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ORIGINAL ARTICLE

Clinical impact of baseline renal function on the safety of radiotherapy with concurrent docetaxel for esophageal cancer in elderly patients

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Abstract

Background We aimed to compare the safety of radiotherapy with concurrent docetaxel (DOC-RT) for esophageal cancer (EC) in elderly patients who were divided into a creatinine clearance (Ccr) < 60 mL/min (Ccr-L) group and a Ccr ≥ 60 mL/min (Ccr-H) group.

Methods Eligible patients included those aged ≥ 76 years who were diagnosed with esophageal squamous cell carcinoma. The patients received radiotherapy (60 Gy in 30 fractions) and concurrent docetaxel (10 mg/m^2 weekly for six cycles), after which toxicity and treatment completion rates were retrospectively evaluated.

Results The 73 elderly EC patients receiving DOC-RT were divided into two groups for evaluation: the Ccr-L group (49 patients) and the Ccr-H group (24 patients). The median survival time for patients in the Ccr-L and Ccr-H groups was 21 and 20 months, respectively ($p = 0.2$). The incidence of grade 1 acute kidney injury was 8% vs. 8% ($p = 1$) in the Ccr-L and Ccr-H groups, respectively. No other hematological or nonhematological toxicities differed between patients in the two groups. No grade 4 or 5 toxicities were observed in the two groups. No significant difference was observed in the treatment completion rates (88% vs. 92%, $p = 1$) between patients in the Ccr-L and Ccr-H groups.

Conclusions Regardless of baseline renal function, DOC-RT is a safe regimen for elderly patients with EC.

Keywords Esophageal cancer · Chemoradiotherapy · Elderly patients · Renal function

Abbreviations

CCI	Charlson Comorbidity Index
Ccr	Creatinine clearance
CI	Confidence interval
CRT	Chemoradiotherapy
DOC	Docetaxel
EC	Esophageal cancer
ECOG PS	Eastern Cooperative Oncology Group performance status
FP	5-Fluorouracil and cisplatin
GNRI	Geriatric Nutritional Risk Index
HR	Hazard ratio
MST	Median survival time
OS	Overall survival
PFS	Progression-free survival
RT	Radiotherapy
UMIN	University Hospital Medical Information Network

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Introduction

With the recent increase in life expectancy, the number of elderly patients with esophageal cancer (EC) has also grown significantly over recent decades, with approximately 30–34% of patients aged ≥ 75 years receiving a diagnosis [1, 2]. The number of elderly patients with chronic kidney disease has also grown; the prevalence is 49–69% among participants aged ≥ 75 years [3].

In Japan, neoadjuvant chemotherapy followed by esophagectomy has been the standard treatment for resectable EC [4, 5]. However, because of limitations related to their physiological condition, elderly patients are generally not considered fit for surgery. Chemoradiotherapy (CRT) has been shown to provide significantly better survival benefits

in patients with EC compared with radiotherapy (RT) alone; specifically, 5-fluorouracil and cisplatin (FP) are designated as the standard regimen [6, 7]. However, clinical trials supporting these standard treatments have not included elderly patients aged ≥ 76 years or those with declining renal function [creatinine clearance (Ccr) < 60 mL/min] [8, 9]. Moreover, a retrospective comparison of the outcomes of RT with concurrent FP between elderly and nonelderly patients with stage II/III (non-T4) EC demonstrated that elderly patients had more frequent hematological adverse events, acute kidney injury, poorer compliance, and significantly inferior survival [10]. Thus, a standard CRT regimen with a lower toxicity and higher efficacy must be established for EC in elderly patients with declining renal function.

Docetaxel (DOC) is an active chemotherapeutic agent for advanced EC [11, 12]. DOC is primarily metabolized to its inactive derivatives by the liver and is excreted into the biliary system; its renal excretion is minimal (less than 5%) [13]. Apart from its cytotoxic activity, DOC possesses radiosensitizing properties through its ability to induce G2–M cell cycle blockade [14, 15].

Accordingly, studies on EC, non-small cell lung cancer, and head and neck cancer have shown that CRT with DOC (DOC-RT) offers promising activity and manageable toxicity [16–21]. Our hospital has reported the use of preoperative DOC-RT for resectable EC patients [17]. A previous phase 1 study in Japan revealed that DOC-RT was tolerable and effective in 20- to 79-year-old patients with localized EC and normal renal function. In such patients, the recommended DOC dose was 10 mg/m^2 weekly [22]. We previously conducted a retrospective study to evaluate the safety and efficacy of concurrent DOC (10 mg/m^2 weekly for six cycles) and RT for elderly patients with EC [23]. However, including our previous study, there are no reports regarding the relationship between DOC-RT in elderly patients with EC and renal function. A recent phase 2 study on concurrent DOC (10 mg/m^2 weekly for six cycles) and RT for locally advanced EC in elderly patients with declining renal function (serum creatinine < 2.0 mg/dL) was prematurely terminated due to the slow accrual of patients [24]. Therefore, the safety of DOC-RT for EC in elderly patients with declining renal function remains unclear.

Thus, using retrospectively collected data, the present study primarily aimed to assess the safety of DOC-RT for EC in elderly patients with a focus on baseline renal function.

Materials and methods

Study population

We retrospectively reviewed the medical records, RT treatment plans, and diagnostic images of patients with EC who satisfied the following criteria: (i) ≥ 76 years of age with pathologically proven esophageal squamous cell carcinoma; (ii) Eastern Cooperative Oncology Group performance status (ECOG PS) [25] of 0–2; (iii) clinical stage of I–IVA or IVB (M1 lymph node) based on the 8th Union for International Cancer Control TNM classification [26]; (iv) treatment with definitive concurrent DOC-RT; (v) no other active cancer. Patients with para-aortic lymph node metastasis or dialysis for declining renal function were excluded. The same study population has been described previously [23]. EC was diagnosed comprehensively through upper gastrointestinal endoscopy, computed tomography, positron emission tomography, and physical examination.

Treatment

External RT was administered using 6- or 10-MV X-rays from a linear accelerator. The daily RT fraction size was 2.0 Gy according to the International Commission on Radiation Units and Measurements reference point and was administered 5 days per week for a total dose of 60 Gy. Elective nodal irradiation including the bilateral supraclavicular and mediastinal lymph node regions was performed in 47 patients, whereas involved-field irradiation covering the primary tumor and lymph node metastases with a margin of 2–4 cm was performed in 26 patients. Elective nodal irradiation tended to be used in patients with advanced cancer. All patients underwent three-dimensional conformal RT using two to four fields to avoid the spinal cord. Among those receiving two-field irradiation, the beam direction was changed after 40 Gy of irradiation. In most of the patients, the percentage of total lung volume exceeding 20 Gy and the mean lung dose did not exceed the constraints of 35% and 20 Gy, respectively. The mean heart dose did not exceed the constraints of 40 Gy. In conjunction with RT, all patients received a chemotherapy regimen consisting of DOC at a weekly dose of 10 mg/m^2 for six consecutive weeks. DOC was administered on an outpatient basis without dose reduction regardless of patient characteristics. After treatment completion, the patients were followed up at 1- or 3-month intervals. The follow-up evaluations included a history and physical examination, blood test, upper gastrointestinal endoscopy, computed tomography, and positron emission tomography. The blood test included complete blood cell count; biochemical marker levels (albumin, electrolytes, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and alkaline phosphatase), and tumor marker levels (squamous cell carcinoma antigen).

Statistical analyses

The response evaluation criteria in solid tumors were used to determine tumor response [27]. Overall survival (OS)

and progression-free survival (PFS) from the treatment start date were calculated using the Kaplan–Meier method. Death from any cause was defined as an event when calculating OS whereas disease progression at any site or death from any cause was defined as an event when calculating PFS. Toxicity was assessed and documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [28]. Toxicities occurring within 3 months or more than 3 months after treatment were defined as acute or late, respectively. Treatment completion was defined as having completed the scheduled RT and DOC.

Comorbidities were estimated using the Charlson Comorbidity Index (CCI), which is based on 12 disease comorbidity categories, with scores ranging from 1 to 6 based on the relative risk of 1-year mortality [29, 30]. Nutritional status was estimated using the geriatric nutritional risk index (GNRI) [31], which combines two nutritional indicators, albumin level and actual body weight compared with ideal body weight. This index was developed by modifying the nutritional risk index for elderly patients. The GNRI formula is as follows:

$$\begin{aligned}\text{GNRI} = {} & \left[1.487 \times \text{pretreatment serum albumin (g/L)}\right] \\ & + \left[41.7 \times \text{pretreatment weight (kg)} \,/\, \text{ideal body weight (kg)}\right].\end{aligned}$$

The participants were classified according to the following cutoff values: high risk, < 92; moderate risk, 92–98; and no risk, > 98 [32]. The GNRI cutoff values were determined according to weight losses of 5% or 10% and abnormal albumin concentrations of 38, 35, and 30 g/L [33].

Ccr was calculated using the Cockcroft–Gault formula [34]:

$$\begin{aligned}&\text{creatinine clearance (mL/min)} \\ &= \left(140 - \text{age [years]}\right) \times \text{weight [kg]} \\ &\quad (\times 0.85 \text{ if female}) / \left(72 \times \text{serum creatinine [mg/dL]}\right).\end{aligned}$$

The patients were divided into two groups according to baseline Ccr values: the Ccr-H group (Ccr ≥ 60 ml/min) or the Ccr-L group (Ccr < 60 ml/min). The Ccr cutoff values were determined according to the standard criteria for full dose of 5-FU and CDDP regimen [35].

A Mann–Whitney *U* test was used for the quantitative data and Fisher's exact test was used for the qualitative data to compare patient characteristics, toxicities, and completion rates between groups. All statistical analyses were performed using EZR version 1.37 [36], and p values < 0.05 (two sided) were considered statistically significant. The retrospective study protocol was reviewed and approved by the Juntendo Hospital review board (approval number: 19–039).

Results

Patient and tumor characteristics

Between January 2009 and May 2018, 84 patients with EC aged ≥ 76 years received radical RT or CRT at our hospital. Among these 84 elderly patients, 4 (5%) received RT with concurrent FP, 7 (8%) received RT alone, and the remaining 73 (87%) received definitive concurrent DOC-RT. Among the 73 elderly EC patients receiving DOC-RT, 49 patients in the Ccr-L group and 24 patients in the Ccr-H group were studied.

The patient and tumor characteristics did not differ between patients in the two groups (Table 1).

Treatment outcomes

The overall response rates, including complete responses in 25 and 6 patients and partial responses in 14 and 12 patients, were 80% and 75% in the Ccr-L and Ccr-H groups, respectively. The 1- and 3-year PFS rates for patients in the Ccr-L group were 42% [95% confidence interval (CI), 27–57%] and 28% (95% CI, 15–42%) compared with 38% (95% CI, 19–56%) and 18% (95% CI, 5–36%) for patients in the Ccr-H group ($p = 0.45$; Fig. 1a), respectively. The 1- and 3-year OS rates for patients in the Ccr-L group were 65% (95% CI, 48–77%) and 39% (95% CI, 23–54%) with a median survival time (MST) of 21 months compared with 62% (95% CI, 40–78%) and 22% (95% CI, 6–43%) with a MST of 20 months for patients in the Ccr-H group ($p = 0.2$; Fig. 1b), respectively. Moreover, 40 patients died of tumor progression, whereas six died of other causes, including gastric bleeding in one patient, heart failure in one patient, suicide in one patient, alcoholic cirrhosis in one patient, and aspiration pneumonia from cerebral infarction in two patients.

Toxicity and completion rates

Table 2 summarizes the toxicities associated with DOC-RT. The toxicities of grades 1–2 and 3 did not differ between patients in the two groups. No grade 4 or 5 toxicities were observed in either group of patients. DOC and RT were discontinued due to deterioration in the general condition of four patients (radiation doses of 22, 34, 38, and 40 Gy, respectively), esophageal fistula in two patients (radiation doses of 40 and 42 Gy, respectively), pneumonia in one patient (radiation dose of 46 Gy), and pain in one patient (radiation dose of 42 Gy), resulting in a DOC-RT completion rate of 88% (43/49 patients) for patients in the Ccr-L group and 92% (22/24 patients) for patients in the Ccr-H group ($p = 1$). DOC and RT were discontinued

Table 1 Patient and tumor characteristics

	Ccr (mL/min)		
	< 60 *n* = 49	≥ 60 *n* = 24	*p*-value
Median age, years (range)	80 (76–90)	81 (76–91)	0.47
≥ 80 years, no. (%)	28 (57)	14 (58)	1
< 80 years, no. (%)	21 (43)	10 (42)	
Gender, no. (%)			
Male	39 (80)	22 (92)	0.32
Female	10 (20)	2 (8)	
Body weight (kg), median (range)	51 (30–72)	54 (41–78)	0.07
Height (cm), median (range)	160 (134–174)	162 (140–180)	0.34
ECOG PS≈			
0	26 (53)	15 (63)	
1	16 (33)	6 (25)	
2	7 (14)	3 (12)	
Location of primary tumor, no. (%)			
Cervix	5 (10)	4 (17)	0.52
Upper thorax	7 (15)	1 (4)	
Middle thorax	27 (55)	13 (54)	
Lower thorax	8 (16)	6 (25)	
Abdomen	2 (4)	0	
T factor, no. (%)			
1	13 (27)	6 (25)	0.43
2	4 (8)	1 (4)	
3	17 (34)	5 (21)	
4	15 (31)	12 (50)	
N factor, no. (%)			
0	22 (45)	7 (29)	0.22
1–3	27 (55)	17 (71)	
cStage, no. (%)			
I	14 (29)	5 (21)	0.43
II	8 (16)	1 (4)	
III	10 (20)	5 (21)	
IVA	14 (29)	10 (42)	
IVB (M1 lymph node)	3 (6)	3 (12)	
History of smoking, no. (%)			0.79
Yes	33 (67)	15 (63)	
No	16 (33)	9 (37)	
Ccr (ml/min), median (range)	48.9 (28.7–59.9)	72.9 (60–94.7)	< 0.001
Serum creatinine (mg/dl), median (range)	0.81 (0.49–2.23)	0.62 (0.38–0.97)	< 0.001
CCI, no. (%)			0.92
2	28 (57)	13 (54)	
3	10 (20)	6 (25)	
4	10 (20)	4 (17)	
5	1 (3)	1 (4)	
GNRI, no. (%)			0.35
< 92	19 (39)	9 (37)	
92–98	17 (34)	5 (21)	
> 98	13 (27)	10 (42)	
Radiation field, no. (%)			0.6
ENI	33 (67)	14 (58)	
IFI	16 (33)	10 (42)	
Median follow-up time (months), median (range)	9 (2–101)	15 (2–56)	
≥ 9 months, no. (%)	26 (53)	16 (66)	0.32
< 9 months, no. (%)	23 (47)	8 (34)	

CC Charlson comorbidity index, *CCr* creatinine clearance, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *ENI* elective nodal irradiation, *GNRI* geriatric nutritional risk index, *IFI* involved-field irradiation

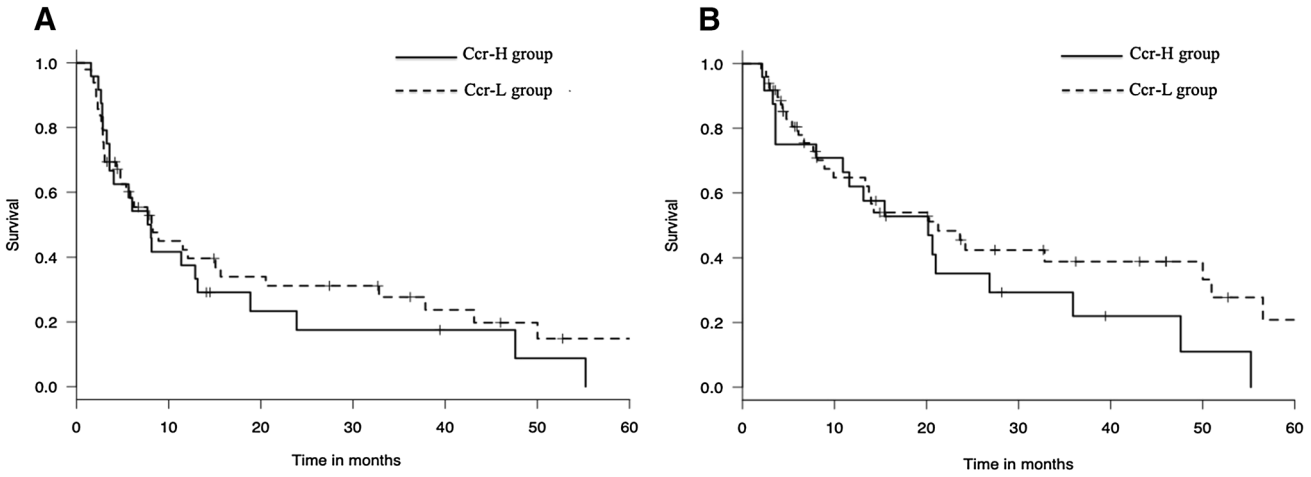

Fig. 1 Kaplan–Meier estimates of (**a**) progression-free survival and (**b**) overall survival in the Ccr-H and Ccr-L groups. *Ccr-H* creatinine clearance ≥ 60 mL/min, *Ccr-L* creatinine clearance < 60 mL/min

Table 2 Treatment toxicities

		Ccr < 60 mL/min $n = 49$, no. (%)		Ccr ≥ 60 mL/min $n = 24$, no. (%)		*p*-value	
		Grade 1–2	Grade 3	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Acute toxicities	Nausea	1 (2)	3 (6)	–	2 (8)	1	1
	Malaise	4 (8)	–	2 (8)	–	1	1
	Dysphagia	1 (2)	2 (4)	1 (4)	1 (4)	1	1
	Esophagitis	20 (41)	2 (4)	9 (38)	3 (13)	1	0.32
	Esophageal fistula	1 (2)	2 (4)	3 (13)	–	0.1	1
	Dermatitis	9 (18)	–	2 (8)	–	0.5	1
	Pneumonitis	6 (12)	1 (2)	2 (8)	–	1	1
	Acute kidney injury	4 (8)	–	2 (8)	–	1	1
	Leukopenia	20 (41)	3 (6)	13 (55)	4 (17)	0.06	0.21
	Anemia	29 (60)	6 (12)	18 (75)	–	0.21	0.17
	Thrombocytopenia	22 (45)	–	10 (42)	–	0.41	1
Late toxicities	Esophageal stenosis	2 (4)	1 (2)	–	2 (8)	1	0.25
	Pleural effusion	19 (39)	–	9 (37)	2 (8)	1	0.11
	Pericardial effusion	10 (20)	1 (2)	6 (25)	–	0.77	1
	Pneumonitis	4 (8)	1 (2)	1 (4)	–	1	1

CCr creatinine clearance

in one patient (who received IFI) and in seven patients (who received ENI), respectively. The remaining patients received RT and DOC as scheduled.

Discussion

The present study was designed to assess the safety of DOC-RT for EC in elderly patients with a focus on baseline renal function (age ≥ 76 years, Ccr < 60 mL/min). Our study demonstrated that DOC-RT was safe in elderly patients with EC who displayed declining renal function.

A retrospective study among elderly patients ($n = 33$) with EC receiving CRT at 60 Gy with concurrent FP reported grade 3/4 leukopenia in 70% of patients, anemia in 52%, thrombocytopenia in 33%, acute kidney injury in 9%, and esophagitis in 9%, with a CRT completion rate of 67%. Moreover, elderly patients developed leukopenia and anemia more frequently and had lower CRT completion rates than nonelderly patients [10]. Another retrospective

study involving elderly patients ($n = 34$) with EC receiving platinum-based CRT showed a high incidence of grade 3/4 neutropenia in 32.3% of patients, acute kidney injury in 17.6%, and grade 5 neutropenia in 2.9% [37]. Accordingly, these reports suggest that platinum-based CRT places elderly patients at a high risk for severe leukopenia and acute kidney injury.

Conversely, the results of a prospective trial demonstrated promising and acceptable toxicity profiles for DOC-RT in patients ($n = 34$) with inoperable EC aged between 41 and 88 years old, in which grade 3/4 toxicities included leukopenia in 9% of patients, anemia in 6%, thrombocytopenia in 3%, and no acute kidney injury. DOC-RT was discontinued due to progressive disease (four patients), deteriorating performance status (one patient), pneumonia (one patient), and an acute abdominal episode (one patient), resulting in a DOC-RT completion rate of 79% (27/34 patients) [21]. Moreover, a phase 2 study on DOC-RT in elderly patients with locally advanced EC showed grade 3/4 leukopenia in 6% of patients, thrombocytopenia in 6%, and no acute kidney injury in the patients, with a treatment completion rate of 88% [24]. However, this phase 2 study was prematurely terminated due to poor patient accrual. Considering the aforementioned findings, the present study demonstrated that DOC-RT had lower hematological toxicity and acute kidney injury rates than platinum-based CRT in elderly patients with EC (Table 3) [10, 21, 24, 37]. Thus, DOC-RT can be a safe regimen for elderly patients with EC in terms of hematological toxicities and acute kidney injury.

There have been a few previous reports on the safety of single-agent DOC therapy in patients with declining renal function. In the first report, the toxicity of DOC therapy was assessed in 11 urothelial carcinoma patients with non-dialysis declining renal function (median Ccr = 28 mL/min), in whom DOC at a tri-weekly dose of 100 mg/m^2 for one to six consecutive weeks was safely administered [38]. In the second report, the toxicity of single-agent DOC therapy (40–60 mg/m^2 tri-weekly for 2–3 cycles) was compared in 34 patients with non-small cell lung cancer who were divided into Ccr < 40 mL/min and Ccr ≥ 40 mL/min groups [39]. No significant association was observed between pretreatment Ccr and hematological and non-hematological toxicities. In addition to previous studies, our study demonstrated the safety of DOC-RT in elderly patients with Ccr < 60 mL/min.

Burno et al. reported that DOC may not be effective for patients with declining renal function compared with patients with normal kidney function [40]. They reported that baseline α1-acid glycoproteins appeared to be an important modulator of DOC pharmacokinetics and pharmacodynamics. Baseline α1-acid glycoprotein levels vary in many physiological states (i.e., age and pregnancy) and

Table 3 Literature review of results for radiotherapy in patients with esophageal cancer

Author	No.	Median age, years (range)	T1/2/3/4 (%)	N0 (%)	cStage I/II/III/IV (%)	Chemotherapy regimen	Median prescribed dose	Treatment completion rate (%)	MST (months)	Leukopenia grade 3–4 (%)	Anemia grade 3–4 (%)	Thrombocytopenia grade 3–4 (%)	Esophagitis grade 3–4 (%)	Renal dysfunction grade 3–4 (%)
Takeuchi[10]	33	74 (71–79)	6/6/88/0	43	0/54/46/0	FP	60 Gy/30 fr	67	14.7	70	52	33	9	9
Mak37	34	79.5 (75–89)	3/21/47/9 (Tx;20)	56	3/41/38/18	Patinum-based	50.4 Gy/28 fr	50	12	–	–	–	38.2	17.6
Font21	34	54 (41–88)	–	–	3/29/65/3	DOC	66 Gy/33 fr	79	6	9	6	3	17	0
Ohba[24]	16	77 (73–81)	25/6/69/0	19	0/34/56/0	DOC	60 Gy/30 fr	88	27.7	6	0	6	31	0
Our report	49 (Ccr < 60 mL/min)	80 (76–90)	27/8/34/31	45	29/16/20/35	DOC	60 Gy/30 fr	88	21	6	12	0	4	0
	24 (Ccr ≥ 60 mL/min)	80 (76–91)	25/4/21/50	29	26/12/21/41	DOC	60 Gy/30 fr	92	20	17	0	0	13	0

5FU 5-fluorouracil, *CCr* creatinine clearance, *DOC* docetaxel, *FP*, *5* fluorouracil plus cisplatin, *MST* median survival time

pathological conditions (i.e., liver cirrhosis and renal disease) and are correlated with a response to therapy. In our study, PFS and OS did not differ between the Ccr-L and Ccr-H groups. In addition to previous studies, PFS and OS for elderly patients with EC may be associated with clinical stage, nutritional status, and CCI rather than with kidney function [41, 42].

The present study has several limitations associated with its retrospective design. First, this retrospective study has selection biases. We enrolled stage I–IV EC patients who were treated with DOC-RT. Thus, we could not demonstrate a benefit of treatment with DOC-RT compared with RT alone. A previous retrospective study suggested that platinum- or taxane-based concurrent CRT (MST, 22.3 months) is superior to sequential CRT (MST, 18.0 months) and RT alone (MST, 12.4 months) in elderly patients with stage I–IV EC [43]. In our study, the MST for elderly patients in the Ccr-L and Ccr-H groups was 21 and 20 months, respectively. In terms of survival, DOC-RT might be a recommended treatment for elderly patients with EC. Second, this study was performed with a relatively small number of patients, which weakens the validity of the results. Finally, Ccr has the risk of being overestimated in elderly patients with low weight and low muscle mass. However, a previous study reported that the Cockcroft–Gault formula was the best predictive equation of Ccr in elderly patients compared with other formulas [44]. Thus, we used the Cockcroft–Gault formula in this study. Moreover, if our patients have more advanced renal dysfunction, our results provide clinically meaningful safe information for DOC-RT in elderly patients with EC.

In conclusion, DOC-RT is a safe regimen for elderly patients with EC, regardless of baseline renal function. To establish a new treatment option, Japanese study groups are conducting a phase I/II clinical trial assessing taxane-based concurrent CRT for EC in elderly patients with renal declining function [the University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000020397].

Author contributions TK prepared the manuscript and conducted the literature search; TK reviewed and edited the manuscript; TK, NS, SM, MT, and KS reviewed the manuscript. All authors have read and approved the final manuscript.

Compliance with ethical standards

Ethical Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and with the Helsinki declaration.

Conflict of interest None.

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