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Prolonged Renal Dysfunction in Patients Undergoing Chemotherapy for Locally Advanced Esophageal Cancer: Treatment Implications and Risk Factors

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Abstract

Background/Aim: The effects of prolonged renal dysfunction in patients undergoing chemotherapy for locally advanced esophageal cancer remain unclear. This study retrospectively investigated its effects on treatment and identified associated risk factors.

Patients and Methods: Patients with locally advanced esophageal squamous cell carcinoma who developed renal dysfunction during their initial chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF) were included. Patients with renal dysfunction were divided into two groups: prolonged and transient renal dysfunction groups. We assessed the effects of prolonged renal dysfunction on treatment outcomes and identified its risk factors using multivariate analysis.

Results: Thirty patients were included in the prolonged renal dysfunction group and 38 in the transient group. The median relative dose intensity of cisplatin was 83.7% in the prolonged group and 95.1% in the transient group (p=0.0009). During the median follow-up period of 21.5 months (range=2-60), the 1-year overall survival rate for patients was significantly lower in the prolonged group compared to the transient group (75.4% *vs.* 97.2%, p=0.034). The pre chemotherapy serum creatinine level ≥0.76 mg/dl (odds ratio=4.37, p=0.013) and urine volume <4,350 ml on day 1 of the first cycle (odds ratio=5.02, p=0.015) were significant risk factors for prolonged renal dysfunction.

Conclusion: Prolonged renal dysfunction during DCF therapy for esophageal cancer reduces the relative dose intensity of cisplatin, potentially compromising survival. The pre chemotherapy serum creatinine level and urine volume on day 1 of the first cycle were identified as risk factors for prolonged renal dysfunction.

Keywords: Esophageal cancer, prolonged renal dysfunction, docetaxel, cisplatin, 5-fluorouracil.

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Introduction

Locally advanced esophageal cancer cannot be controlled by surgery alone. Therefore, multidisciplinary treatment combining surgery, chemotherapy, and radiotherapy is implemented for such cancer. In Japan, the standard treatment for resectable advanced esophageal cancer consists of radical surgery following neoadjuvant chemotherapy. Preoperative chemotherapy with docetaxel, cisplatin, and 5-fluorouracil, collectively referred to as DCF therapy, is considered the standard neoadjuvant treatment based on the results of a randomized phase III trial (1). A chemoselection strategy incorporating DCF therapy has also been developed due to the high efficacy of this regimen (2, 3). These treatments involve induction chemotherapy with DCF, followed by an evaluation of treatment response.

Because the goal of DCF therapy for locally advanced esophageal cancer is to improve the rate of complete resection and extend survival, completing the treatment without reducing the cisplatin dose is crucial. The dose-limiting toxicity of cisplatin is renal impairment, which occurs in approximately 20-30% of patients receiving treatment (4-6). The primary mechanism of nephrotoxicity is tubular injury, which is dose-dependent and cumulative (4, 7, 8). Moreover, cisplatin-induced nephrotoxicity can be transient or prolonged. In cases where renal impairment persists, dose reduction of cisplatin may lead to a reduced therapeutic effect of DCF therapy. However, studies on prolonged nephrotoxicity are scarce, and much about this condition remains largely unknown. Identifying the characteristics of patients at risk of prolonged nephrotoxicity and implementing preventive measures in advance could help mitigate this adverse event and minimize its effects on treatment. Therefore, this retrospective study aimed to evaluate the effects of prolonged nephrotoxicity associated with DCF therapy in locally advanced esophageal cancer and identify predisposing factors contributing to its occurrence.

Patients and Methods

Patients. Patients diagnosed with primary esophageal cancer at Kitasato University Hospital between January 1, 2012, and December 31, 2021, who met the following inclusion criteria were included in this study:
1) Histologically diagnosed with squamous cell carcinoma.
2) Received neoadjuvant or induction DCF therapy as the initial chemotherapy.
3) Classified as having clinical stage IA-III carcinoma according to the seventh edition of the TNM classification by the Union for International Cancer Control.
4) Developed renal impairment during DCF therapy [creatinine clearance (Ccr) rate <60 ml/min].
The exclusion criteria were as follows:
1) Concurrent active malignancy in other organs.
2) History of chemotherapy for malignancies in other organs.
3) Initial dose reduction of anticancer agents from the first cycle.
4) Completion of only one cycle of DCF therapy.
5) Concomitant radiotherapy administered simultaneously with DCF therapy.
6) Pre-existing renal impairment (Ccr rate <60 ml/min) or hepatic dysfunction (aspartate aminotransferase level >100 U/l, alanine aminotransferase level >100 U/l, total bilirubin level >2.0 mg/dl) at the start of treatment.
7) Absence of clinical laboratory data within 2 weeks before chemotherapy initiation or during each treatment cycle.

Chemotherapy. In neoadjuvant or induction DCF therapy for esophageal cancer, docetaxel (70-75 mg/m^2) was administered as a 1-h intravenous infusion on day 1, cisplatin (70-75 mg/m^2) as a 2-h intravenous infusion on day 1, and 5-fluorouracil (750 mg/m^2) as a continuous intravenous infusion from day 1 to 5. One treatment cycle consisted of 21 days, and in principle, three cycles were administered. To prevent renal impairment, 2,000 ml of electrolyte infusion was administered on the day before chemotherapy, followed by 2,500 ml of extracellular fluid

replacement solution and 300 ml of D-mannitol on day 1 of chemotherapy. In addition, 2,000 ml extracellular fluid replacement solution was administered daily for 4 days from day 2 to 5. When urine volume was insufficient despite these infusions, 20 mg of furosemide was administered intravenously. Appropriate antiemetic agents were administered to prevent nausea and vomiting in accordance with Japanese and international clinical guidelines. Prophylactic antibiotics and granulocyte colony-stimulating factor were administered to prevent febrile neutropenia.

Clinical variables. Clinical data of the patients were collected from medical records. The following data were recorded at the start of the first chemotherapy cycle: age, sex, height, weight, body surface area, performance status, clinical stage, medical history, smoking history, alcohol consumption history, and concomitant medications (nonsteroidal anti-inflammatory drugs and antibiotics). In addition, data on serum albumin, serum creatinine (Scr), and Ccr were collected. All available data on Scr and Ccr throughout the treatment period were collected to obtain a detailed understanding of renal function changes. Urine volume (UV) on the day of chemotherapy administration in the first cycle (day 1) and the total urine volume from day 1 to 5 of chemotherapy were also recorded. Data on anticancer drug dosages, dose intervals and interruptions, and dose reductions were collected for each chemotherapy cycle. The concomitant use of magnesium preparations, which may have a protective effect against renal impairment, was also investigated. The clinical stage was classified according to the seventh edition of the TNM classification by the Union for International Cancer Control. Performance status was assessed using the Eastern Cooperative Oncology Group performance status scale. Ccr rate was calculated using the Cockcroft–Gault equation. Overall survival (OS) was measured from the start date of treatment to the date of death or last follow-up. The follow-up period was defined as 5 years from treatment initiation.

Nephrotoxicity. Scr is commonly used as an indicator for renal function assessment. However, Ccr reflects renal function more sensitively. Therefore, Ccr immediately before administration is generally used for cisplatin dose adjustments (9). Renal impairment was defined in this study as a decrease in the Ccr rate to <60 ml/min. Furthermore, among patients who developed renal impairment, those with a Ccr rate ≥60 ml/min at the start of the final chemotherapy cycle were classified as the transient dysfunction group, while those with a Ccr rate <60 ml/min were classified as the prolonged dysfunction group, thereby dividing the patients into two groups.

Statistical analysis. Both univariate and multivariate analyses were performed to investigate the factors affecting the prolongation of renal impairment. For the analyses, continuous variables were categorized by dichotomizing each dataset at the median, considering the presence of outliers and asymmetric distributions. Fisher's exact test was used for univariate analysis. Firth logistic regression was applied for multivariate analysis. The explanatory variables included in the multivariate analysis were selected based on previous reports and clinical relevance, including comorbid hypertension, diabetes or cardiovascular thrombosis and embolism, albumin level, Scr level, Ccr rate, UV day 1, and UV day 1 to 5 (10-13).

We compared the two groups in terms of dose reduction rate, the relative dose intensity (RDI) of cisplatin, and OS to assess the effects of prolonged renal impairment on the therapeutic efficacy of DCF therapy. Cisplatin RDI was calculated using the following formula:

Actual dose intensity/Planned dose intensity ×100%.

Actual dose intensity was determined based on the actual administered dose and dosing intervals of cisplatin in each cycle. Fisher's exact test was used to compare the dose reduction rate between the two groups, while the Mann–Whitney *U*-test was used to compare the RDI between the two groups. Kaplan–Meier survival curves were generated, and survival curves were compared using the log-rank test for OS analysis.

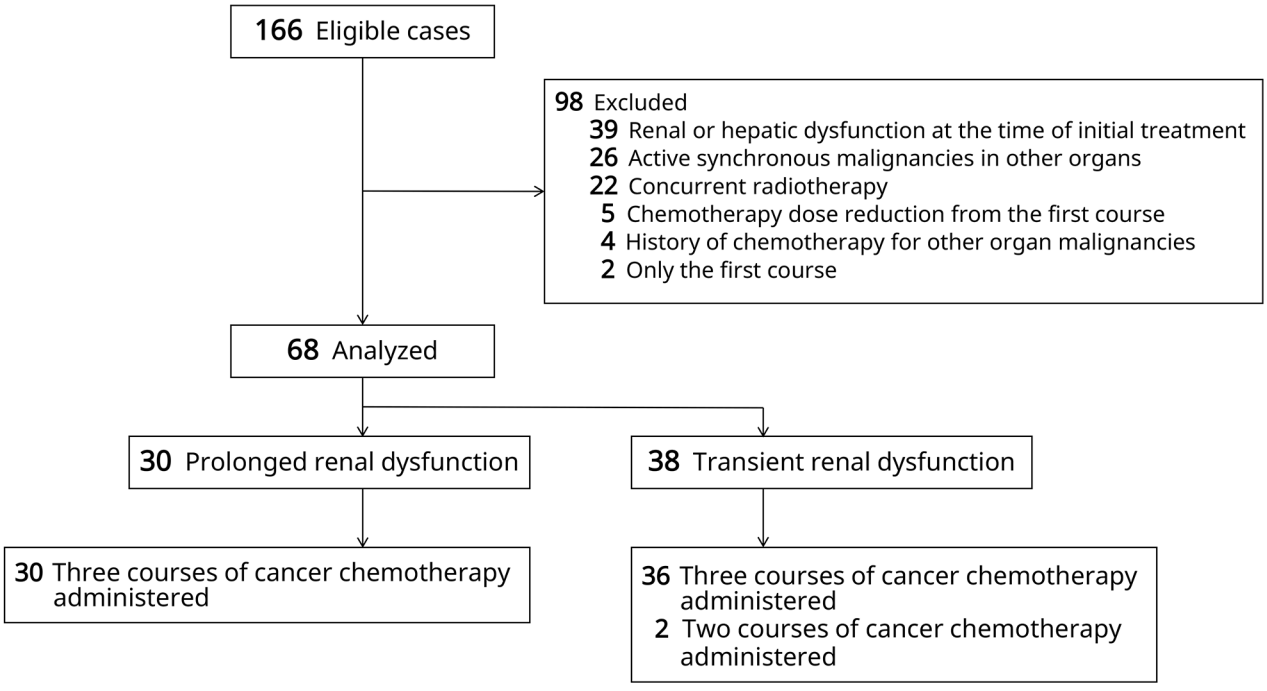

Figure 1. *Patient flow diagram.*

A statistical significance level of 0.05 was applied for all statistical tests. JMP Pro 17.0.0 (JMP Statistical Discovery LLC, Cary, NC, USA) was used for statistical analyses.

Ethics approval. This study was performed in line with the principles of the Declaration of Helsinki. It was approved by the Institutional Ethics Committee of Kitasato University School of Medicine (approval no. B15-19).

Results

The patient flow diagram in this study is presented in Figure 1. Of the 166 eligible patients, 68 were included in the analysis after excluding 98 patients. When the patients were classified into renal dysfunction groups, 30 patients (44%) were included in the prolonged renal dysfunction group, while 38 (56%) were in the transient renal dysfunction group. All patients in the prolonged group received three courses of DCF therapy, while in the transient group, 36 patients (95%) received three courses, and two patients (5%) received two courses. Regarding DCF therapy, 27 patients (90%) in the prolonged group received neoadjuvant therapy, while three (10%) received induction therapy. Similarly, in the transient group, 35 patients (92%) received neoadjuvant therapy, while three (8%) received induction therapy. The treatments following DCF therapy were similar between the two groups.

The baseline characteristics of both groups are shown in Table I. Sixteen patients (53%) in the prolonged renal dysfunction group and 23 (61%) in the transient group received concomitant oral magnesium supplements. One patient (3%) in the prolonged renal dysfunction group and three (8%) in the transient group received intravenous magnesium supplementation. The number of patients who developed renal dysfunction in courses 1, 2, and 3 were 52 (76%), 12 (18%), and 4 (6%), respectively. Changes in renal function for the two groups are shown in Figure 2. The Ccr after the start of treatment did not return to the pretreatment level, neither in the prolonged group nor in the transient group.

Table I. *Patient characteristics at the start of the first chemotherapy cycle.*

Variable		Renal dysfunction	
		Prolonged (n=30)	Transient (n=38)
Sex, n (%)	Male	27 (90)	28 (74)
	Female	3 (10)	10 (26)
Age (years)	Median (range)	64.5 (51-75)	64 (42-74)
Body mass index (kg/m^2)	Median (range)	20.1 (16.0-27.1)	20.9 (15.8-27.7)
Clinical stage†, n (%)	I	5 (17)	5 (13)
	II	18 (60)	13 (34)
	III	7 (23)	20 (53)
Complications of HTN, DM, CVT, embolism, n (%)	Yes	11 (37)	13 (34)
	No	19 (63)	25 (66)
Concomitant use of NSAIDs or antibiotics, n (%)	Yes	0 (0)	3 (8)
	No	30 (100)	35 (92)
Smoking history, n (%)	Yes	27 (90)	32 (84)
	No	2 (7)	5 (13)
Alcohol consumption history, n (%)	Yes	29 (97)	36 (95)
	No	0 (0)	1 (3)
Performance status score, n (%)	0	12 (40)	15 (39)
	1	18 (60)	23 (61)
Serum albumin level (g/dl)	Median (range)	3.9 (2.9-4.4)	4.0 (2.4-5.0)
Creatinine level (mg/dl)	Median (range)	0.82 (0.44-1.08)	0.74 (0.39-0.98)
Creatinine clearance rate (ml/min)‡	Median (range)	72.0 (61-99)	75.5 (61-130)

CVT: Cardiovascular thrombosis; DM: diabetes mellitus; HTN: hypertension; NSAIDs: nonsteroidal anti-inflammatory drugs. †Union for International Cancer Control, seventh edition. ‡Creatinine clearance rate was calculated using the Cockcroft–Gault equation.

The results of univariate and multivariate analyses for factors associated with prolonged renal dysfunction are presented in Table II. In the multivariate analysis, Scr level ≥0.76 mg/dl immediately before the first cycle of chemotherapy and UV day 1 <4350 ml were identified as risk factors for prolonged renal dysfunction (Scr: odds ratio=4.37, 95% confidence interval=1.25-18.83, p=0.013; UV day 1: odds ratio=5.02, 95% confidence interval=1.25-24.54, p=0.015).

Regarding dose reduction in DCF therapy, 24 patients (80%) in the prolonged renal dysfunction group and six (16%) in the transient group required dose reduction (p<0.0001). Among the 30 patients with dose reduction, 24 (80%) had a reduction in cisplatin only. The median RDI of cisplatin was significantly lower in the prolonged renal dysfunction group than in the group with transient renal dysfunction, at 83.7% (range=28.7-100.3%) and 95.1% (range=58.8-101.6%), respectively (p=0.0009). During the median follow-up period of 21.5 months (range=2-60), the 1- and 3-year OS rates for patients in the prolonged renal dysfunction group were significantly lower than those in the group with transient renal dysfunction (1-year OS: 75.4% *vs.* 97.2%; 3-year OS: 47.5% *vs.* 72.5%, respectively; p=0.034) (Figure 3).

Discussion

In this study, the RDI of cisplatin was significantly lower in the group with prolonged renal dysfunction than in the transient renal dysfunction group. These findings indicate that prolonged renal dysfunction may impede the completion of cisplatin administration, thereby diminishing treatment efficacy. Furthermore, OS was significantly lower in the prolonged renal dysfunction group, despite the group with transient renal dysfunction having a higher proportion of patients with stage III esophageal cancer. Imamura *et al.* reported that patients who developed acute kidney injury (AKI) due to high-dose cisplatin had poorer OS than those

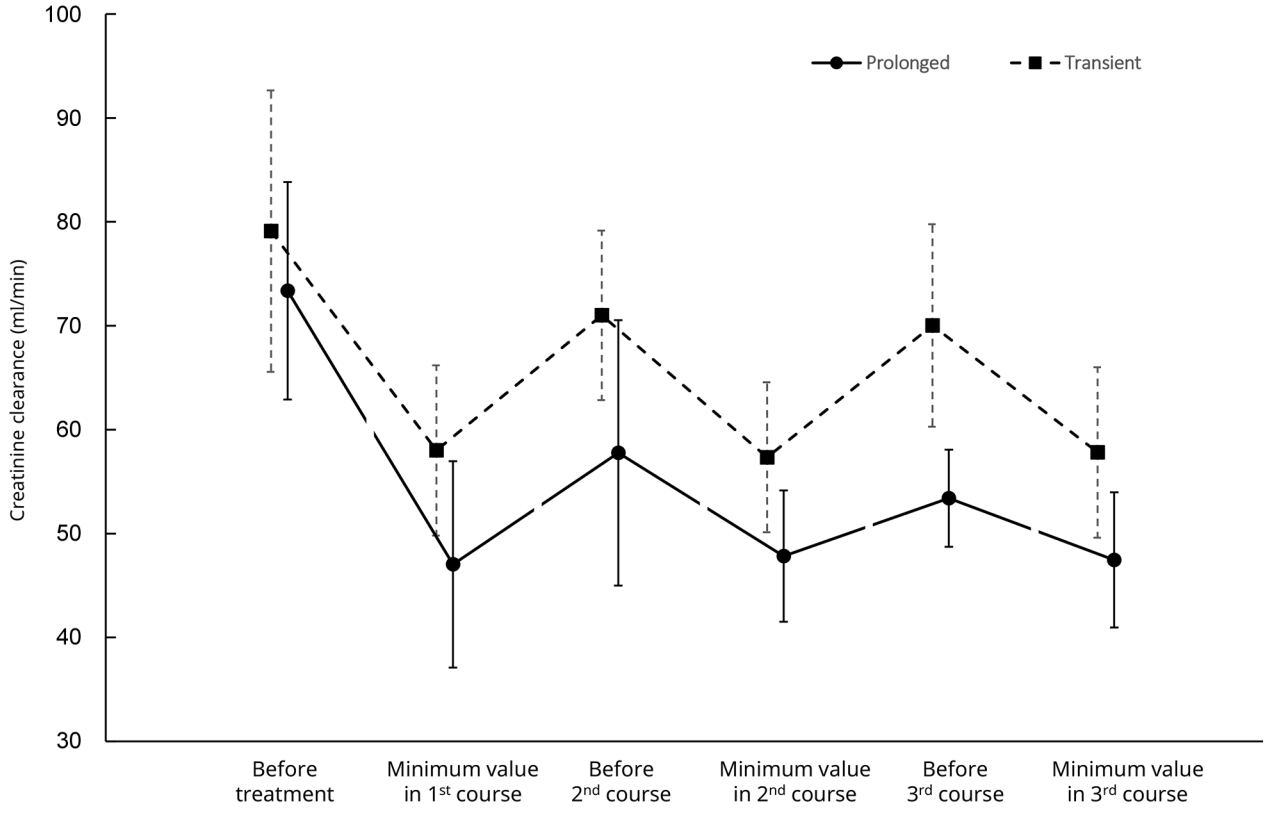

Figure 2. *Mean (±standard deviation) of creatinine clearance values during the treatment period in the two groups.*

without AKI (14). Considering our own findings as well, prolonged renal dysfunction appears to have a particularly significant impact.

The risk factors for prolonged renal dysfunction were a prechemotherapy Scr level of ≥0.76 mg/dl and a UV of <4,350 ml on the first day of chemotherapy in the initial course. Therefore, careful monitoring of renal function and proactive measures to mitigate renal deterioration in cases with these factors may improve the therapeutic efficacy of DCF therapy. Regarding dose reduction in DCF therapy, because no significant difference was observed between the dose reduction rate in the non-nephrotoxicity group from our previous study (13) and the transient renal dysfunction group in this study, the persistence of renal dysfunction is suggested to have the greatest effect on the decline in the therapeutic efficacy of DCF therapy.

AKI is a condition characterized by a rapid decline in kidney function over a short period. While some patients recover transiently, others show progression to chronic kidney disease (CKD). Recently, the AKI-to-CKD transition has attracted attention (15-17). Kellum *et al.* showed that AKI with a higher likelihood of progressing to CKD is more often persistent AKI rather than transient AKI (18). Considering our study findings, a prechemotherapy Scr level of ≥0.76 mg/dl and a UV of <4,350 ml on the first day of chemotherapy in the initial course may also be risk factors for CKD in patients undergoing DCF therapy for esophageal cancer. Although hypertension, diabetes, and cardiovascular disease were not identified as risk factors for prolonged renal dysfunction in this study, they are well-known major risk factors for CKD (19). Therefore, patients with these diseases who also have risk factors for prolonged renal dysfunction should be monitored

Table II. *Risk factors for prolonged renal dysfunction in patients undergoing chemotherapy for esophageal cancer.*

Variable†		Renal dysfunction, n (%)		Univariate		Multivariate	
		Prolonged (n=30)	Transient (n=38)	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Sex	Male	27 (90)	28 (74)	3.21 (0.80-12.96)	0.124	–	–
	Female	3 (10)	10 (26)				
Age	≥64 Years	17 (57)	22 (58)	0.95 (0.36-2.50)	>0.99	–	–
	<64 Years	13 (43)	16 (42)				
Complications of HTN, DM, CVT, embolism	Yes	11 (37)	13 (34)	1.11 (0.41-3.03)	>0.99	0.80 (0.22-2.71)	0.738
	No	19 (63)	25 (66)				
Concomitant use of NSAIDs or antibiotics on the day of chemotherapy	Yes	0 (0)	3 (8)	–	0.249	–	–
	No	30 (100)	35 (92)				
Smoking history	Yes	27 (90)	32 (84)	2.11 (0.38-11.76)	0.453	–	–
	No	2 (7)	5 (13)				
Alcohol consumption history	Yes	29 (97)	36 (95)	–	>0.99	–	–
	No	0 (0)	1 (3)				
Performance status score	0	12 (40)	15 (39)	0.98 (0.37-2.60)	>0.99	–	–
	1	18 (60)	23 (61)				
Serum albumin level	≥4.0 g/dl	14 (47)	23 (61)	1.75 (0.67-4.62)	0.329	1.96 (0.60-6.96)	0.240
	<4.0 g/dl	16 (53)	15 (39)				
Creatinine level	≥0.76 mg/dl	21 (70)	16 (42)	3.21 (1.17-8.83)	**0.029**	4.37 (1.25-18.83)	**0.013**
	<0.76 mg/dl	9 (30)	22 (58)				
Creatinine clearance rate	≥75 ml/min	13 (43)	23 (61)	2.01 (0.76-5.30)	0.222	2.25 (0.70-7.76)	0.152
	<75 ml/min	17 (57)	15 (39)				
Concomitant use of oral Mg preparations during treatment	Yes	16 (53)	23 (61)	0.75 (0.28-1.96)	0.625	–	–
	No	14 (47)	15 (39)				
Concomitant use of iv. Mg preparations during treatment period	Yes	1 (3)	3 (8)	0.40 (0.04-4.08)	0.625	–	–
	No	29 (97)	35 (92)				
Urine volume on day 1 of the first cycle	≥4,350 ml	10 (33)	22 (58)	3.05 (1.08-8.56)	**0.044**	5.02 (1.25-24.54)	**0.015**
	<4,350 ml	18 (60)	13 (34)				
Total urine volume from day 1 to 5 of the first cycle	≥20,155 ml	11 (37)	18 (47)	2.01 (0.71-5.74)	0.292	0.71 (0.18-2.63)	0.597
	<20,155 ml	16 (53)	13 (34)				

OR: Odds ratio; CI: confidence interval; CVT: cardiovascular thrombosis; DM: diabetes mellitus; HTN: hypertension; iv.: intravenous; NSAIDs: nonsteroidal anti-inflammatory drugs; Mg: magnesium. †Continuous variables were categorized by dichotomizing each dataset at the median. The data on age, performance status, serum albumin and creatinine levels, and creatinine clearance rate were collected immediately before the first chemotherapy cycle. Statistically significant *p*-values are shown in bold.

for renal function over the long term, even after the completion of chemotherapy.

CKD is associated with an increased risk of all-cause and cardiovascular mortality and end-stage renal disease (20-22). Therefore, early detection and intervention for persistent AKI, which may progress to CKD, are crucial. Several biomarkers have been reported to predict cisplatin-induced AKI earlier than conventional indicators such as Scr. Measuring these biomarkers may also allow for earlier detection of persistent AKI (23, 24). Recently, many reports have suggested that magnesium administration is effective in preventing cisplatin-induced nephrotoxicity (6, 25-32). Cisplatin-induced nephrotoxicity primarily results from tubular damage, particularly affecting the S3 segment of the proximal tubule (33). This mechanism is believed to involve the expression of organic cation transporter 2 (OCT2), an organic cation transporter, through which cisplatin is taken up into the renal tubules, leading to tubular damage (34, 35). When hypomagnesemia occurs due to cisplatin administration, OCT2 is overexpressed, suggesting that magnesium supplementation may help prevent cisplatin-induced nephrotoxicity (36). Continuous damage to the S3 segment of the proximal tubule can

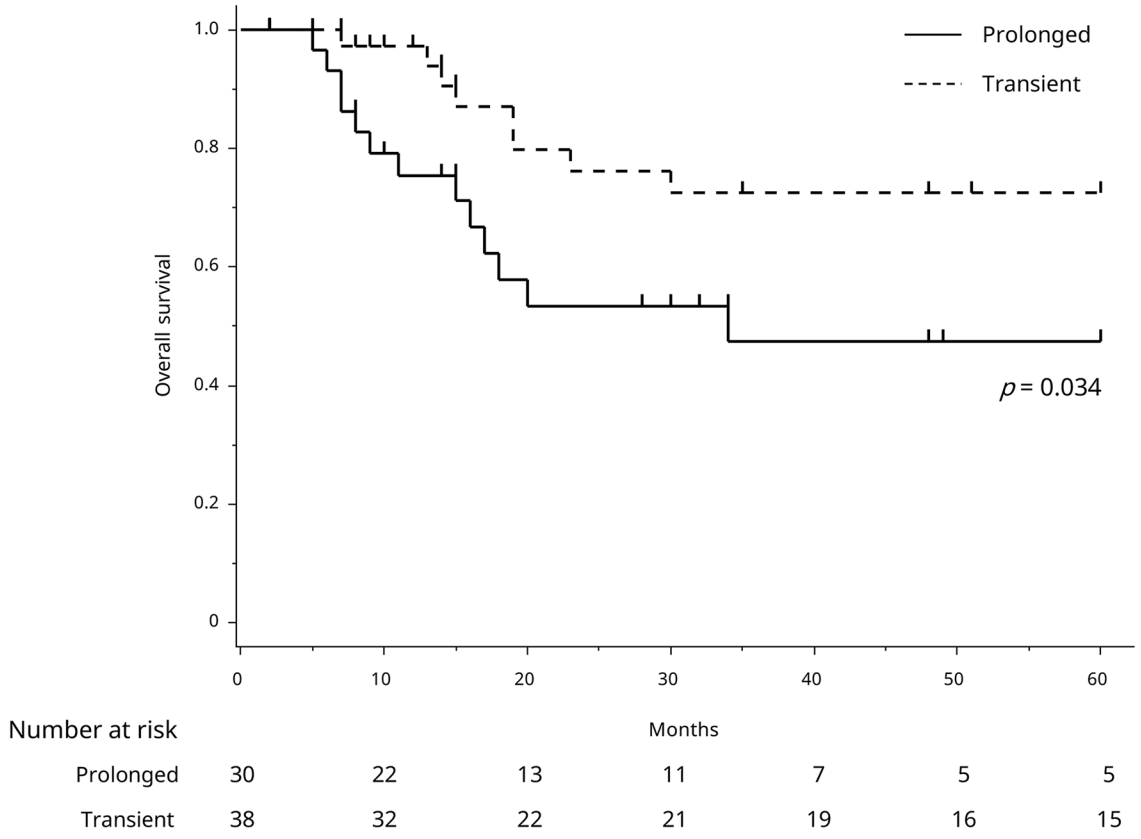

Figure 3. *Kaplan–Meier overall survival curves according to renal dysfunction in patients under therapy for esophageal cancer. The median follow-up period for the prolonged and the transient dysfunction groups was 16.5 months and 41.5 months, respectively.*

lead to prolonged renal dysfunction (37). Therefore, magnesium supplementation may also help prevent the persistence of cisplatin-induced nephrotoxicity. We are currently conducting a phase II clinical trial to evaluate the efficacy of prophylactic magnesium administration for renal dysfunction in patients undergoing DCF therapy for esophageal cancer. Given that patients with risk factors for prolonged renal dysfunction identified in this study may benefit more from this intervention, a detailed subgroup analysis will be conducted.

Study limitations. Nonsteroidal anti-inflammatory drugs and antibiotics are well-known drugs that can cause drug-induced nephrotoxicity, and their concomitant use may affect the occurrence and persistence of renal dysfunction during DCF therapy. However, due to the small number of cases with concomitant drug use in this study, we could not evaluate their effects. In addition, this study did not investigate the details of adverse effects other than renal dysfunction associated with DCF therapy. Because approximately 80% of dose reductions involved only cisplatin, presumably nephrotoxicity, the dose-limiting toxicity of cisplatin, had the greatest effect on DCF dose reduction. However, other adverse effects that could affect cisplatin dosage, such as nausea and vomiting, should also be examined.

Conclusion

Prolonged renal dysfunction reduces the RDI of cisplatin during DCF therapy for locally advanced esophageal cancer, potentially compromising treatment efficacy,

such as lowering overall survival. A prechemotherapy Scr level ≥0.76 mg/dl and a UV <4,350 ml on the first day of the initial course are risk factors for prolonged renal dysfunction in DCF therapy for esophageal cancer.

Conflicts of Interest

The Authors have no relevant financial or nonfinancial interests to disclose.

Authors' Contributions

All Authors contributed to the study conception and design. J.M. and T.H. collected and analyzed patient data. J.M. wrote the first draft of the manuscript. All Authors reviewed previous versions of the manuscript and read and approved the final manuscript.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, the AI-based tools ChatGPT by OpenAI and DeepL Translator by DeepL SE were used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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