ORIGINAL

Study on prediction of early adverse events by CapeOX therapy in patients with colorectal cancer

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Abstract : CapeOX is a regimen used as postoperative adjuvant chemotherapy for the treatment of advanced recurrent colorectal cancer. If early adverse events occur, treatment may not progress as planned and further dose reduction may be necessary. In this study, we investigated whether pre-treatment medical records could be used to predict adverse events in order to prevent adverse events caused by CapeOX treatment. The 178 patients were classified into two groups (97 in the adverse event positive group and 81 in the adverse event-negative group) based on withdrawal or postponement of four or fewer courses. In univariate analysis, age, height, weight, body surface area (BSA), creatinine clearance, muscle mass, and lean body mass were associated with early adverse events ($P < 0.05$). The area under the receiver operating characteristic curve obtained by Stepwise logistic regression analysis using the Akaike information criterion method was 0.832. For nested k-fold cross validation, the accuracy rates of the support vector machine, random forest, and logistic regression algorithms were 0.71, 0.70, and 0.75, respectively. The results of the present study suggest that a logistic regression prediction model may be useful in predicting early adverse events caused by CapeOX therapy in patients with colorectal cancer. J. Med. Invest. 71 : 141-147, February, 2024

Keywords **:** *CapeOX, early adverse events, multivariate logistic regression, nested k-fold cross validation, prediction*

INTRODUCTION

Cancer is the leading cause of death in Japan. By cancer type, colorectal cancer was the leading cause of morbidity in 2019 and the second leading cause of death in 2021 (1) ; therefore, improving treatment outcomes for colorectal cancer is important. Among the various drug combination regimens for the treatment of colorectal cancer, CapeOX is used as a postoperative adjuvant chemotherapy and in the treatment of advanced recurrent cancer (2). Grade 3 or higher adverse events with CapeOX therapy for advanced recurrent colorectal cancer include diarrhea in 20%, neutropenia in less than 8%, thrombocytopenia in less than 7%, and hand-foot syndrome in 6% (3). In addition, grade 3 or higher adverse events with postoperative adjuvant chemotherapy were reported as peripheral neuropathy in 11%, neutropenia in 9%, hand-foot syndrome in 5%, and thrombocytopenia in 5% (4).

CapeOX therapy is a combination of capecitabine and oxaliplatin, with oxaliplatin infusion over 2 hours on day 1, followed by capecitabine twice daily after breakfast and dinner for 14 days starting that evening or the next morning, with a 7-day rest period, and treatment repeated every 21 days. Capecitabine is an oral antineoplastic agent that is gradually converted to fluorouracil (5-FU) in a stepwise manner, thereby reducing its activity in the bone marrow and gastrointestinal tract, reducing systemic exposure, and delivering tumor-selective high doses of 5-FU. After administration, the unchanged drug is absorbed from the gastrointestinal tract and metabolized to 5'-deoxy-5-fluorocytidine (5'-DFCR) by carboxylesterase (CE), which is mainly localized in the liver, and converted to 5'-deoxy-5-fluorouridine (5'-DFUR) by highly active cytidine deaminase (CD) in the liver and tumor tissue. 5'-DFUR is subsequently converted to active 5-FU by highly active thymidine phosphorylase (TP) in tumor tissue, resulting in higher concentrations of 5-FU in the tumor tissue. Increased blood levels of 5'-DFUR have been reported in patients with renal impairment, and are associated with adverse events (5). Oxaliplatin forms biotransformants such as monoaco-monochloro-1,2-diaminocyclohexane (DACH) platinum and diaco-DACH platinum, which covalently bind to DNA strands in tumor cells to form platinum-DNA cross-links both within and between DNA strands. These crosslinks are thought to inhibit DNA replication and transcription, resulting in reduced cell proliferation. Among patients with impaired renal function, those with a creatinine clearance (Ccr) of less than 60 mL/min have been shown to have increased blood levels and decreased clearance compared to those with a Ccr of 60 mL/min or greater (6).

At the start of treatment, renal and hepatic function should be assessed and, if necessary, the dosage and administration should be changed to those described in the "Guidelines for Proper Use." However, if side effects develop early, treatment may not progress as planned, and further dose reduction may be necessary. Therefore, it is important to predict the early onset of adverse events to complete a 3-month dosing schedule.

Machine learning is a branch of artificial intelligence (AI) that explores the study and construction of computer algorithms that learn data and build on the results. The main objective of machine learning models is to build computer systems that learn from predefined databases and generate prediction, classification, and detection models (7). In recent years, the number of databases has increased with the digitization of medical records, clinical laboratories, and imaging tests. Machine learning is intended to use these as sources of information for the prevention, early diagnosis, and treatment of diseases. The number of

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machine learning papers is increasing in a variety of areas, such as predicting the side effects of drugs in older adults, predicting side effects of anticancer drugs, and correlating survival with clinical data (8-10). The number of reports on machine learning in oncology has increased in recent years. Before 2012, there were no reports, but the number gradually increased to 27 papers in 2023. The largest number of papers were related to the prediction of side effects and efficacy of immune checkpoint inhibitors, followed by 17 papers on the prediction of side effects and efficacy of radiotherapy, and then 8 papers on side effects of cytotoxic anticancer drugs. In most patients, antineoplastic drugs cause adverse events, leading to treatment discontinuation. Therefore, by anticipating patients more susceptible to adverse events, it becomes feasible to implement personalized measures such as selecting appropriate premedication and ensuring vigilant follow-up during treatment, potentially averting severe side effects (11). In this study, we investigated whether pretreatment case records could be used to predict adverse events using nested k-fold cross validation in a machine learning model. Nested k-fold cross validation is a method that divides the model into inner and outer cross validation, selects hyperparameters in the inner cross validation, and uses the selected hyperparameters to evaluate the accuracy of the outer cross validation model (12). This is useful to properly validate the estimation performance of the model when the sample size is limited.

MATERIALS AND METHODS

Subjects

This study included 178 patients who started CapeOX therapy as first-line chemotherapy for colorectal cancer at the Tokushima Red Cross Hospital between January 2010 and December 2018. Eligible patients were 20 years of age or older with histologically confirmed colorectal cancer, no prior chemotherapy, and who had received at least four courses of CapeOX. CapeOX therapy is a combination of capecitabine and oxaliplatin, with oxaliplatin infusion over 2 hours on day 1, followed by capecitabine twice daily after breakfast and dinner for 14 days starting that night or the next morning, with a 7-day rest period, and treatment repeated every 21 days. Capecitabine dosing was modified according to body surface area (BSA) as described in the package insert. Briefly, 2,400 mg/day for less than 1.36 m^2, 3,000 mg/day for 1.36 to 1.66 m^2, 3,600 mg/day for 1.66 to 1.96 m^2, and 4,200 mg for 1.96 m^2 or greater. Supportive care consisted of aprepitant 125 mg 60-90 minutes prior to starting oxaliplatin and dexamethasone 6.6 mg and granisetron (3 mg) infusion 30 min prior. On days two and three after infusion, 80 mg of aprepitant was administered in the morning. Patients who had received postoperative adjuvant chemotherapy with oral anticancer agents or chemotherapy for other cancers before starting CapeOX therapy were excluded.

This study was approved by the Ethics Committees of Tokushima University Hospital (approval reference number : 2425-5) and Tokushima Red Cross Hospital.

Collection of clinical data

Information on age, sex, height, weight, BSA, body mass index (BMI), purpose of treatment, dose, serum creatinine level (Scr), Ccr, hemoglobin level, lactate dehydrogenase level, neutrophil count (NEUT), lymphocyte count (LYMP), neutrophil/lymphocyte count (NLR), adverse events, treatment schedule, and information on dose reduction, and treatment delay or discontinuation were collected from medical records. Patient age, sex, and height were self-reported. Body weight was measured using a Tanita scale (Tanita Corp., Tokyo, Japan) during outpatient visits. BSA (m^2) was calculated using the Du Bois formula (weight (kg) $^{0.425}$ × height (cm) $^{0.725}$ × 0.007184), and BMI (kg/m^2) was calculated using weight (kg) and height (m). Ccr was calculated from age, weight, and Scr using the Cockroft-Gault formula (13). Muscle, visceral fat, and subcutaneous fat mass were obtained from computed tomography (CT) scans (Aquilion ONE (Canon Medical Systems Co., Ltd., Tochigi, Japan) and SOMATOM Sensation Cardiac 64 (Siemens Healthineers AG, Erlangen, Germany) performed before treatment initiation. The cross-sectional areas (mm^2) of the acquired images were measured using a three-dimensional image analysis system (SYNAPSE VINCENT, Fujifilm Co., Ltd., Tokyo, Japan), an image processing terminal, to generate muscle and visceral/subcutaneous fat images. The imaging conditions were a tube voltage of 120 kV, tube current set at 50-550 mA using an automatic tube current control mechanism (Auto Exposer Control), and images of 3-mm slice thickness. Muscle, visceral fat, and subcutaneous fat were assessed by two radiologists with 8 and 16 years of clinical experience, respectively, who identified and measured the muscle and fat. For muscle assessment, images were selected at the level of the transverse process of the third lumbar vertebra, and the cross-sectional area was measured using a CT value of -29 to 150 Hounsfield unit (HU) window width as a threshold. For fat assessment, images that did not include the kidney and iliac bone near the umbilicus were selected, and the cross-sectional area was measured using a CT window width of -200 to -50 HU as a threshold. If no image that did not include the kidneys or the iliac crest was available, an image near the umbilicus that did not include the kidneys was selected.

Treatment delays and discontinuations and the reasons for them were identified from the medical records, and adverse events were graded according to the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE ; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40). Patients were divided into two groups : those who had a treatment delay or discontinuation due to an adverse event within four courses (AE-positive group) and those who did not have an initial adverse event (AE-negative group).

Statistical analysis

The Mann-Whitney U test was used to compare continuous variables, and Fisher's test was used to compare nominal variables between the AE-positive and AE-negative groups. Stepwise logistic regression analysis using the Akaike Information Criterion (AIC) model was used to identify factors associated with AE positivity, and receiver operating characteristic (ROC) analysis was used to assess predictive accuracy. All statistical analyses were performed using EZR statistical software (14), which extends the capabilities of R and R Commander (The R Project for Statistical Computing ; http://www.r-project.org). Statistical significance was set at $P < 0.05$.

Nested k-fold cross validation

Nested k-fold cross validation (12) was used to assess the prediction accuracy for unknown data. The dataset of 178 individuals was randomly classified into ten parts for outer cross-validation : 80% for training and 20% for testing. Next, the training data were randomly classified into three parts for inner cross-validation : 80% and 20% were used for training and testing, respectively. Hyperparameters were selected from the inner cross-validation and test data from the outer cross-validation were used to assess the accuracy of the model. Predictive models were constructed using support vector machine (SVM), random forest (RF), and logistic regression (LR) algorithms. Hyperparameter tuning was performed using gamma and C for SVM, n_estimator and max_depth for RF, and C, solver, penalty,

and n_features_to_select for LR. The accuracy of each model was assessed by nested k-fold cross validation (12) using the scikit-learn package in Python 3.7 environment (15).

RESULTS

Characteristics of the patients

Between 2010 and 2018, 219 patients received CapeOX therapy for the treatment of colorectal cancer at the Japanese Red Cross Tokushima Hospital, including 178 patients who received chemotherapy for the first time. Patients from the period 2010 to 2018 were included, as this timeframe corresponds to when they were actively engaged in the process, involving teaching them medication management and handling adverse events. Of these, 97 (54.5%) had to postpone or discontinue treatment within four courses due to adverse events. The characteristics of the 178 patients included in this study are summarized in Table 1. The age was higher in the AE-positive group than in the AE-negative group (median : 69 vs. 66 years, $P = 0.027$). Height was lower in the AE-positive group (median : 159. 1 vs. 163.3 cm, $P = 0.0022$). Body weight was lower in the AE-positive group (median : 53.9 vs. 58.9 kg, $P = 0.0011$). BSA was lower in the AE-positive group (median : 1.53 vs. 1.64 m^2, $P < 0.001$). Ccr was lower in the AE-positive group (median : 60.8 vs. 72.0 mL/min, $P < 0.001$). Total muscle cross-sectional area at the third lumbar vertebra was lower in the AE-positive group (median : 10547.9 vs. 11685.6 mm^2, $P = 0.0035$). Lean body mass (LBM) calculated from the total muscle cross-sectional area was lower in the AE-positive group (median : 37.7 vs. 41.1 kg, $P = 0.0035$). The dose of oxaliplatin per BSA was higher in the AE-positive group, but was close to the baseline dose (130 mg/m^2) of the regimen (median : 128.2 vs. 126.6 mg/m^2, $P = 0.013$). Oxaliplatin dose divided by LBM was higher in the AE-positive group (median : 5.22 vs. 4.98 mg/kg,

Table 1. Clinical characteristics of subjects

Characteristic	AE-positive (n = 97)	AE-negative (n = 81)	*P*-value
Age (year)*	69 (63–74)	66 (58–72)	0.027
Sex—male#	52 (53.6)	54 (66.7)	0.092
Treatment objectives —adjuvant#	71 (73.2)	53 (65.4)	0.33
Site—Colon#	70 (72.2)	53 (65.4)	0.42
Body height (cm)*	159.1 (152–163.6)	163.3 (157–168.2)	0.0022
Body weight (kg)*	53.9 (48–59.5)	58.9 (52–65.6)	0.0011
BMI (cm/kg^2)*	21.7 (19.7–23.1)	22.4 (20.3–23.9)	0.090
BSA (m^2)*	1.53 (1.44–1.65)	1.64 (1.53–1.72)	< 0.001
Serum creatinine level (mg/dL)*	0.74 (0.63–0.88)	0.71 (0.60–0.87)	0.39
Creatinine clearance (mL/min)*	60.8 (51.4–75.6)	72.0 (62.7–85.7)	< 0.001
Visceral fat (cm^2)*	79.5 (49.4–115.5)	92.7 (47.5–124.2)	0.53
Subcutaneous fat (cm^2)*	113.3 (78.8–143.6)	101.8 (55.2–149.0)	0.43
Total fat (cm^2)*	200.0 (126.3–262.2)	198.6 (119.2–274.0)	0.97
Ratio of subcutaneous to visceral fat*	0.73 (0.52–1.02)	0.87 (0.60–1.30)	0.38
Total muscle cross-sectional area at L3 (mm^2)*	10547.9 (8639.4–11960.4)	11685.6 (9806.6–13436.3)	0.0035
LBM (kg)*	37.7 (32.0–41.9)	41.1 (35.5–46.4)	0.0035
L-OHP (mg/m^2)*	128.2 (125.0–129.9)	126.6 (124.3–128.8)	0.013
L-OHP (mg/body)*	200 (180–220)	200 (190–220)	0.016
L-OHP/LBM (mg/kg)*	5.22 (4.83–5.69)	4.98 (4.57–5.44)	0.012
Capecitabine (mg)*	3000 (3000–3000)	3000(3000–3600)	0.12
Capecitabine/LBM (mg/kg)*	80.40 (73.94–88.53)	77.21 (70.31–84.56)	0.029
Hemoglobin (mg/dL)*	12.3 (11.1–13.3)	12.7 (11.7–13.6)	0.17
LDH (U/L)*	183 (156–207)	181 (159–206)	0.97
NEUT*	2880 (2200–3569)	3620 (2910–4580)	< 0.001
LYMP*	1630 (1300–2098)	1892 (1500–2210)	0.059
NLR*	1.62 (1.20–2.42)	1.94 (1.45–2.70)	0.022
Platelet ($\times 10^4$)*	21.3 (18.0–26.8)	26.0 (20.7–30.8)	< 0.001
Combination with bevacizumab#	20 (20.6)	23 (28.4)	0.29

The AE-positive group had a treatment delay or discontinuation due to an adverse event within four courses, while the AE-negative group did not have an initial adverse event. The Mann-Whitney U test was used to compare continuous variables, and Fisher's test was used to compare nominal variables between the AE-positive and AE-negative groups.
IQR : interquartile range ; BMI : body mass index ; BSA : body surface area ; L3 : third lumbar vertebrae3 ; LBM : lean body mass ; L-OHP : oxaliplatin ; LDH : lactate dehydrogenase ; NEUT : neutrophil ; LYMP : lymphocyte ; NLR : ratio of neutrophil to lymphocyte
: no. (%), * : median (IQR)

$P = 0.012$). The proportion of capecitabine divided by LBM was greater in the AE-positive group (median : 80.4 vs. 77.2 mg/kg, $P = 0.029$). The neutrophil count at baseline was lower in the AE-positive group (median : 2880 vs. 3620, $P < 0.001$). Neutrophil count divided by lymphocyte count (NLR) was lower in the AE-positive group (median : 1.62 vs. 1.94, $P = 0.022$). Pretreatment platelet counts were lower in the AE-positive group (median : 21.3×10^4 vs. 26.0×10^4, $P < 0.001$). Sex, purpose of treatment, site, BMI, Scr, visceral fat, subcutaneous fat, capecitabine dose, hemoglobin (Hb), serum lactate dehydrogenase (LDH), lymphocyte count, and concomitant bevacizumab use were not significantly different between the AE-positive and AE-negative groups.

The most common early adverse events were grade 3 neutropenia and diarrhea, which occurred in 17 (17.5%) patients. Grade 2 thrombocytopenia was the second most common (16 (16.5%)), followed by grade 3 decreased appetite, grade 2 fatigue (12 (12.4%) each), and peripheral neuropathy (11 (11.3%)), grade 2 nausea (9(9.3%)), grade 2 palmar-plantar erythrodysesthesia syndrome (8(8.2%)), grade 2 aspartate aminotransferase increased, alanine aminotransferase increased (3(3.1%)) (Table 2). Other adverse events included two ileus, elevated amylase levels, decreased vision, visual field narrowing, pharyngeal discomfort and prolonged INR with warfarin.

Table 2. Adverse event to postponement for four courses

Adverse event	N (%)
Neutropenia (Grade3)	17 (17.5)
Diarrhea (Grade3)	17 (17.5)
Thrombocytopenia (Grade2)	16 (16.5)
Thrombocytopenia (Grade3)	1 (1.0)
Appetite loss (Grade3)	12 (12.4)
Fatigue (Grade2)	12 (12.4)
Peripheral sensory neuropathy (Grade2)	11 (11.3)
Nausea (Grade2)	9 (9.3)
Palmar-plantar erythrodysesthesia syndrome (Grade2)	8 (8.2)
Aspartate aminotransferase increased (Grade2) Alanine aminotransferase increased (Grade2)	3 (3.1)
Other	7 (7.2)

The % is related to the adverse event positive group.

Prediction of early adverse events

This study will develop a predictive model for adverse events that have led to treatment postponement or dose reduction due to early onset of adverse events. To begin, stepwise logistic regression analysis using the AIC method was used to select the variables for the model. The original variables obtained from the calculations were used as explanatory variables. BMI and BSA were excluded from the analysis because they were calculated based on height and weight. Ccr was calculated from Scr, age, and body weight, and LBM was calculated from the total muscle cross-sectional area of the third lumbar vertebra. Therefore, these variables were excluded. Oxaliplatin doses per BSA and capecitabine doses per body were used. Stepwise logistic regression analysis was performed using age, sex, treatment objectives (adjuvant), site (colon), body height, body weight, Scr, visceral fat, subcutaneous fat, total muscle cross-sectional area at the third lumbar vertebra, oxaliplatin dose per BSA, capecitabine dose per body, Hb, LDH, NEUT, LYMP, platelets, and bevacizumab combination as variables. Stepwise logistic regression analysis using the AIC method resulted in the selection of body weight, Scr, oxaliplatin dose per BSA, capectabine dose per body, NEUT, platelet count, and subcutaneous fat as variables for the model. Table 3 shows the odds ratio (OR), 95% confidence interval (CI), and *P*-value by stepwise logistic regression analysis using the AIC method. Body weight (OR = 0.83, 95% CI = 0.77 -0.90, $P < 0.001$), Scr (OR = 43.3, 95% CI = 4.1 -464.0, $P = 0.0018$), oxaliplatin dose per BSA (OR = 1.08, 95% CI = 1.01 -1.15, $P = 0.017$), NEUT (OR = 0.999, 95% CI = 0.999 -1.000, $P = 0.0032$), platelets (OR = 0.946, 95% CI = 0.897-0.998, $P = 0.042$) and subcutaneous fat (OR = 1.01, 95% CI = 1.00-1.01, $P = 0.010$) were associated with early adverse events. The area under the ROC curve (AUC) obtained by logistic analysis was 0.832 (95% CI = 0.771–0.893), indicating moderate accuracy (Figure 1).

Table 3. Multivariate logistic regression analysis using the AIC model of factors associated with treatment postponement or interruption due to adverse events within four courses

	OR (95% CI)	*P*-value
Body weight	0.83 (0.77–0.90)	< 0.001
Serum creatinine level	43.3 (4.1–464.0)	0.0018
Dose of L-OHP per BSA	1.08 (1.01–1.15)	0.017
Dose of Capectabine per body	1.00 (1.00–1.00)	0.078
NEUT	0.999 (0.999–1.000)	0.0032
Platelet	0.946 (0.897–0.998)	0.042
Subcutaneous fat	1.01 (1.00–1.01)	0.010

Data are shown as odds ratio (OR), 95% confidence interval (CI), and *P*-value.
AIC : Akaike Information Criterion ; L-OHP : oxaliplatin ; BSA : body surface area ; NEUT : neutrophil

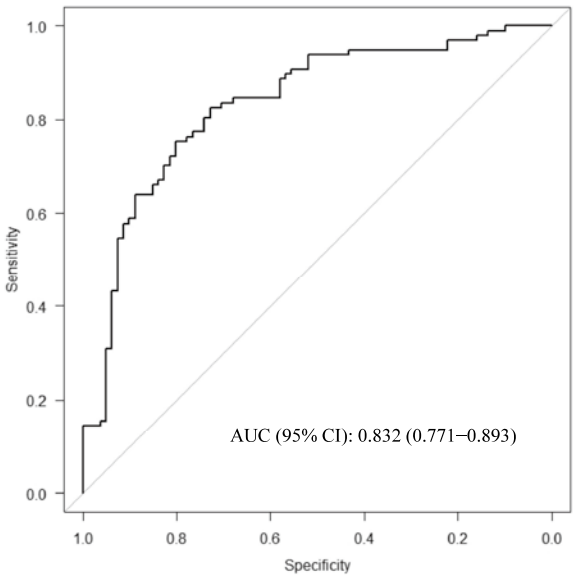

Figure 1. ROC curve and AUC obtained by logistic analysis using body weight, Scr, dose of oxaliplatin per BSA, NEUT, platelet and subcutaneous fat.
ROC, receiver operating characteristic ; AUC, area under the curve ; Scr, serum creatinine level ; BSA, body surface area ; NEUT, neutrophil count.

Accuracy rates were then evaluated using nested k-fold cross validation. Explanatory variables, including body weight, Scr, oxaliplatin dose per BSA, NEUT, platelet count, and subcutaneous fat, were identified through stepwise logistic regression analysis using the AIC method, as they were associated with early adverse events. SVM, RF, and LR were employed as algorithms. The accuracy rates of SVM, RF, and LR were 0.71, 0.70, and 0.75, respectively, with LR achieving the highest accuracy (Table 4). The LR model with the best predictive performance exhibited a sensitivity of 0.72, specificity of 0.79, positive predictive value of 0.84, negative predictive value of 0.65, and F1-score of 0.78, particularly excelling in positive predictive value. The optimized hyperparameter combination was C = 10, solver = liblinear, penalty = I2, and n_features_to_select : 4.

Table 4. Accuracy by support vector machines, random forest and logistic regression

	Accuracy rate
Support vector machines	0.71 ± 0.06
Random Forests	0.70 ± 0.09
Logistic Regression	0.75 ± 0.00

DISCUSSION

A phase III trial of CapeOX in advanced or metastatic colorectal cancer was conducted in Europe in 2008 and showed non-inferiority in progression-free survival compared to 5- fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) (3). CapeOX has been available in Japan since 2009. In contrast to FOLFOX4 therapy in terms of safety, CapeOX therapy had more adverse events of grade 3 or higher diarrhea (19%) and hand-foot syndrome (6%). It has also been reported that CapeOX therapy with capecitabine, an oral drug, is a simpler regimen for some patients, because FOLFOX4 therapy requires the insertion of a catheter for continuous fluorouracil administration. In addition, a Phase III trial conducted as an adjuvant therapy for postsurgical colon cancer patients after curative resection of the primary tumor showed the superiority of CapeOX therapy over the combination of levofolinate calcium and fluorouracil (4). This regimen has been used in Japan since 2011. The most frequently reported grade 3 or higher adverse events of CapeOX as adjuvant therapy in Japanese patients were neutropenia (19.3%), thrombocytopenia (7.0%), diarrhea (7.0%), and decreased appetite (5.3%) (16), and similar adverse events occurred in this study, resulting in treatment postponement or dose reduction.

The CapeOX regimen is a combination of capecitabine and oxaliplatin. A typical adverse effect of oxaliplatin is peripheral neuropathy, which persists even after treatment. The ACHIEVE study (17) was conducted to determine the optimal duration of FOLFOX and CapeOX as adjuvant postoperative chemotherapy and evaluated six months (eight courses) and three months (four courses). The results suggest that a 3-month treatment may not be less effective than a 6-month treatment, and the need to determine the duration of treatment on a case-by-case basis is discussed. Regarding peripheral neuropathy, the incidence of grade 2 or higher neurotoxicity was 14% in the 3-month group and 37% in the 6-month group ($P < 0.001$), and grade 3 or higher neurotoxicity was 0.9% and 6% ($P < 0.001$), respectively, both significantly lower in the 3-month group. In addition, an international integrated analysis project (IDEA) showed the non-inferiority of 3-month versus 6-month treatment for patients with stage IIIA colon cancer at a low risk of recurrence (18).

Based on the above, the goal was to complete 3 months of treatment as planned, and patients who required dose postponement, dose reduction, or withdrawal due to side effects within four courses were defined as the early side effect group. In this study, 54.5% of patients required discontinuation or dose reduction within four courses. Reasons for discontinuation and dose reductions were grade 3 neutropenia, grade 2 or greater thrombocytopenia and grade 3 diarrhea, similar to previous reports (3, 16). As patients are treated on an outpatient basis and experience adverse events at home, they need to understand in advance when adverse events may occur, what actions to take in response to adverse events, and what symptoms require contact with their healthcare providers. However, not all patients and their families understand and initiate treatment for the first time (19). Therefore, pharmacists need to identify patients who require special attention, provide initial counseling, monitor and evaluate side effects, and engage them to ensure that they can safely continue treatment. CapeOX therapy is an important regimen in the treatment of colorectal cancer, both as an adjuvant therapy and in the treatment of advanced or metastatic disease, and pharmacists need to help ensure that patients receiving this therapy are treated safely.

This study elucidated the background factors that may prevent patients from continuing treatment as planned owing to adverse events. In the univariate analysis, age, height, weight, BSA, Ccr, muscle mass, and LBM were associated with early adverse events. Multivariate logistic regression analysis showed that body weight, serum creatinine level, oxaliplatin dose per BSA, baseline neutrophil and platelet counts, and subcutaneous fat were factors associated with the early development of adverse events. Previous studies have reported that the only factor leading to early discontinuation of CapeOX therapy in patients over 65 years of age is a Ccr rate of less than 50 mL/min (20). The Ccr reported here was calculated using the Cockroft-Gault formula, which is similar to our report, because body weight and serum creatinine levels are factors.

Capecitabine is metabolized in the body. As fluorouracil is a hydrophilic drug, its volume of distribution is highly correlated with muscle mass. Therefore, a decrease in muscle mass is expected to decrease fluorouracil clearance, which has been reported to lead to increased exposure and adverse events (21). In addition, because oxaliplatin is lipophilic (22), its pharmacokinetics have been reported to be more dependent on body weight and fat than on muscle. This is related to the fact that the results of the multivariate logistic regression analysis indicated that subcutaneous fat was one of the factors.

Traditionally, the dosage of anticancer drugs has been calculated based on BSA. It has been reported that there is a difference between BSA and LBM for the same BSA (23). It has also been reported that LBM is an excellent factor for determining drug dosage (24), there is an association between LBM and adverse events of anticancer drugs, and that a smaller LBM may result in more adverse events (25-27). Oxaliplatin doses normalized by LBM have been shown to be strongly associated with side effects and peripheral neuropathy, which are dose modifiers in individual patients (23). In the present study, capecitabine and oxaliplatin doses were also divided by LBM and compared between the two groups. Both drugs are associated with a high incidence of early adverse events, which may have influenced their development of adverse events.

Neutrophil and platelet counts have been shown to be a factor in the development of early adverse events. However, patients should be carefully informed about myelosuppression, its timing, and symptoms, such as fever and bleeding tendency, as the number of early adverse events at baseline is sufficient to initiate

treatment. According to the univariate analysis, the muscle mass of the third lumbar spine was a significant risk factor for early adverse events, but this significant difference disappeared in the multivariate analysis. This may be due to the high correlation between sex and muscle mass. These results allow the tailored counseling of individual patients based on an understanding of their individual laboratory values and expected risks.

We used multivariate logistic regression analysis and k-fold cross-validation to examine the accuracy of predicting early adverse events. In this study, a multivariate logistic regression predicting early adverse events in terms of body weight, oxaliplatin dose per BSA, neutrophil count, platelet count, and subcutaneous fat had an AUC of 0.832, 95% CI = 0.771−0.893. In nested k-fold cross validation, the accuracy rates for SVM, RF, and LR were 0.71, 0.70, and 0.75, respectively. This model can predict whether patients will develop early adverse events after CapeOX therapy initiation. There has been one report of cardiotoxicity within 30 days of starting fluoropyrimidine chemotherapy in patients with colorectal cancer (28). Pre-existing heart disease, surgery and older age were identified as factors predicting the development of cardiotoxicity within 30 days. The accuracy of prediction was compared between XGBoost, logistic regression and RF, and the XGBoost method was reported to be more accurate than logistic regression and RF with an AUC of 0.816.

We found that multivariate logistic regression gave the most accurate results at 0.832. Multivariate logistic regression is a statistical technique that evaluates the relationship between multiple independent variables and binary outcomes. By adjusting for various risk factors and clinical confounders, such as age and sex, this algorithm has helped to identify predictors of early adverse events. A number of machine learning models are available and must be selected based on specific combinations of features. By selecting the best parameters, a suitable predictive model can be built. We have compared our results with SVM, RF and LR. SVM tries to find the best hyperplane to divide into different classes. RF is an ensemble learning method that builds many decision trees and combines their predictions. Among these models, LR showed the highest accuracy rate of 0.75.

Regarding the factors associated with the occurrence of CapeOX adverse events, Nozawa *et al*. reported that female sex is a factor in postoperative adjuvant therapy (29). Watanabe *et al*. reported that there is no relevant patient information at baseline (30), and Yamazaki *et al*. reported that renal function decline at the start of treatment affects postoperative adjuvant chemotherapy in the elderly (20). In advanced recurrent colorectal cancer, Kurk *et al*. have reported an increased risk of grade 3 or higher adverse events due to loss of muscle mass during treatment rather than loss of muscle mass at the start of treatment (31), so this is the first paper to report a model predicting risk factors for the development of early adverse events with CapeOX at the start of treatment.

Our study had some limitations. It was a retrospective study conducted in clinical practice. Patients who did not undergo CT before treatment initiation were excluded. Therefore, the information on patients who were not included in the study may be insufficient. The starting dose varied from patient to patient because it was reduced based on renal function or at the discretion of the physician. In addition, patient information was reviewed only until the end of the four courses, and subsequent adverse events and treatment efficacy were not evaluated. Despite these limitations, the purpose of this study was to determine the occurrence of early adverse events associated with CapeOX therapy in clinical practice and the factors involved, providing meaningful information for predicting the risk of patients initiating CapeOX therapy.

CONCLUSION

We found significant differences in age, height, weight, BSA, Ccr, muscle mass of the third lumbar vertebra, LBM, dose of L-OHP per body surface area, actual dose of L-OHP (L-OHP DOSE), L-OHP DOSE/LBM, capecitabine dose/LBM, neutrophil count, lymphocyte count, and platelet count between the groups. These differences in patient backgrounds may influence the early development of adverse events. Multivariate logistic regression analysis showed that body weight, oxaliplatin dose per BSA, neutrophil count, platelet count, and subcutaneous fat were associated with early adverse events. A logistic regression prediction model using these factors exhibited high accuracy. Therefore, this model may contribute to the prediction of early onset of adverse associated with CapeOX therapy.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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