Patients with T4N0 and T1-3N1 colon cancer and a high preoperative carcinoembryonic antigen level benefit from adjuvant chemotherapy with oxaliplatin for 6 months

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Abstract. A shorter duration of oxaliplatin adjuvant chemotherapy has recently emerged as a potential option for patients with high-risk stage II and low-risk stage III (T1-3N1) colon cancer (CC). The present study aimed to elucidate the risk factors for recurrence in these patient populations and to identify the appropriate indications for shortened treatment durations. The present study retrospectively analyzed 396 patients who underwent curative surgery for pathological T4N0 or stage III CC, followed by adjuvant chemotherapy, at two institutes. Overall, 234 patients with T4N0 and low-risk stage III CC were categorized into the low-risk group and 162 patients with high-risk stage III CC into the high-risk group. The 3-year relapse-free survival rate was significantly higher in the low-risk group than in the high-risk group. Multivariate Cox model analysis of the low-risk group revealed that high preoperative serum levels of carcinoembryonic antigen (CEA) and incomplete 6-month adjuvant chemotherapy with oxaliplatin were independent poor prognostic factors. The prognosis of patients in the low-risk group who had abnormal CEA levels and did not complete the 6-month adjuvant treatment with oxaliplatin was similar to that of patients in the high-risk group. However, the prognosis of patients in the low-risk group with high CEA levels improved with a 6-month adjuvant treatment with oxaliplatin to a similar level to that of all patients with low CEA levels in the low-risk group. In conclusion, the present study suggested that the duration of adjuvant chemotherapy with oxaliplatin should not be shortened in patients with high preoperative CEA levels, even in the low-risk group.

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Introduction

Colon cancer (CC) is the fifth most common cancer worldwide, with an annual worldwide incidence of approximately 1,148,500 cases and 576,800 deaths (1). However, CC prognosis has improved in recent years owing to advances in chemotherapy and the development of various anticancer drugs. Currently, CC up to stage III has a relatively good prognosis if treated with appropriate anticancer agents (2,3).

The American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines identify various high-risk factors for recurrence in patients with stage II CC. Postoperative adjuvant chemotherapy is recommended for patients with pathological stage (pStage) II CC with the identified risk factors and for those with pStage III CC (4-8). T4 has been reported to be the most powerful prognostic factor among the risk factors for stage II CC (9). In contrast, patients with pathological T1-3N1 (pT1-3N1) CC have a relatively low risk of recurrence. Previous studies have discussed the possibility of shortening the duration of chemotherapy with oxaliplatin for patients with low-risk stage III CC (10,11) based on data demonstrating that shortening the administration duration does not worsen prognosis but rather decreases adverse events. However, certain patients receiving adjuvant chemotherapy have poor prognoses, and the International Duration Evaluation of Adjuvant Therapy (IDEA) Collaboration has identified the following study limitations. First, the study included an integrated analysis of six studies; however, subgroup analyses were performed without adjusting for multiplicity. Second, no standardized follow-up procedures were performed in the six trials, including intervals for imaging and laboratory assessments. Third, the study did not examine recurrence in the low-risk group based on clinicopathological background factors. Certain patients in the low-risk group may have a higher probability of recurrence. Therefore, shortening the duration of adjuvant chemotherapy based on the pStage remains controversial (10,12,13).

We aimed to elucidate the risk factors for CC in a group with a low recurrence risk and investigate the effect of a shorter duration of oxaliplatin treatment. We believe the results of this analysis will contribute to a better prognosis by identifying the patients for whom postoperative adjuvant chemotherapy duration should be shortened.

Materials and methods

Patients and data collection. This study included 396 patients who underwent surgery for CC at the Kyoto Prefectural University of Medicine between January 2008 and December 2020 and at the Japanese Red Cross Kyoto Daiichi Hospital between January 2013 and December 2020. The inclusion criteria were as follows: patients (a) pathologically diagnosed with colon adenocarcinoma, (b) with pT4N0 and pStage III CC (14), (c) undergoing curative resection for CC, and (d) who received adjuvant chemotherapy (at any time). Patients who underwent emergency primary tumor resection were excluded. In the present study, CC was defined as colon cancer from the cecum to the sigmoid colon or rectal sigmoid colon cancer. Appendiceal and rectal cancers were excluded from this study.

The present study was a retrospective analysis of de-identified data. The requirement for written informed consent from individual participants was waived owing to the retrospective design, in accordance with the standards of the Kyoto Prefectural University of Medicine Institutional Medical Ethics Review Committee. The present study was approved by the ethics committee of Kyoto Prefectural University of Medicine (approval no. ERB-C-1178, 1178-1, 1178-2, 1178-3). We submitted the notification required by the Ministry of Health, Labor, and Welfare to the Japanese Red Cross Kyoto Daiichi Hospital and obtained permission to access the database through proper procedures. After creating the correspondence table, all information identifying individual patients was excluded, and only the information to be used for analysis was received from Kyoto Daiichi Red Cross Hospital. The correspondence table is maintained at Kyoto Daiichi Red Cross Hospital. The dates when the databases were accessed for data collection and data collection started were April 1, 2023 for Kyoto Prefectural University of Medicine and July 29, 2024 for the Japanese Red Cross Kyoto Daiichi Hospital.

Measurement of tumor markers. Preoperative tumor markers utilized in the analysis were measured during the first outpatient visit (approximately 1 month preoperatively), and postoperative tumor markers were measured during the first postoperative visit (approximately 1 month postoperatively).

Surgical procedure, follow-up, and diagnosis of recurrence. Primary tumor resection and lymph node dissection were performed according to the JSCCR Guidelines for the Treatment of Colorectal Cancer (8). Resected specimens were assessed by pathologists based on the tumor-node-metastasis (TNM) (8th edition) staging system by the Union for International Cancer Control (UICC) (14). After primary tumor resection for CC, patients were followed up at regular intervals by determining serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 levels every 3 months; computed tomography of the chest, abdomen, and pelvis every 6 months; and colonoscopy at 1 and 3 years postoperatively, according to the JSCCR guidelines (8). The first follow-up was performed 1 month after primary tumor resection, and patients were subsequently followed up every 3 months for up to 3 years. All patients were followed up until their death or at least 3 years after primary tumor resection. After primary tumor resection, adjuvant chemotherapy regimens were recommended based on the JSCCR guidelines,

Table I. Clinicopathological characteristics of pT4N0 or pStage III patients with adjuvant chemotherapy.

Variables	All patients (n=396)
Age, years	
Median	68
Range	21-87
Sex, n	
Male	213
Female	183
CEA[a], n	
<5 ng/ml	224
≥5 ng/ml	172
CA19-9[a], n	
<37 U/ml	346
≥37 U/ml	50
Obstruction, n	
Absence	339
Presence	57
Lymph node dissection, n	
≥12	333
<12	63
pT, n	
pT1	27
pT2	24
pT3	210
pT4	135
pN, n	
Absence	33
Presence	363
Venous invasion, n	
Absence	146
Presence	250
Lymphatic invasion, n	
Absence	101
Presence	295
Histopathological type, n	
Differentiated	349
Undifferentiated	47

[a]Before primary tumor resection. CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; pN, pathological N stage; pT, pathological T stage.

Table II. Summary of adjuvant chemotherapy in pT4N0 or pT1-3N1 patients.

Chemotherapy regimen	All patients, n (%) (n=234)	T4N0 patients, n (%) (n=33)	T1-2N1 patients, n (%) (n=49)	T3N1 patients, n (%) (n=152)
UFT	79 (33.8)	15 (45.5)	14 (28.6)	50 (32.9)
S-1	6 (2.6)	1 (3.0)	1 (2.0)	4 (2.6)
Capecitabine	36 (15.4)	5 (15.2)	7 (14.3)	24 (15.8)
CAPOX	99 (42.3)	10 (30.3)	24 (49.0)	65 (42.8)
FOLFOX	13 (5.6)	2 (6.1)	2 (4.1)	9 (5.9)
SOX	1 (0.4)	0 (0.0)	1 (2.0)	0 (0.0)
Usage of oxaliplatin	113 (48.3)	12 (36.4)	27 (55.1)	74 (48.7)
Completeness of 6-month treatment with oxaliplatin	46 (19.7)	1 (3.0)	12 (24.5)	33 (21.7)

UFT, uracil/tegafur; S-1, tegafur/gimeracil/oteracil potassium; CAPOX, capecitabine and oxaliplatin; FOLFOX, fluorouracil, leucovorin and oxaliplatin; SOX, tegafur/gimeracil/oteracil potassium and oxaliplatin.

unless the patient's performance status was unsuitable for the recommended chemotherapy regimens or if the patient declined chemotherapy.

Statistical analysis. Data are presented as medians (ranges) and percentages. Prognostic curves were generated using the Kaplan-Meier method, and the log-rank test was performed to evaluate intergroup differences. Significant parameters in the univariate analyses were further assessed using multivariate Cox models. Preoperative and postoperative high CEA levels were considered as separate two types of multivariate Cox models because of confounding. In one model (model #1), preoperative CEA level was incorporated as an explanatory variable. In the other model (model #2), postoperative CEA level was incorporated as an explanatory variable. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazard models. The statistical significance of the differences was set at $P<0.05$, as derived from two-tailed tests. Statistical analyses were performed using the JMP software version 10 (JMP, Cary, NC, USA).

Results

Clinicopathological characteristics and survival analyses of all patients. The clinicopathological characteristics of 396 patients are presented in Table I. The median age of the patients was 68 years, with 213 male (53.8%) and 183 female (46.2%) patients. Most patients had advanced T (T3/T4) stage CC (345/396, 87.1%) and positive lymph nodes (363/396, 91.7%) with their primary tumors. Overall, 234 (59.1%) were classified into the low-risk group, including those with pT4N0 or low-risk pStage III (T1-3N1) CC, whereas 162 (40.9%) were in the high-risk group, including those with high-risk pStage III (T4N1 or any T, N2) CC. In total, 92 patients completed 6 months of adjuvant chemotherapy with oxaliplatin. The median follow-up period after colectomy was 36 months (average, 34.5 months; range, 3.6-36 months). The 3-year recurrence-free survival (RFS) rate of the low-risk group, for which the duration of adjuvant chemotherapy may be shortened, was significantly better than that of the high-risk group, for which conventional adjuvant chemotherapy is recommended (low-risk group: 80.8% vs. high-risk group: 67.8%, P=0.001; Fig. 1).

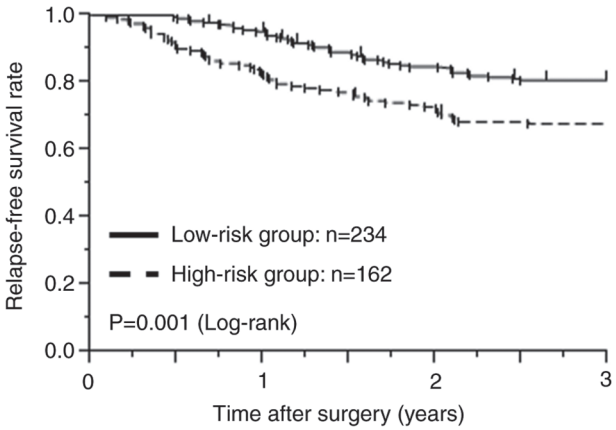

Figure 1. Relapse-free survival after surgery in patients with T4N0 and stage III colon cancer divided into low- and high-risk groups.

Clinicopathological characteristics and survival analyses of patients in the low-risk group. We examined the prognostic factors of 234 patients in the low-risk group, including those with pT4N0 and low-risk stage III CC. The details of adjuvant chemotherapy are summarized in Table II. Of the 234 patients, 113 (48.3%) received an oxaliplatin-based regimen, and 46 (19.7%) completed 6 months of oxaliplatin treatment. The median follow-up period after colectomy was 36 months (average, 34.9 months; range, 3.6-36 months). We classified the patients into two groups according to various clinicopathological background factors and conducted univariate and multivariate analyses for the 3-year RFS, as shown in Table III. The univariate analysis demonstrated that patients with a high preoperative serum CEA level (≥5 ng/ml), a high postoperative serum CEA level, and those who did not receive the 6-month treatment with oxaliplatin had poor 3-year RFS. The survival curves are depicted in Fig. 2. The 3-year RFS rate in patients with high preoperative CEA levels was 71.6%, significantly

Table III. Univariate and multivariate survival analyses of RFS in pT4N0 or pT1-3N1 patients with adjuvant chemotherapy.

		Univariate analysis		Multivariate analysis (model #1)		Multivariate analysis (model #2)	
Variables	All patients, n (n=234)	3-year RFS, %	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years							
<65	87	81.2	0.885				
≥65	147	80.5					
Sex							
Male	135	80.9	0.950				
Female	99	80.6					
CEA[a], ng/ml							
<5	151	85.8	0.011[c]	1 (reference)			
≥5	83	71.6		2.120 (1.171-3.858)	0.013[c]	NA	NA
CEA[b], ng/ml							
<5	214	83.4	<0.001[c]			1 (reference)	
≥5	20	50.0		NA	NA	3.456 (1.557-6.897)	0.004[c]
CA19-9[a], U/ml							
<37	216	82.0	0.124				
≥37	18	66.7					
CA19-9[b], U/ml							
<37	230	80.9	0.695				
≥37	4	75.0					
Obstruction							
Absence	202	82.3	0.158				
Presence	32	70.3					
Lymph node dissection							
≥12	191	90.2	0.123				
<12	43	78.8					
Venous invasion							
Absence	101	80.6	0.997				
Presence	133	80.9					
Lymphatic invasion							
Absence	75	85.3	0.226				
Presence	159	78.5					
Histopathological type							
Differentiated	208	79.3	0.152				
Undifferentiated	26	92.3					
Completeness of 6-month treatment with oxaliplatin							
Yes	46	91.3	0.045[c]	1 (reference)		1 (reference)	
No	188	78.1		2.737 (1.103-9.118)	0.028[c]	2.592 (1.043-8.643)	0.039[c]

[a]Before primary tumor resection. [b]After primary tumor resection. [c]P<0.05 (significant difference between the two groups). Preoperative and postoperative high CEA levels were considered as two separate types of multivariate Cox models because of confounding. In model #1, preoperative CEA level was incorporated and in model #2, postoperative CEA level was an explanatory variable. RFS, relapse-free survival; HR, hazard ratio; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NA, not applicable.

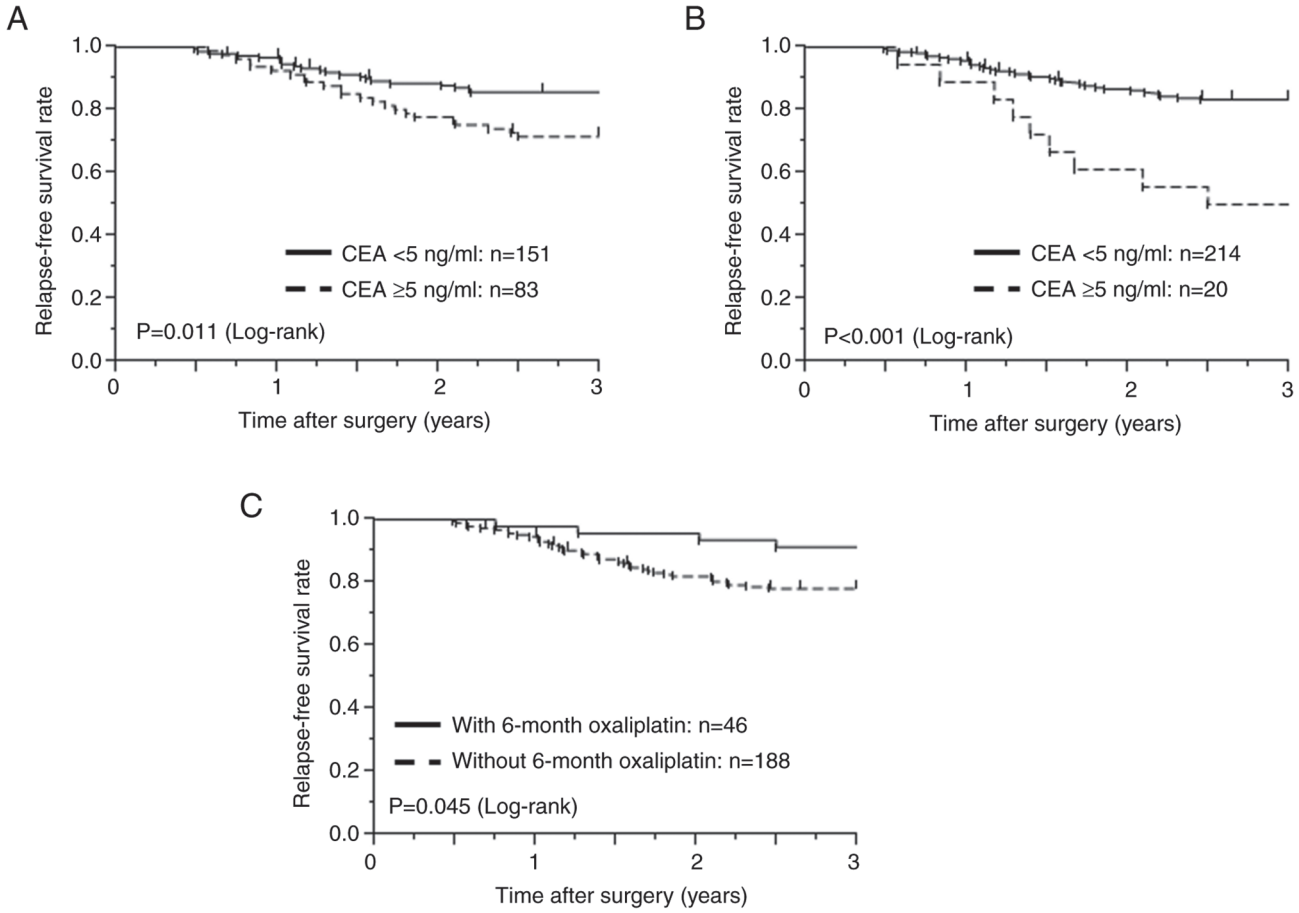

Figure 2. Relapse-free survival after surgery in the low-risk group stratified by (A) preoperative CEA levels and (B) postoperative CEA levels, and (C) with or without treatment with an oxaliplatin-based regimen for 6 months. CEA, carcinoembryonic antigen.

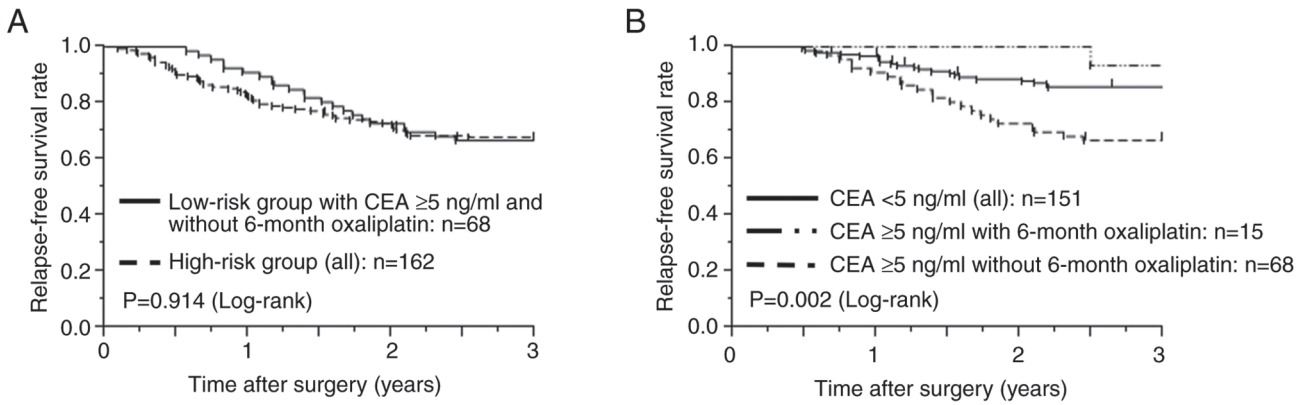

Figure 3. (A) Relapse-free survival curves comparing patients with preoperative CEA levels >5 ng/ml and without 6 months of treatment with an oxaliplatin-based regimen in the low-risk group with all patients with high-risk stage III colon cancer. (B) Relapse-free survival curves stratified by preoperative CEA levels and completeness or incompleteness of treatment with the oxaliplatin-based regimen for all patients in the low-risk group. CEA, carcinoembryonic antigen.

lower than that in patients with low preoperative CEA levels (85.8%; P=0.011, Fig. 2A), and postoperative CEA was also significantly different on univariate analysis (P<0.001, Fig. 2B). The 3-year RFS rate in patients who did not receive the 6-month treatment with oxaliplatin was 78.1%, significantly lower than that in patients who received the 6-month treatment with oxaliplatin (91.3%; P=0.045, Fig. 2C). The multivariate Cox model #1 demonstrated that a high preoperative CEA level (HR, 2.120; 95% CI, 1.171-3.858; P=0.013) and incomplete 6-month adjuvant chemotherapy with oxaliplatin (HR, 2.737; 95% CI, 1.103-9.118; P=0.028) were independent risk factors for poor RFS. In multivariate Cox model #2, a high postoperative CEA (HR, 3.456; 95% CI, 1.557-6.897; P=0.004) and incomplete 6-month adjuvant chemotherapy with oxaliplatin (HR, 2.592; 95% CI, 1.043-8.643; P=0.039) were identified as independent risk factors for poor RFS. Further analyses were

performed to investigate the effect of high preoperative CEA levels on prognosis. The 3-year RFS rate of the 68 patients in the low-risk group who had abnormal preoperative CEA levels and did not complete the 6-month adjuvant treatment with oxaliplatin was similar to that of all patients in the high-risk group (3-year RFS rates: 66.7% vs. 67.8%, P=0.914, Fig. 3A). However, among patients in the low-risk group, the 3-year RFS of those with high preoperative CEA levels who received the 6-month treatment with oxaliplatin (93.3%) was similar to that of all patients with low preoperative CEA levels (85.8%, P=0.402) and tended to be better than that of patients with high preoperative CEA levels who did not receive the 6-month treatment with oxaliplatin (66.7%, P=0.044) (Fig. 3B).

Discussion

In the present study, we investigated the relationship between various clinicopathological factors and recurrence in patients with T4N0 and Stage III CC who received adjuvant chemotherapy. We performed multivariate Cox model analysis for patients in the low-risk group (T4N0 and low-risk stage III CC) and identified two factors, high preoperative serum CEA levels and incomplete 6-month adjuvant chemotherapy with oxaliplatin, as independent risk factors for poor RFS. Furthermore, patients in the low-risk group with high CEA levels and without the 6-month oxaliplatin had a poor prognosis, similar to that of patients in the high-risk group. However, the prognosis of patients in the low-risk group with high CEA levels improved with a 6-month adjuvant treatment with oxaliplatin to a similar level to that of all patients with low CEA levels in the low-risk group. This study identified patients for whom chemotherapy duration should not be shortened by determining the prognostic factors in those with T4N0 and low-risk stage III CC.

In recent years, the concepts of high-risk stage II, low-risk stage III, and high-risk stage III CC have been established for CC, and distinctions between treatment strategies according to the risk of recurrence have been discussed (10,15-19). A previous study demonstrated that pT4 has high prognostic importance in stage II-III CC and that pT4 stage II CC has a worse prognosis than does low-risk (pT1-2N1-2) stage III CC (20). Another previous study revealed worse 5-year disease-free survival (DFS) rates in patients with T4N0 tumors than in those with T1-2N1 tumors (5-year DFS: 73.6 vs. 88.0%) (21). Staging paradoxes have been reported in our institution, particularly in pT4N0 and pT1-3N1 CC (22). Therefore, whether pT4N0 and pT1-3N1 can be considered equal-risk groups remains unclear. However, in this study, patients with pT4 CC, representing the high-risk stage II group, and those with pT1-3N1 CC, representing the low-risk stage III group, were classified together as a group in which adjuvant therapy duration could be shortened to 3 months, because pT4N0 and pT1-3N1 have a lower risk of recurrence than do other high-risk stage III CCs.

Numerous reports have indicated that high-risk stage II and low-risk stage III CC can be treated with a shorter duration of adjuvant chemotherapy, and such cases are often encountered in clinical practice (10,11,23). The JSCCR guidelines recommend 6 months of adjuvant chemotherapy for high-risk stage II, low-risk stage III, and high-risk stage III CC; however, 3 months of adjuvant chemotherapy is also an option if capecitabine and oxaliplatin (CAPOX) are used (8). In contrast, ASCO and ESMO state that postoperative adjuvant chemotherapy should be administered for 6 months for high-risk stage III CC, whereas either 6 or 3 months of adjuvant chemotherapy may be offered for high-risk stage II and low-risk stage III CC (4-6,24). The NCCN suggests adjuvant treatment options of 3 months of CAPOX or 3-6 months of fluorouracil, leucovorin, and oxaliplatin (FOLFOX) for high-risk stage II and low-risk stage III CC (7). Minor differences exist between the guidelines; nevertheless, the worldwide trend is to shorten the duration of postoperative adjuvant chemotherapy with oxaliplatin from 6 to 3 months in patients with high-risk stage II and low-risk stage III CC. In addition, the ACHIEVE-2, open-label, multicenter, randomized phase III trial, demonstrated that the shortened therapy duration did not affect the 3-year disease-free survival rate, suggesting that a 3-month course of CAPOX can be an effective treatment option (25).

However, some reports have shown that chemotherapy duration should not be shortened, suggesting that a shorter CAPOX duration is significantly associated with worse survival (26,27). The IDEA study did not examine the low-risk recurrence group based on clinicopathological background factors in detail; therefore, some patients in the low-risk recurrence group may have had a high probability of recurrence (10). We agree that the low-risk group can generally be treated with CAPOX for a shorter duration and support the ACHIEVE-2 results and the IDEA study results; however, considering the controversial reports in the literature, we believe that certain high-risk cases may exist within the low-risk group. This is the reason for the discrepancy between the ACHIEVE-2 results and the results of the present study, and we believe that most of the low-risk group may shorten postoperative adjuvant chemotherapy, but some among the low-risk group should not shorten chemotherapy. Therefore, in the present study, we investigated the prognosis of a low-risk group based on various clinicopathological background factors, focusing on the factors used to determine high-risk stage II CC.

In the present study, a high preoperative CEA level was identified as a poor prognostic factor by analyzing the data of patients with high-risk stage II and low-risk stage III CC, which are considered to have a relatively low risk of recurrence among the stages for which chemotherapy is recommended. Multiple previous reports have suggested that a high preoperative CEA level is a poor prognostic factor for CC (28-30). The findings of this study are consistent with those of previous reports, even when the patient populations are restricted to those with high-risk stage II and low-risk stage III CC. Moreover, preoperative serum CA19-9 may be a prognostic factor for high-risk stage II and low-risk stage III CC, as some reports demonstrated that preoperative serum CA19-9 was an additional prognostic factor for CC (31,32). However, the number of patients with CA19-9-positivity was small in the present study and did not reach statistical significance; therefore, CA19-9 was not considered a prognostic factor in this study. We aim to examine the prognostic effect of CA19-9 in future studies with the accumulation of additional cases. In addition, some researchers have claimed that a postoperative, rather than preoperative, high CEA level is an independent poor prognostic factor (33,34). In our study, high

postoperative CEA level was also an independent prognostic factor (HR, 3.456; 95% CI, 1.557-6.897; P=0.004), as shown in Fig. 2B and Table III. Therefore, we suggest that the duration of chemotherapy with oxaliplatin should not be shortened in patients with high postoperative CEA levels. However, it has long been known that serum CEA levels generally decrease after curative resection in CC because CEA is produced by cancer cells, and thus the number of patients with high postoperative CEA levels is small and sensitivity is low in this study (35,36); therefore, high postoperative CEA levels may be unsuitable as a marker to identify patients for whom adjuvant chemotherapy duration should not be shortened because of the small number of patients with high postoperative CEA values and low sensitivity. We recommend that preoperative high CEA level be utilized as a biomarker for 6 months of oxaliplatin treatment.

Notably, the 3-year RFS rate of patients with high CEA levels in the low-risk group was similar to that of all patients in the high-risk group. Interestingly, this study showed that among patients in the low-risk group, the prognosis of patients with high CEA levels improved with a 6-month adjuvant treatment with oxaliplatin to a level similar to that of all patients with low CEA levels. These results suggest that the duration of adjuvant chemotherapy with oxaliplatin should not be shortened in patients in the low-risk group with preoperative CEA levels >5 ng/ml. To the best of our knowledge, this is the first report to examine the risk factors for recurrence in patients with high-risk stage II and low-risk stage III CC using available data in general clinical practice.

The present study has several limitations. First, a large number of patients in this study were treated with a regimen that did not include oxaliplatin. The JSCCR guidelines did not strongly recommend oxaliplatin-based regimens, and recommended fluoride pyrimidines alone and oxaliplatin-based regimens equally until the 2016 edition; the 2019 guidelines strongly recommend oxaliplatin-based regimens for stage III CC. In addition, no recommendation for postoperative adjuvant chemotherapy for patients with high-risk stage II CC was proposed until 2019 (8,37). Therefore, multiple patients in this cohort were treated with regimens that did not include oxaliplatin owing to different treatment strategies initiated during different years (38,39). We analyzed a relatively large cohort from two centers to overcome this limitation; however, our results require validation in a larger prospective patient cohort from multiple institutions. Second, in the low-risk group, the 3-year RFS rate of patients with high CEA levels treated with an oxaliplatin-based regimen for 6 months was comparable to that of patients with low CEA levels; however, whether this relationship was non-inferior remains unclear. Third, we did not consider cases with positive perineural invasion (40,41), tumor budding (42,43), or poor nutritional indices (44,45), which have recently attracted attention as prognostic factors owing to their associations with a poor prognosis. The usual duration of chemotherapy should be considered for low-risk groups with recurrence or poor prognostic factors.

Despite these limitations, this study challenges the current argument that it is acceptable to shorten the duration of adjuvant chemotherapy for all patients with T4N0 and low-risk stage III CC. Furthermore, this study identified the prognostic factors for this patient population. Further prospective studies with larger sample sizes are necessary to identify patients for whom adjuvant chemotherapy duration can be appropriately shortened.

In conclusion, this study demonstrated that patients with high preoperative serum CEA levels had poor prognoses among those with T4N0 and low-risk stage III CC, suggesting that the duration of adjuvant chemotherapy should not be uniformly shortened.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HIn and HS contributed to the conception and design of the study. All authors discussed the patient's treatment plan at a preoperative conference. HIn, HS, JK, KN, TA, YK and EO performed the surgeries. HIn, HS, JK, KN, TA, TO, YY, HK, RM, AS, HIk, TK and HF collected the clinical samples, acquired data and assessed the clinical data. HIn and HS contributed to the analysis and interpretation of data, and writing of the manuscript. HIn, HS, YK, TA, KN, JK, TO, YY, HK, RM, AS, HIk, TK, HF and EO discussed and revised the analysis and interpretation of data. In addition, YK and EO made critical revisions. HIn, HS and YK confirmed the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The present retrospective study was approved by the Medical Ethics Review Committee of the Kyoto Prefectural University of Medicine (approval nos. ERB-C-1178, 1178-1, 1178-2, 1178-3; Kyoto, Japan). It was determined to be a retrospective analysis of de-identified data, and the requirement for obtaining written informed consent from the participants was waived, in accordance with the standards of the Kyoto Prefectural University of Medicine Institutional Medical Ethics Review Committee. The notification required by the Ministry of Health, Labor and Welfare was submitted to the Japanese Red Cross Kyoto Daiichi Hospital (Kyoto, Japan) and permission was obtained to access the database through proper procedures.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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