistical significance was defined as a 2-tailed $p < .05$.

Statistical analysis was performed using JMP Pro 11.0.0 statistical software (SAS Institute, Cary, NC).

RESULTS

Study population

The 460 patients had a median age of 63 years (average 62.6years, range 36-96 years), with 180 patients (39.1%) treated mainly by surgery, 114 (24.8%) by radiotherapy and 166 (36.1%) by chemoradiotherapy. Other patient characteristics are shown in Table 1. The median Ccr was 79.0 mL/min (average 81.1 mL/min, range 5.3-208 mL/min). Four hundred and three patients (87.6%) showed a Ccr ≥50 mL/min and 57 (12.4%) a Ccr <50 mL/min. The average age of the Ccr <50 group was older than that for the Ccr ≥50 group ($p<0.001$, Kruskal–Wallis test). The Ccr <50 group showed a significantly different overall distribution of main treatment ($\chi2=22.31$, $p<0.001$), presence of chemotherapy ($\chi2=16.69$, $p<0.001$), and alcohol consumption ($\chi2=15.24$, $p<0.001$) when compared to the Ccr ≥50 group.

Survival analysis

As prognostic factors, age, sex, stage, subsite, the presence of surgery, radiotherapy, and chemotherapy, alcohol consumption, smoking status, hypertension, diabetes mellitus, and Ccr were analyzed. Age was associated with worse overall survival (OS) (hazard ratio [HR]1.02; 95% confidence interval [CI]1.00-1.03; p=.005, Table 2). Further, stage IVB (HR 1.76; 95%CI 1.09-2.73; p=.02), radiotherapy (HR 1.27; 95%CI 1.01-1.62; p=.04), and Ccr<50 (HR 2.52; 95%CI 1.54-3.93;

p=0.0004) were associated with worse OS on univariate analyses. Patients with a Ccr<50 also showed statistically worse OS than those with Ccr≥50 (p<0.0001, log-rank test, Figure 1). On the other hand, surgery (HR 0.78; 95%CI 0.63-0.97; p=.03) and hypertension (HR 0.58; 95%CI 0.32-0.97; p=.04) were associated with better OS on univariate analyses. On multivariate analysis, age, stage, hypertension, and Ccr <50 showed a significant association with OS. Similarly, age, sex, stage and Ccr<50 showed significant associations with DSS on multivariate analysis.

DISCUSSION

We observed that renal function was a significant prognostic factor among patients with SCC-OP in this study. Patients with end stage renal disease were reported to be at increased overall risk for cancer [11]. However, to our knowledge, this is the first report to suggest that renal function is a prognostic variable in patients with cancer. The landmark study, RTOG 91-11 compared induction cisplatin plus fluorouracil followed by RT, concomitant cisplatin/RT, and RT alone. Eligibility for this study included a Ccr of at least 50 ml/min [12]. Further, patients with a Ccr of 50-60 were treated the same as those with Ccr≥60, not like those with Ccr<50 in this study population. Therefore, a Ccr of 50 was used as a cut-off value in this study.

In order to understand why renal function was a prognostic factor among patients with SCC-OP, we first speculated that patients with impaired renal function could not receive adequate treatment including chemotherapy even if it were needed and resulted in worse OS. Indeed, the percentage of patients with a Ccr <50 was significantly higher among those not receiving

chemotherapy than in those receiving chemotherapy. And the treatment regimens of choice might have been a little less aggressive in patients with impaired renal function and/or some patients with impaired renal function might have been less likely to undergo the planned treatment. Indeed, of 12 patients with Ccr <50 were treated with some kind of chemotherapy. Four patients received cisplatin-based regimens, although all 4 patients did not manage to complete the planned therapy. Three patients received cisplatin analogues, such as carboplatin or nedaplatin, which produce less nephrotoxicity. The remaining 4 patients received chemotherapy which did not include platinum (Table 3). On the other hand, 81.6% (165/202) of patients with Ccr≥50 who received chemotherapy, also received cisplatin. Therefore, we speculated that the patients with poor renal function were indicated for less aggressive treatment and had a poor prognosis.

In addition, several studies have recently found an association between moderate chronic kidney diseases and increased overall cancer risk [13,14]. Therefore, we speculated that patients with Ccr<50 were more likely to die of other cancers and analyzed the cause of death by renal function among all patients. Patients dying of OPC accounted for 47.4% of the Ccr<50 group and 27% of the Ccr≥50 group. As for patients dying of other cancers, 3/57 patients (5.3%) with Ccr<50 (gastric cancer, lung cancer, and unclear) and 7/403 patients (1.7%) in the Ccr≥50 group died of other cancers. Other cancer deaths might have contributed to our finding in this study that renal function was a prognostic factor. However, the main reason underlying this finding is considered to be death due to OPC.

Next, we focused on patients with early stage (stage I-II) disease who were not usually

indicated for chemotherapy. Radiotherapy alone or surgery alone is considered to be sufficient for such patients. However, Ccr was also found to be an independent prognostic factor among patients with stage I-II disease by multivariate analysis (data not shown). Therefore, it is difficult to say why patients with stage I-II disease and impaired renal function had a poor prognosis based on these results.

The two main causes of chronic kidney disease in adults are diabetes mellitus and hypertension [15]. Diabetes mellitus and hypertension are caused by smoking and alcohol consumption. These factors are also a cause of oropharyngeal cancer, although HPV-related OPC has been increasing sharply in recent years. Therefore, in this study, we expected that a lot of patients would present with diabetes mellitus and hypertension. According to the National Health and Nutrition Survey of Japan, 2004 [16] , the ratio of people with HbA1c ≥ 6.1% among the 50-59, 60-69, and 70+ age groups were 10.2%, 13.6%, and 18.0%, respectively. In addition, the ratio of people with systolic blood pressure ≥ 140mmHg, diastolic blood pressure ≥ 90mmHg, or taking antihypertensive drugs among the 50-59, 60-69, and 70+ age groups were 47.2%, 61.4%, and 72.3%, respectively. In this study, 57/460 (12.4%) of the patients had diabetes mellitus and 57/460 (12.4%) also had hypertension. The comorbidities of diabetes and hypertension were not considered to be high compared with those reported in the national survey. However, since the information on the presence or absence of diabetes and hypertension in this study was gathered through patient interviews in most cases, the information might not have been entirely correct. Hypertension was also associated with better OS based on the multivariate analysis in this study. Although we

examined the relevant data carefully, we could not identify any possible mechanism by which to explain this association. Therefore, further discussion of the comorbidities of diabetes and hypertension among OP-SCC patients is of limited value here. Further, 22.0% (101/460) of patients in this study had a Ccr <60, which is defined as chronic kidney disease. The figure appears to be considerably higher than that among the Japanese general adult population, which was reported to be 12.9% [17]. Comorbidity has been reported to have an impact on survival in head and neck cancer [4-7]. Patients with chronic kidney disease might have severe comorbidity. However, as this study data was multi-institutional and gathered retrospectively, it is of limited value in drawing conclusions.

The data used in this study was from patients treated between April 2005 and March 2007. During that period, molecular-targeted agents were not available for patients with head and neck cancer in Japan. Further, HPV status was not examined routinely even in patients with SCC-OP. Actually, HPV status was examined in 25 patients in 2 institutions; however, only two patients (8%) were found to be HPV positive. According to other reports, the HPV-positive rate has been rising sharply in recent years [1,3]. However, cisplatin has been and will continue to be the most important key drug for the treatment of patients with SCC-OP, despite the introduction of molecular-targeted agents for the treatment of SCC-OP and the increase in HPV-related SCC-OP, which has a better prognosis than HPV-negative SCC-OP [1,3,18]. Therefore, the results provided herein will be useful in better selecting treatments for SCC-OP. In particular, patients with advanced OPC and poor renal function should be treated by surgery, if possible, for now as radiation alone

is not sufficient to eradicate advanced cancer and the application of chemoradiotherapy is difficult for such patients. In addition, radiotherapy with cetuximab could become a treatment of choice for such patients as the patients may be able to tolerate cetuximab. However, in the near future, we hope that immunotherapy such as PD-1/PD-L1 antibody, will be applicable for patients with poor renal function in the same way as it is for those with normal renal function. Recently, age, obesity, and marital status were reported to be prognostic factors for head and neck cancer [19-21]. These simple clinical factors must be also useful in clarifying the most appropriate treatment for each patient with SCC-OP.

In conclusion, we report for the first time that impaired renal function is an independent predictor of increased risk of death in patients with SCC-OP. Although this result was derived using data from patients with OPC during the study period in Japan only, and should not be generalized to include other cohorts, a system for deciding the treatment for each patient must be produced using not only complicated biological factors but also simple clinical factors so that it is easily understandable by head and neck oncologists all over the world.

REFERENCES

[1] Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the united states. J Clin Oncol. 2011;29:4294-4301.

[2] Japan Society for Head and Neck Cancer. Cancer registry committee. Report of head and neck cancer registry of Japan clinical statistics of registered patients 2012. Jpn J Head Neck Cancer 2014. 40(supplement) 1–14; Available from URL: http://www.jshnc.umin.ne.jp/pdf/2012syourei_houkoku.pdf.

[3] Saito Y, Yoshida M, Ushiku T, et al. Prognostic value of p16 expression and alcohol consumption in Japanese patients with oropharyngeal squamous cell carcinoma. Cancer 2013;119:2005-2011.

[4] Wells CK, Stoller JK, Feinstein AR, Horwitz RI. Comorbid and clinical determinants of prognosis in endometrial cancer. Arch Intern Med. 1984;144: 2004-2009.

[5] Feinstein AR, Wells CK. A clinical-severity staging system for patients with lung cancer. Medicine (Baltimore). 1990;69:1-33.

[6] Clemens JD, Feinstein AR, Holabird N, Cartwright S. A new clinical-anatomic staging system for evaluating prognosis and treatment of prostatic cancer. J Chronic Dis. 1986;39:913-928.

[7] Homma A, Sakashita T, Oridate N, et al. Importance of comorbidity in hypopharyngeal cancer. Head Neck. 2010;32:148-153.

[8] Sakashita T, Homma A, Hayashi R, et al. The role of initial neck dissection for patients with node-positive oropharyngeal squamous cell carcinomas. Oral Oncol. 2014;50:657-661.

[9] Kano S, Homma A, Hayashi R, et al. Matched-pair analysis in patients with advanced oropharyngeal cancer: surgery versus concurrent chemoradiotherapy. Oncology. 2013;84:290-298.

[10] Kano S, Homma A, Hayashi R, et al. Salvage surgery for recurrent oropharyngeal cancer after chemoradiotherapy. Int J Clin Oncol. 2013;18:817-823.

[11] Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for end-stage renal disease: An international collaborative study. Lancet 1999;354 (9173): 93–99.

[12] Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091–2098.

[13] Wong G, Hayen A, Chapman JR, Webster AC, et al. Association of CKD and cancer risk in older people. J Am Soc Nephrol 2009;20:1341-1350.

[14] Jørgensen L, Heuch I, Jenssen T, Jacobsen BK. Association of albuminuria and cancer incidence. J Am Soc Nephrol 2008;19:992-998.

[15] National Kidney Foundation. About chronic kidney disease. https://www.kidney.org/kidneydisease/aboutckd

[16] Ministry of Health, Labour and Welfare. The National Health and Nutrition Examination Survey of Japan, 2004. http://www.mhlw.go.jp/houdou/2008/04/dl/h0430-2k.pdf. [Japanese]

[17] Japanese Society of Nephrology. Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012. p5-7. Available from URL: http://www.jsn.or.jp/guideline/pdf/CKDguide2012.pdf . [Japanese]

[18] Mizumachi T, Kano S, Sakashita T, et al. Improved survival of Japanese patients with human papillomavirus-positive oropharyngeal squamous cell carcinoma. Int J Clin Oncol. 2013;18:824-828.

[19] Iyengar NM, Kochhar A, Morris PG, et al. Impact of obesity on the survival of patients with early-stage squamous cell carcinoma of the oral tongue. Cancer. 2014;120:983-991.

[20] Ryan Camilon P, Stokes WA, Nguyen SA, Lentsch EJ. The prognostic significance of age in oropharyngeal squamous cell carcinoma. Oral Oncol. 2014;50:431-436.

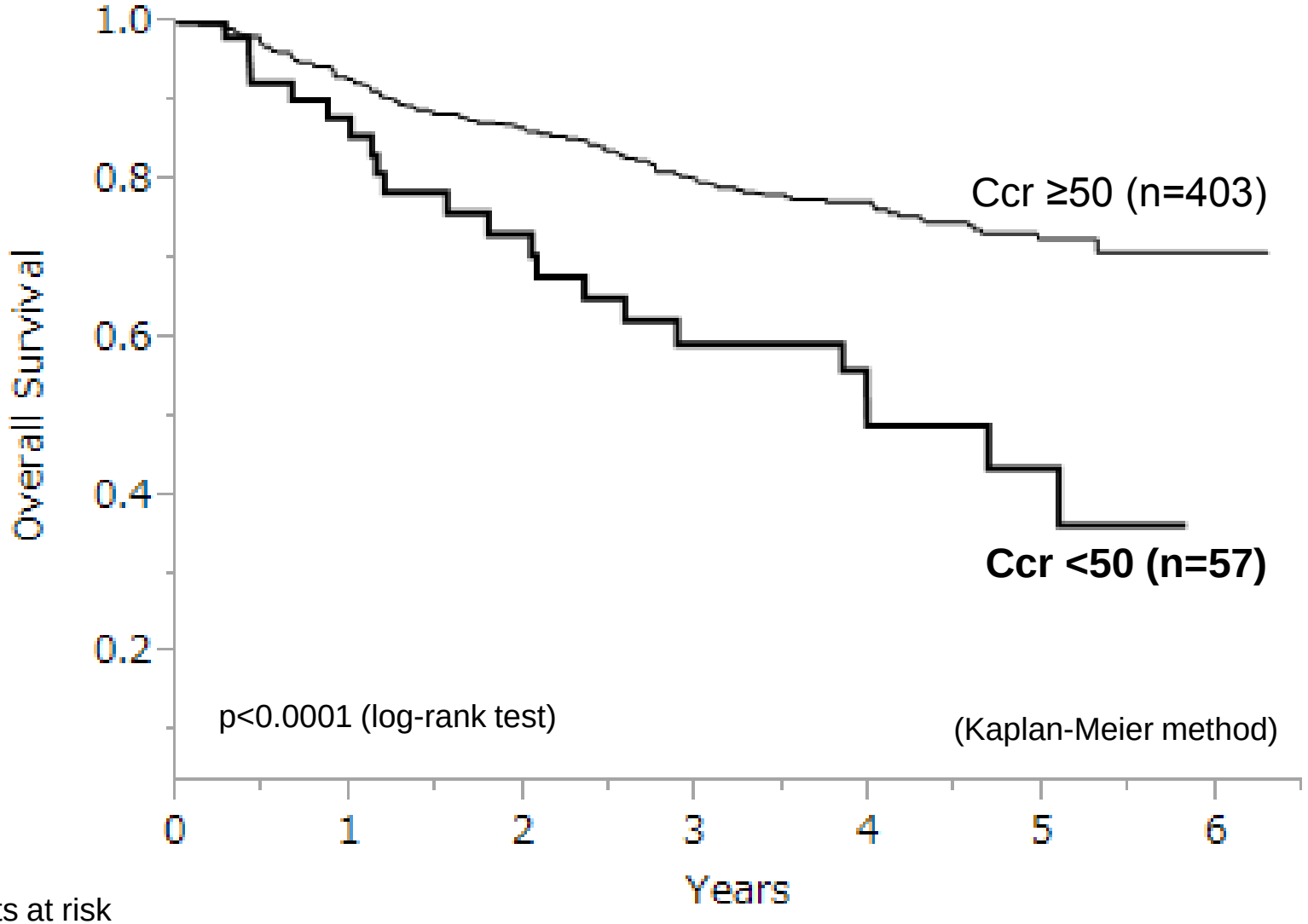
[21] Inverso G, Mahal BA, Aizer AA, Donoff RB, Chau NG, Haddad RI. Marital status and head and neck cancer outcomes. Cancer. 2015;12:1273-1278.

Figure Legend

Figure 1.

Overall survival according to renal function

Figure 1. Overall survival according to renal function



Patients at risk

Ccr ≥50	403	356	313	279	226	98	3
Ccr <50	57	38	28	21	15	8	0

Table 1. Baseline Characteristics of Patients

Clinical variables	Ccr ≥50 No. of patients	Ccr <50 No. of patients	*p*
Age, y			
Median (range)	62(36-84)	74(54-96)	<.001
Sex			
Female	57	5	
Male	346	52	.27
Stage			
I-II	97	15	
III-IVA	270	38	
IVB	36	4	.85
Subsite			
lateral wall	249	27	
Anterior wall	93	16	
Superior wall	38	11	
Posterior wall	23	3	.08
Main treatment			
Surgery	161	19	
Radiotherapy	86	28	
Chemoradiotherapy	156	10	<.001
Surgery			
Yes	176	19	
No	227	38	.14
Radiotherapy			
Yes	295	41	
No	108	16	.84
Chemotherapy			
Yes	201	12	
No	202	45	<.001
Alcohol			
Never	75	19	
Former	21	8	
Current	307	30	<.001
Smoking			
Never	77	11	
Former	76	18	
Current	250	28	.07
Hypertension			
No	333	44	
Yes	70	13	.32
Diabetes mellitus			
No	369	52	
Yes	34	5	.93

Table 2. Overall survival and Disease-specific survival in Univariate Analysis and Multivariate Models

Clinical variables	Overall Survival						Disease-specific survival					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI	*p*
Age (per year for increase)	1.02	1.00-1.03	.005	1.02	1.00-1.04	.02	1.03	1.01-1.05	.002	1.02	1.00-1.04	.002
Sex												
Female	Ref.											
Male	1.16	0.87-1.59	.32				2.58	1.39-5.47	.002	2.10	1.10-4.53	.002
Stage												
I - II	Ref.											
III - IVA	1.11	0.88-1.42	.39	2.42	1.41-4.44	0.001	3.10	1.80-5.80	<.001	3.00	1.72-5.69	<.001
IVB	1.76	1.09-2.73	.02	5.55	2.66-11.70	<.001	9.24	4.80-18.65	<.001	8.57	4.32-17.81	<.001
Subsite												
Lateral wall	Ref.											
Anterior wall	1.09	0.83-1.42	.52				1.25	0.83-1.84	.28			
Superior wall	1.22	0.84-1.71	.29				0.95	0.49-1.68	.87			
Posterior wall	0.92	0.54-1.46	.74				1.30	0.61-2.46	.47			
Surgery												
No	Ref.											
Yes	0.78	0.63-0.97	.03	1.02	0.60-1.66	.94	0.73	0.51-1.03	.07			
Radiotherapy												
No	Ref.											
Yes	1.27	1.01-1.62	.04	1.11	0.60-2.03	.75	1.64	1.10-2.55	.02	1.12	0.73-1.77	.61
Chemotherapy												
No	Ref.											
Yes	1.16	0.81-1.66	.42				1.35	0.96-1.89	.08			
Alcohol												
Never	Ref.											
Former	1.01	0.60-1.61	.97				1.47	0.69-2.89	.30			
Current	1.04	0.80-1.37	.76				1.07	0.71-1.68	.76			
Smoking												
Never	Ref.											
Former	0.87	0.62-1.20	.39				1.12	0.61-2.06	.71	1.05	0.57-1.95	.88
Current	0.95	0.72-1.25	.69				1.63	1.03-2.71	.04	1.38	0.85-2.36	.20
Diabetes mellitus												
No	Ref.											
Yes	1.18	0.60-2.10	.61				1.44	0.81-2.39	.20			
Hypertension												
No	Ref.											
Yes	0.58	0.32-0.97	.04	0.49	0.27-0.83	.007	0.82	0.50-1.26	.38			
Renal function												
Ccr ≥50	Ref.											
Ccr <50	2.52	1.54-3.93	<.001	1.85	1.07-3.09	.03	2.58	1.66-3.87	<.001	1.99	1.20-3.22	.009

Abbreviations: HR, hazard ratio; CI, confidence interval; Ref., reference (HR=1.0)

Table 3. Treatment details for patients with Ccr <50 who received chemotherapy

Treatment	No. of patients
CCDP+RT	2
CDDP+DOC+5FU+RT	1
CDDP+5FU → RT	1
CBDCA+5FU+RT	1
NDP+5FU+RT	1
NDP+RT	1
DOC+5FU+RT	1
DOC+RT	2
S1+RT	1
S1 → DOC+RT	1
Total	12

CDDP, cisplatin; RT, radiotherapy; DOC, docetaxel; 5FU, 5-fluorouracil;
CBDCA, carboplatin; NDP, nedaplatin; S1, combination oral drug tegafur/gimeracil/oteracil