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# Dose Adjustment of Oxaliplatin Based on Renal Function in Patients With Metastatic Colorectal Cancer

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**Abstract.** *Background/Aim: The effect of renal dysfunction on the toxicity and efficacy of oxaliplatin remains unclear. We investigated the association between creatinine clearance (Ccr), a marker of renal function, and the toxicity and efficacy of oxaliplatin in patients with metastatic colorectal cancer (mCRC). Patients and Methods: Patients with mCRC who received oxaliplatin-based chemotherapy as first-line treatment were included in this study. Primary outcome was peripheral neuropathy (Grade ≥2), while secondary outcomes included neutropenia (Grade ≥3), thrombocytopenia (Grade ≥2) and overall survival (OS). Results: A total of 145 patients with mCRC were eligible. Incidence rates of peripheral neuropathy (Grade ≥2), neutropenia (Grade ≥3) and thrombocytopenia (Grade ≥2) were 30.3%, 37.2% and 16.6%, respectively, and median OS was 29.1 months. Cox proportional hazards analysis indicated that there was no significant relationship between Ccr and any adverse event, or between Ccr and OS. Conclusion: Dose reduction of oxaliplatin based on Ccr is not recommended in patients with mCRC.*

Platinum anticancer drugs such as cisplatin and carboplatin are mainly excreted through the kidneys, and clearance rates are therefore reduced with renal dysfunction (1, 2). Anticancer drugs have a narrow therapeutic window and elevated plasma drug concentrations may cause life-threatening adverse events. Therefore, the doses of these anticancer drugs should be adjusted according to renal function. Kintzel and Dorr (3) have recommended that their doses should be modified as follows: fraction of dose = f × (Kf-1) + 1, where Kf=patient's creatinine clearance (Ccr)/120 and f=rate of renal excretion of the intact chemotherapy agent or its active metabolites. Carboplatin dose is commonly determined using the Calvert formula (4): dose (mg)=target area under the concentration time curve (AUC) × (GFR+25).

In comparison, dose adjustment for oxaliplatin based on renal function is uncommon, irrespective of the increased renal excretion rate of this compound (5). Oxaliplatin is a third-generation platinum analog which is effective against metastatic colorectal cancer (mCRC) when given together with fluoropyrimidines and monoclonal antibodies to inhibit vascular endothelial growth factor (VEGF) (6-8) and epidermal growth factor receptors (EGFR) (9, 10).

Adverse events associated with administration of oxaliplatin include myelosuppression, peripheral neuropathy, nausea and vomiting (11, 12). Takimoto *et al*. (13) have evaluated the incidence and severity of adverse events in 37 patients with mCRC grouped by renal function, namely normal (Ccr≥60 ml/min), mild (Ccr 40-59 ml/min), moderate (Ccr 20-39 ml/min), and severe dysfunction (Ccr<20 ml/min). They showed that the incidence and severity of adverse events including nausea, vomiting, constipation, peripheral neuropathy, fatigue and laryngodysesthesia did not differ among patients with Ccr levels higher than 20 ml/min. Further, they showed no significant changes in the incidence of oxaliplatin-associated adverse events in 34 patients with mCRC who received 130 mg/m$^2$ of oxaliplatin, despite renal impairment (Ccr>20 ml/min)-dependent increases in the AUC for oxaliplatin (14). Nikanjam *et al*. (15) have reported that oxaliplatin clearance varied 6.7-fold within the range of serum creatinine values among patients with advanced malignancy treated with 60-130 mg/m$^2$ oxaliplatin.

We have recently reported a significant association between Ccr value and incidence of grade >2 nausea in patients with colorectal cancer receiving oxaliplatin, and showed that patients with impaired renal function (Ccr<60 ml/min) were

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at high risk for grade >2 nausea [odds ratio (OR)=2.61, 95% confidence interval (CI)=1.04-6.55, $p$=0.042] (16). That report limited its evaluation of adverse events to those occurring only during first chemotherapy cycle, and the relationship between Ccr and peripheral neuropathy, or Ccr and overall survival (OS) was not examined. In addition, Yamazaki *et al*. have found that the incidence of grade 3 CAPOX-related AEs was higher in a Ccr-L (Ccr<50 ml/min) group (42.3%) than a Ccr-H (Ccr≥50 ml/min) group (31.3%), and that the proportion of subjects who discontinued treatment within the first four cycles as a result of AEs was also higher in the Ccr-L group (21.1% *versus* 2.9%, respectively) (17). Similarly to our previous study, however, they collected and analyzed data during the first 4 cycles of CAPOX therapy only, and did not evaluate effectiveness.

Here, to better understand the effect of renal dysfunction on treatment with oxaliplatin, we investigated the association between creatinine clearance (Ccr) and the toxicity and efficacy of oxaliplatin in mCRC patients receiving this agent until disease progression.

## Patients and Methods

*Patients*. This was a retrospective observational study of data obtained from patient electronic medical records at our hospital. Study subjects were patients with mCRC who received first-line cancer chemotherapy, including oxaliplatin, at Gifu University Hospital between January 2010 and December 2017. Patients with a reduction in the initial dose of oxaliplatin due to poor performance status (Eastern Cooperative Oncology Group score ≥2) or discontinuation without image evaluation were excluded. Ccr was estimated using the Cockcroft-Gault equation.

*Chemotherapy*. Patients received either a modified FOLFOX6 regimen every 2 weeks, or a capecitabine plus oxaliplatin (CAPOX) regimen or S-1 plus oxaliplatin (SOX) regimen every 3 weeks. The modified FOLFOX6 regimen consisted of a 2 h bolus injection of 85 mg/m$^2$ oxaliplatin, a 2 h bolus injection of 200 mg/m$^2$ L-leucovorin, and 10 min bolus injection of 400 mg/m$^2$ 5-fluorouracil (5-FU), which was followed by continuous infusion of 2,400 mg/m$^2$ 5-FU for an additional 46 h. CAPOX comprised of a 2 h bolus injection of 130 mg/m$^2$ oxaliplatin and oral administration of 2,000 mg/m$^2$ capecitabine twice a day from days 1 to 15, then a break for 7 days. SOX consisted of a 2 h bolus injection of 130 mg/m$^2$ oxaliplatin and oral administration of 80 mg/m$^2$ S-1 twice a day from day 1 to day 15, followed by a break for 7 days. The starting doses of capecitabine in patients with a Ccr<50 ml/min and of S-1 in those with Ccr<60 ml/min were reduced to 75%. All patients were given the regular initial dose of oxaliplatin in the first cycle. Patients experiencing severe adverse events, assessed according to institutional standards, received lower doses in subsequent cycles. Doses were not re-escalated in these patients even if the adverse event disappeared.

*Adverse events*. Adverse events included peripheral neuropathy, neutropenia and thrombocytopenia and were graded according to the Common Terminology Criteria for Adverse Events version 4.0 (18). The incidence of peripheral neuropathy (Grade ≥2) was used as the primary indicator of the safety of chemotherapy.

*Efficacy of chemotherapy*. OS was used as the primary indicator of the efficacy of chemotherapy. OS was defined as the time from initiation of therapy to death. Time to treatment failure (TTF) was assessed as the time from the initiation to the end of therapy with oxaliplatin. Tumor response was determined, using computed tomography scans, as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) based on Response Evaluation Criteria in Solid Tumors guideline version 1.1. (19). Overall response rate was determined as CR+PR, and disease control rate (DCR) as CR+PR+SD.

*Statistical analyses*. Statistical analyses were conducted using IBM SPSS version 22 (IBM Japan Ltd., Tokyo, Japan), R software version 3.5.1 (20) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA). $p$-Values less than 0.05 were considered significant. Patient characteristics were described as median with 25$^{th}$ and 75$^{th}$ percentiles for continuous variables, and by frequency and percentage for categorical variables.

The primary study outcome was time-to-peripheral neuropathy (Grade ≥2) from the initial administration of oxaliplatin. For the primary analysis, the effect of Ccr on peripheral neuropathy was assessed using a Cox proportional hazards regression model with adjustment for covariates including age and sex. Secondary outcomes included time-to-neutropenia (Grade ≥3), time-to-thrombocytopenia (Grade ≥2) and OS. Secondary outcomes were analysed by Cox proportional hazards regression with adjustment for covariates. Carcinoembryonic antigen (CEA), neutrophil-lymphocyte ratio (NLR), and the modified Glasgow prognostic score (mGPS) have been reported as prognostic factors in mCRC patients (21-23). In addition, conversion surgery, wherein systemic therapy in patients with initially unresectable distant metastasis opens the possibility of R0 resection (24, 25), is known to substantially extend survival time. For analysis related to OS, covariates were based on clinical judgment and previous research to include age, sex, mGPS, conversion surgery, CEA and NLR owing to their strong expected associations with OS. CEA, NLR and mGPS were treated as continuous variables. Conversion surgery was applied to time-dependent covariates. In addition, to clarify Ccr's possible confounding of adverse events, TTF and tumor response, a Cox proportional hazards regression with adjustment for age and sex was performed.

Efficacy and safety were compared between patients with impaired (Ccr<60 ml/min) and normal renal function (Ccr≥60 ml/min). A Kaplan–Meier estimate and log-rank test were used to assess OS by level of renal function. TTF was compared using the log rank test, and the incidence of adverse events and tumor response were compared using the chi-square test.

*Ethics statement*. This study was performed in accordance with the guideline for human studies mandated by the ethics committee of Gifu University Graduate School of Medicine following notification by the Japanese Government (Institutional review board approval No. 2018-222). Given that the study was retrospective, informed consent from patients was not required. All study procedures involving humans were conducted in accordance with the ethical standards required by our institution, the national research committee, and/or the 1964 Helsinki Declaration and later amendments, or with comparable ethical standards.

Table I. *Patient demographics.*

| | | |
|---|---|---|
| Number of patients (male/female) | 145 | (91/54) |
| Age, median (mini–max, years) | 65.0 | (34-86) |
| Body weight (kg) | 55.5 | (48.5-62.5) |
| Body mass index (BMI, kg/m2) | 21.1 | (19.5-23.4) |
| Aspartate aminotransferase (U/l) | 19.0 | (16.0-27.0) |
| Alanine aminotransferase (U/l) | 18.0 | (11.0-27.0) |
| Serum creatinine (mg/dl) | 0.67 | (0.54-0.77) |
| Creatinine clearance (ml/min) | 85.2 | (69.1-106.0) |
| Total bilirubin (mg/dl) | 0.6 | (0.5-0.8) |
| Neutrophil (/μl) | 3460 | (2678-4440) |
| Hemoglobin (g/dl) | 12.1 | (10.6-13.0) |
| Platelet (/μl) | 24.5 | (20.4-32.4) |
| Albumin (g/dl) | 3.9 | 3.6-4.2 |
| CRP (mg/dl) | 0.15 | 0.06-1.29 |
| Lymph (/μl) | 1557 | 1230-1962 |
| Carcinoembryonic antigen (CEA, ng/ml) | 10.1 | 3.6-63.9 |
| Carbohydrate antigen 19-9 (CA19-9, U/ml) | 25.7 | 7.6-98.75 |
| Modified Glasgow prognostic score (mGPS, 0/1/2) | 102/18/25 | |
| Neutrophil-lymphocyte ratio (NLR) | 2.2 | 1.5-3.3 |
| RAS mutation n, % | 53 | 36.6 |
| Postoperative recurrence n, % | 44 | 30.3 |
| Metastatic cancer n, % | 113 | 77.9 |
| Chemotherapy regimens | 99 | 34.5% |
| FOLFOX base (L-OHP: 80 mg/m$^2$), n, % | 104 | 71.7% |
| CAPOX base (L-OHP: 130 mg/m$^2$), n, % | 25 | 17.2% |
| SOX base (L-OHP: 130 mg/m$^2$), n, % | 16 | 11.0% |
| Combination of molecular targeted drugs | | |
| Bevacizumab, n, % | 74 | 51.3% |
| Cetuximab or Panitumumab, n, % | 48 | 33.3% |
| None, n, % | 22 | 15.3% |

All data indicate median, 25-75$^{th}$ percentiles unless otherwise indicated. FOLFOX: Fluorouracil, leucovorin and oxaliplatin; CAPOX: capecitabine and oxaliplatin; SOX: gimeracil/oteracil/tegafur (S-1) and oxaliplatin.

## Results

*Patient demographics*. A total of 170 patients with mCRC who received first-line chemotherapy which included oxaliplatin were found to be eligible. Among these, 25 patients were excluded as they had been treated with a reduced initial dose of oxaliplatin due to a poor ECOG performance status of ≥2 or because they discontinued treatment with no image evaluation. Data for the remaining 145 patients were analyzed. Patient demographics are shown in Table I. Among the 145 patients studied, 91 (62.8%) were male and 54 (37.2%) were female. The proportions of patients receiving the modified FOLFOX6 regimen, CAPOX regimen and SOX regimen was 71.7%, 17.2% and 11.0%, respectively. Among the 145 studied patients, the number with impaired (Ccr<60 ml/min) and normal renal function (Ccr≥60 ml/min) was 14 (9.7%) and 131 (90.3%), respectively.

*Efficacy and safety oxaliplatin-based chemotherapy in mCRC patients*. The relative dose intensity (RDI) of oxaliplatin was 0.65 [interquartile range (IQR)=0.48-0.82]. Median OS was 29.1 months (IQR=17.3-49.1), overall response rate (CR+PR) was 54.1% and median TTF was 9.4 months (IQR=5.7-12.9). The reason for discontinuations was progressive disease, conversion surgery, and adverse events (such as severe peripheral neuropathy or fatigue), with rates of 54.5%, 24.8% and 20.7%, respectively. The incidence rate of neutropenia (Grade ≥3), thrombocytopenia (Grade ≥2), and peripheral neuropathy (Grade ≥2) were 37.2%, 16.6%, and 30.3%, respectively.

*Relationship between Ccr and adverse events*. The Cox proportional regression analysis showed that Ccr was not a significant risk for grade ≥2 peripheral neuropathy [hazard ratio (HR)=1.37, 95%CI=0.72-2.6, $p$=0.625] (Table II). In

Table II. *Cox proportional hazards analyses of Ccr associated with peripheral neuropathy (Grade ≥2), neutropenia (Grade ≥3) and thrombocytopenia (Grade ≥2) in mCRC patients receiving oxaliplatin-based chemotherapy.*

| Adverse event | HR | 95%CI | $p$-Value |
|---|---|---|---|
| Peripheral neuropathy (Grade ≥2) | 1.37 | (0.72-2.6) | 0.625 |
| Neutropenia (Grade ≥3) | 0.82 | (0.47-1.42) | 0.683 |
| Thrombocytopenia (Grade ≥2) | 1.38 | (0.6-3.22) | 0.285 |

Hazard ratio (HR), 95% confidence interval (CI) and interquartile range (IQR) are shown. All Cox proportional hazards analyses were adjusted for age and sex.

Table III. *Cox proportional hazards analysis of OS in CRC patients receiving oxaliplatin-based chemotherapy.*

| Factor | HR | 95%CI | $p$-Value |
|---|---|---|---|
| Ccr (IQR=69.1-106) | 1.36 | (0.88-2.1) | 0.284 |
| Age (IQR=56-70) | 1.59 | (1.08-2.34) | 0.019 |
| Female | 0.65 | (0.4-1.05) | 0.076 |
| mGPS (IQR=0-2) | 2.3 | (1.29-4.13) | 0.005 |
| Conversion surgery | 0.16 | (0.09-0.28) | <0.001 |
| CEA (IQR=3.6-63.9) | 1.03 | (1.01-1.05) | 0.002 |
| NLR (IQR=1.52-3.33) | 1.32 | (1.04-1.69) | 0.023 |

Hazard ratio (HR), 95% confidence interval (CI) and interquartile range (IQR) are shown. Conversion surgery was a time-varying exposure.

Table IV. *Cox proportional hazards analyses of Ccr associated with time to treatment failure and time to tumor response in mCRC patients receiving oxaliplatin-based chemotherapy.*

| Outcome | HR | 95%CI | $p$-Value |
|---|---|---|---|
| Time to treatment failure | 0.99 | (0.98-1.00) | 0.102 |
| Tumor response | 0.99 | (0.99-1.01) | 0.875 |

HR: Hazard ratio; CI: confidence interval; IQR: interquartile range. All Cox proportional hazards analyses were adjusted for age and sex.

Table V. *Comparison of median time to treatment failure, response rate and conversion surgery rate between patients with impaired (Ccr<60 ml/min) and normal renal function (Ccr≥60 ml/min).*

| | Impaired renal function (Ccr <60 ml/min) (N=14) | Normal renal function (Ccr ≥60 ml/min) (N=131) | *p*-Value |
|---|---|---|---|
| Median time to treatment failure (months, 95%CI) | 12.4 (10.3-14.5) | 9.7 (8.9-10.6) | 0.279[a] |
| Response rate (CR+PR) (%) | 35.7% | 56.5% | 0.230[b] |
| Conversion surgery rate (%) | 14.3% | 42.7% | 0.046[b] |

[a]Log-rank test, [b]chi-squared test. CR: Complete response; PR: partial response.

addition, Ccr was not a significant risk for Grade ≥3 neutropenia (HR=0.82, 95%CI=0.47-1.42, $p$=0.683) or Grade ≥2 thrombocytopenia (HR=1.38, 95%CI=0.6-3.22, $p$=0.285) (Table II).

*Relationship between Ccr and indicators of efficacy.* We investigated whether renal dysfunction affected the efficacy of chemotherapy which included oxaliplatin using time varying Cox proportional hazards regression. The results showed no significant relationship between Ccr and OS (HR=1.36, 95%CI=0.88-2.1, $p$=0.284) after adjustment for age, sex, mGPS, conversion surgery, CEA and NLR (Table III). Further, Cox proportional hazards regressions indicated that CCr was not a significant risk factor for TTF or tumor response (Table IV). However, conversion surgery was significantly correlated with OS in mCRC patients (HR=0.16, 95%CI=0.09-0.28, $p$<0.001).

*Comparison of efficacy and safety among patients with impaired (Ccr<60 ml/min) and normal renal function (Ccr≥60 ml/min).* Patients with impaired (Ccr<60 ml/min) and normal renal function (Ccr≥60 ml/min) showed no difference concerning the incidence of peripheral neuropathy (Grade ≥2), neutropenia (Grade ≥3) and thrombocytopenia (Grade ≥2) (Figure 1). Conversion surgery rate was significantly increased in patients with normal renal function compared with those with impaired renal function (Table V), and response rate tended to be higher, albeit without significance (Table V). In contrast, median TTF and OS did not significantly differ between the groups (Table V, Figure 2).

## Discussion

In this study, we found no significant association between Ccr and the toxicity and efficacy of oxaliplatin-based first-line chemotherapy in subjects with mCRC receiving this agent until progression. The incidence of peripheral neuropathy (Grade ≥2), neutropenia (Grade ≥3) and thrombocytopenia (Grade ≥2) did not significantly differ between those with impaired (Ccr<60 ml/min) and normal renal function (Ccr≥60 ml/min). In addition, OS and TTF also showed no difference between the two groups. These findings suggest that oxaliplatin dose should not be reduced based on decreased Ccr in patients with mCRC.

Recent studies have described the effectiveness of chemotherapy in the treatment of mCRC. The use of molecular target anticancer agents, including bevacizumab (BEV), cetuximab and panitumumab, in combination with cytotoxic anticancer agents like oxaliplatin, irinotecan and 5-FU has extended OS to over 30 months (26). Oxaliplatin-based chemotherapy such as mFOLFOX, CAPOX, and SOX is first-line treatment for metastatic colorectal cancer. Despite its high renal excretion rate, however, dose adjustment for oxaliplatin based on renal function is uncommon in clinical practice. To determine the necessity of dose adjustment of oxaliplatin associated with decreased renal function, we conducted a retrospective study which analyzed the relationship between Ccr and the dose limited toxicity, and Ccr and efficacy, in mCRC patients receiving oxaliplatin.

Yamazaki *et al.* have reported a median progression-free survival (PFS) and OS for mFOLFOX6 + Bev of 10.7 and 28.9 months, respectively, in WJOG4407G, a randomized, open-label, phase III trial held in Japan (27). These values are consistent with the median OS and TTF values in our present study (OS, 29.1 months; TTF, 9.4 months). In contrast, the incidence of peripheral neuropathy (Grade ≥2) in our study was lower than that in WJOG4407G (26) (30.3% *versus* 52.0%), and our proportion of patients subjected to conversion surgery was as high as 24.8%, compared to 12% in WJOG4407G (27). We, therefore, consider that the lower exposure to oxaliplatin reduced the incidence of peripheral neuropathy (Grade ≥2).

Our study showed that there was no significant association between Ccr, a marker of renal function, and adverse events such as peripheral neuropathy, neutropenia and thrombocytopenia in mCRC patients receiving first-line chemotherapy which included oxaliplatin. In contrast, we have previously reported that the incidence of grade >2 nausea had a negative correlation with Ccr values on multivariable logistic regression analysis (OR=0.48, 95%CI=0.27-0.87, $p$=0.049) (16).

Our present findings raise an interesting question: why does peripheral neuropathy show no significant relationship with renal function, unlike the case of nausea? The AUC of oxaliplatin is significantly increased in patients with moderate

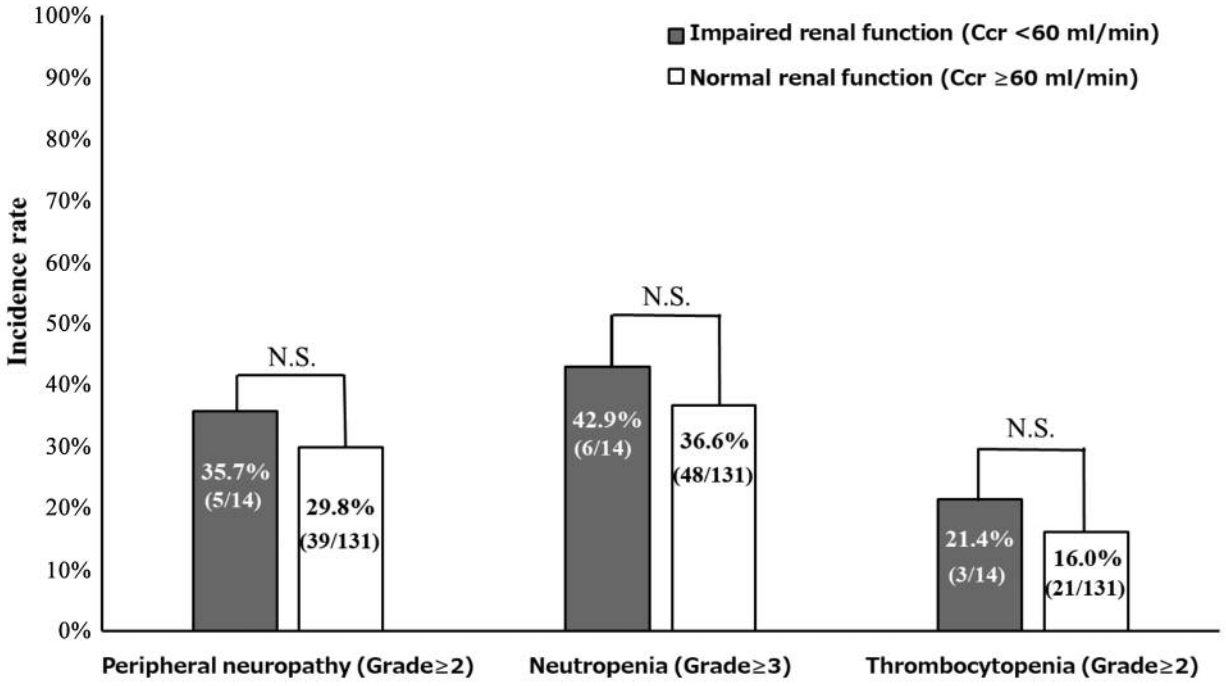


Figure 1. *Incidence rates of peripheral neuropathy (Grade ≥2), neutropenia (Grade ≥3) and thrombocytopenia (Grade ≥2) in patients with impaired (Ccr <60 ml/min) and normal renal function (Ccr≥60 ml/min). N.S.: Not significant.*

renal impairment and clearance of ultrafiltrate platinum is significantly decreased (28). Nevertheless, while Merkel *et al*. have shown a significant increase in AUC of oxaliplatin in patients suffering from nausea on day 1, no relationship of Cmax and AUC with other toxicity symptoms, including peripheral neuropathy was observed (29). Delord *et al*. have also shown that the pharmacokinetic data could not be correlated with the development of neuropathy (30). These reports suggest that an elevated AUC of oxaliplatin is associated with nausea, but not peripheral neuropathy. We interpret these past and our present results as recommending against dose adjustment of oxaliplatin based on renal function, but for a strengthening of antiemetic measures.

In the present study, although we observed no significant relationship between Ccr and efficacy, including OS, TTF and tumor response, the conversion surgery rate was significantly higher in patients with normal renal function than in those with impaired renal function (14.3% *versus* 42.7%, $p$=0.001). Currie *et al*. have reported that patients with chronic kidney disease (CKD) may be more likely to present cardiovascular complications after CRC resection and be at elevated risk of noncancer death (31). When evaluating the possibility of successful surgery, surgeons consider not only the ability to remove all cancer cells, but also organ function and complications after surgery. This likely explains the lower rate of conversion surgery in patients with impaired rather than normal renal function.

In contrast, the Cox proportional hazard analysis showed that conversion surgery was significantly correlated with OS in mCRC patients. In previous studies, first-line chemotherapy which included oxaliplatin combined with VEGF antibody or EGFR antibody allowed many mCRC patients to be treated with conversion surgery (8, 26, 32-34). In our present study, the rate conversion surgery to patients with oxaliplatin-based chemotherapy was about 40%. Even in patients with impaired renal function (Ccr<60 ml/min), initial administration of a standard oxaliplatin dose enabled transition to conversion surgery in 14% of them. Given that an appropriate initial dose is associated with high efficacy, such as conversion, we consider that an initial dose reduction of oxaliplatin based on renal function should be avoided.

Several limitations of our study should be mentioned. First, it was conducted with a retrospective design and analysed data from a single center. Second, Ccr was estimated using the Cockcroft-Gault equation, which carries a risk of under- or overestimation of renal function compared to actual measurement values. Third, the study did not report pharmacokinetic data.

## Conclusion

We investigated whether a reduction in renal function would affect the incidence of adverse events associated with oxaliplatin, and the therapeutic effect in mCRC patients. A

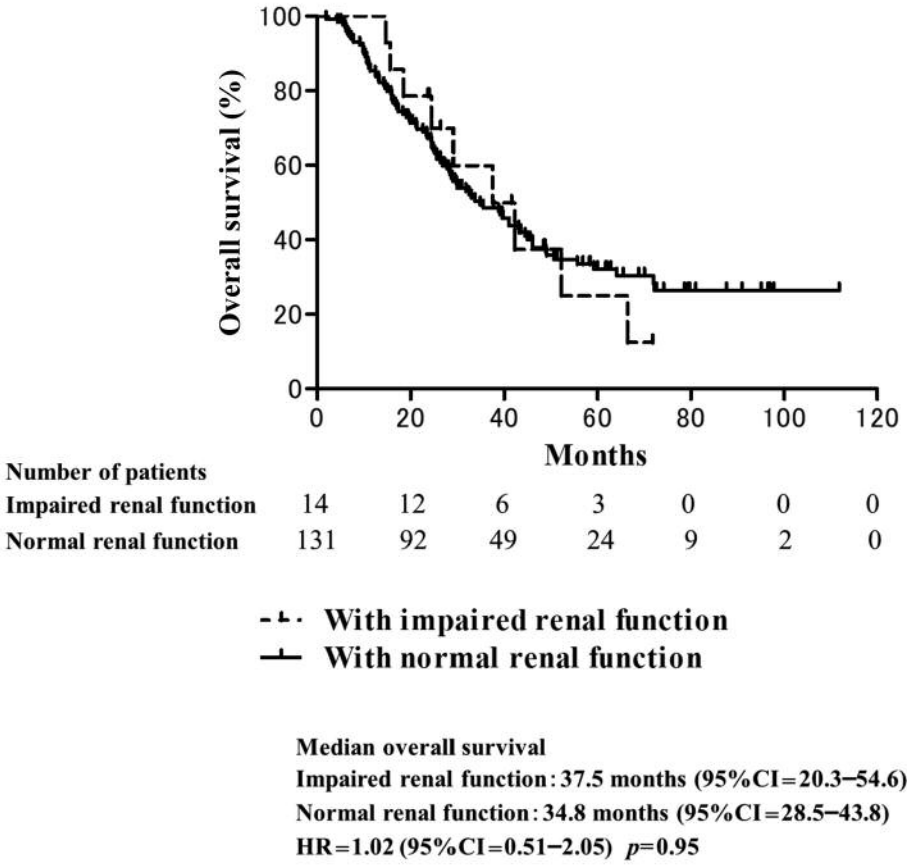


Figure 2. *The Kaplan–Meier curves for comparison of overall survival of patients with metastatic colorectal cancer who received oxaliplatin-based chemotherapy. The solid line represents patients with normal renal function (Ccr≥60 ml/min) and the dashed line represents those with impaired renal function (Ccr<60 ml/min).*

Cox proportional hazards analysis indicated that there was no significant relationship between Ccr and any adverse event, or between Ccr and overall survival. Therefore, a dose reduction of oxaliplatin based on Ccr is not recommended in patients with mCRC.

## Conflicts of Interest

K. Yoshida has received honoraria for lectures from Chugai Pharmaceutical, Olympus, Taiho Pharmaceutical, Yakult Honsha, Covidien, Merck Sharp & Dohme, Bristol-Myers Squibb, Daiichi Sankyo, Nippon Kayaku, Ono Pharmaceutical, Takeda Pharmaceutical, Merck Serono, Eli Lilly and Company, Johnson & Johnson, Sanofi, Eisai, Tsumura, EA Pharma, Otsuka Pharmaceutical, Bayer Yakuhin, Terumo, Asahi Kasei, Denka, Teijin, SBI Pharmaceuticals, Intuitive Surgical, Novartis Pharma, and Pfizer; as well as research funding from Ono Pharmaceutical, Chugai Pharmaceutical, Takeda Pharmaceutical, Daiichi Sankyo, Eli Lilly and Company, Otsuka Pharmaceutical, Yakult Honsha, Taiho Pharmaceutical, Merck Sharp & Dohme, Asahi Kasei, Merck Serono, Tsumura, Covidien, Eisai, Johnson & Johnson, Sanofi, Nippon Kayaku, Astellas Pharma, Toyama Chemical, Kyowa Hakko Kirin, Kinetic Concepts, Abbott Japan, and Toray Industries outside the submitted work. T. Takahashi has received honoraria for lectures from Takeda Pharmaceutical and Sanofi; as well as research funding from Yakult Honsha. The other authors report no conflicts of interest.

## Authors' Contributions

H.F. conceived the study concepts. D.W. and H.F. conducted the claim data analysis. H.F. and T.I. performed the statistical analyses. Y.Y. and H.I. provided technical support. N.M., T.T. and K.Y. contributed to the interpretation of data and assisted in the preparation of the manuscript. D.W., H.F., and Y.Y. drafted the initial manuscript. H.I., T.I., N.M., T.T, K.Y., and A.S. conducted the critical revision of the manuscript. All Authors reviewed the manuscript.

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