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ORIGINAL ARTICLE

A high preoperative carbohydrate antigen 19-9 level is a risk factor for recurrence in stage II colorectal cancer

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ABSTRACT

Background: Many risk factors for recurrence in stage II colorectal cancer (CRC) have been proposed, and the efficacy of adjuvant chemotherapy is still controversial. This study aimed to identify risk factors for tumor recurrence and assess whether they are related to the benefits of adjuvant chemotherapy in stage II CRC.

Material and methods: Patients with stage II CRC that was curatively operated on in a tertiary hospital between 2005 and 2014 were analyzed. Cox's proportional hazards models were applied to identify risk factors for recurrence and overall mortality. Kaplan-Meier methods were used to evaluate whether adjuvant chemotherapy was beneficial in terms of recurrence-free survival (RFS).

Results: A total of 384 patients were identified, among whom 38 (10%) received adjuvant chemotherapy. In a median follow-up of 48.6 months, 52 patients (14%) developed recurrence. Multivariate analyses identified two independent parameters that significantly decreased RFS; pathological T4 [hazard ratio (HR), 2.34; 95% confidence interval (CI), 1.31–4.15; $p = .0045$) and preoperative carbohydrate antigen (CA) 19-9 > 37 U/ml (HR 1.96; 95% CI 1.02–3.58; $p = .045$). These factors also inversely correlated with overall survival; T4: HR 2.10, $p = .019$) and CA 19-9 > 37 U/ml (HR 2.15, $p = .025$). The combination of T4 and CA 19-9 > 37 U/ml resulted in an increased HR (3.52) for recurrence. However, adjuvant chemotherapy did not improve RFS in patients with these features.

Conclusion: The present study demonstrated elevated CA 19-9 levels as well as T4 independently predicted worse long-term outcomes in patients with stage II CRC. However, the characterization of patients who gain survival advantages by adjuvant chemotherapy requires further investigation.

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Colorectal cancer (CRC) is one of the most prevalent malignancies worldwide [1]. Surgical resection is the cornerstone of management for patients with stage II CRC, which penetrates the layer of the muscularis propria without locoregional lymph node or distant metastases [2,3]. As only approximately one quarter of patients are expected to develop recurrence within five years of the diagnosis of stage II CRC, major published guidelines state that the routine implementation of adjuvant chemotherapy is not recommended for these patients [2,3].

Several clinicopathological characteristics have been identified as risk factors for recurrence in stage II CRC, and are often applied to the selection of patients for adjuvant chemotherapy in clinical practice. These characteristics initially included T4 tumors, perforation, suboptimal lymph node sampling and poor differentiation [2]. Bowel obstruction, lymphovascular invasion, perineural invasion and positive resection margins were subsequently added by other guidelines [3,4]. However, not all of these features were consistently proven to be high-risk factors for recurrence in different populations of stage II CRC, and, more importantly, most factors were not shown to be associated with survival benefits by adjuvant chemotherapy [5,6]. Based on these findings, we considered that other clinicopathological parameters need to be extensively searched in terms of recurrence in addition to the aforementioned risk factors.

This study was designed to identify risk factors for tumor recurrence among a wide range of clinicopathological parameters including perioperative factors in stage II CRC. We also investigated whether adjuvant chemotherapy was beneficial for stage II CRC patients with the identified risk factors.

Material and methods

Patients and data retrieval

We retrospectively reviewed patients who were pathologically diagnosed with stage II primary CRC resected curatively (R0 resection) at the Department of Surgical Oncology, the University of Tokyo between January 2005 and December 2014. We excluded patients with inflammatory bowel disease-associated cancer, Lynch syndrome, cancer of the appendix vermiformis, and anal fistula-associated cancer.

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Supplemental data for this article can be accessed here.

Patients who underwent preoperative radiation and/or chemotherapy for CRC, concurrently received anti-neoplastic therapy, or simultaneously had other malignancies were also excluded. All patient data regarding gender, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), lymphocyte count, serum albumin and hemoglobin levels, before any treatment, serum tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 just before surgery, and the pathological parameters of the primary tumor, namely, location, size, histological grade, lymphatic and venous invasion, perineural invasion, depth, the number of regional lymph nodes retrieved, obstruction, and perforation were documented. Perioperative data such as blood transfusion, complications including anastomotic leakage and surgical site infection were retrieved from medical charts. The regimen and duration of adjuvant chemotherapy were noted if administered.

The normal upper limits of serum CEA and CA 19-9 are 5 ng/ml and 37 U/ml, respectively. The normal lower limit of albumin is 4.1 g/dl, whereas that of serum hemoglobin is 13.7 g/dl for men and 11.6 g/dl for women in our institute. The histopathological description of primary CRC was based on the seventh edition of the American Joint Committee on Cancer and the International Union Against Cancer Tumor-Node Metastasis (AJCC/UICC TNM) grading system [7]. Postoperative complications were graded by the Clavien-Dindo classification [8].

The study protocol was approved by the local ethics committees in the University of Tokyo (reference number: 3252-(1)), and thus meets the standards of the Declaration of Helsinki in its revised version of 1975 and its later amendments.

Adjuvant chemotherapy, radiological evaluation and follow-up

Tegafur/uracil 300 mg/m^2 with or without 75 mg/m^2 leucovorin per day were orally administered on Days 1–28 every five weeks [9]. S-1 (tegafur/gimeracil/oteracil potassium) was orally administered at a dose of 40–60 mg corresponding to the body surface area, twice daily for 28 consecutive days, followed by a 14-day rest [10]. Capecitabine was administered at a dose of 1250 mg/m^2, twice daily on Days 1–14 every 21 days [11]. CapeOX (intravenous oxaliplatin 130 mg/m^2 over two hours on Day 1 plus oral capecitabine 1000 mg/m^2 twice per day on Days 1–14) was repeated every three weeks [12]. These postoperative treatments basically continued for six months. The selection of regimens depended on doctors' discretion. Dose reductions and the cessation of chemotherapy were considered based on the patient's condition and preference.

Computed tomography (CT) scans were performed at the end of the chemotherapy, and every 6–12 months thereafter. When serum tumor marker levels increased in an accelerated manner or in new manifestation of symptoms suggesting recurrent disease, CT scans and other imaging modalities such as magnetic resonance imaging and positron emission tomography were additionally carried out.

Recurrence-free survival (RFS) was defined as the time between surgery and the date of diagnosis of any recurrence. Surviving patients were censored at the last time point of patient contact either directly or indirectly.

Statistical analyses

Predictive factors for recurrence were estimated by univariate and multivariate analyses using the Cox proportional hazard model, in which continuous variables were dichotomized by their median/mean values (age, tumor size, and lymphocyte count), or preset cutoff levels as mentioned above (serum albumin, hemoglobin, CEA and CA 19-9). The Kaplan-Meier method was used to estimate RFS, and the log-rank test to analyze differences in survival between the groups. All the statistical analysis of the data was performed using JMP Version 12.2.0 (SAS Institute Inc., Cary, NC, USA), with p-values less than .05 being considered significant.

Results

Patient profiles

A total of 384 patients (225 men and mean age: 68 years old) underwent curative resection of primary stage II CRC during the study period. The baseline characteristics of these patients are shown in Table 1. Most patients had a good PS. Rectal cancer accounted for 26% of patients (100 patients). The primary tumor was, on average, 49 mm in diameter, and pathological T4 in 25% of patients (95 patients). One third of patients (139 patients) had obstructive cancer, with nine being accompanied by perforation. Three hundred and sixty patients (94%) had CRC of well or moderately differentiated adenocarcinomas. Lymphatic invasion, venous invasion and perineural invasion were histologically proven in 57 (15%), 282 (73%), and 30 patients (8%), respectively. In 57 patients (15%), less than 12 lymph nodes were retrieved. Absolute lymphocyte counts ranged between 200/μl and 8500/μl before any treatment (median 1611/μl). Preoperative serum albumin and hemoglobin levels were 3.7 g/dl and 12.0 g/dl on average, respectively. Based on cutoff values, 238 patients (62%) had hypoalbuminemia, and 239 (62%) were anemic. Elevated CEA and CA 19-9 levels were observed in 182 (47%) and 57 patients (15%), respectively, before surgery.

Thirty-three patients (9%) received blood transfusions during surgery. As postoperative complications, six patients (2%) had leakage at the anastomotic site and 33 (9%) surgical site infections (grade 2 or more). Ninety-four patients (24%) had grade 2 or more severe postoperative complications.

Adjuvant chemotherapy

Approximately 10% of patients (38 patients) received adjuvant chemotherapy. Twenty-eight patients received tegafur-uracil (plus leucovorin), four S-1, and five capecitabine. Only one patient received CapeOX therapy. No patient was treated by a biologic-including regimen. The median period of

Table 1. Profiles of stage II CRC patients (n = 384).

Variable	Number (%) or value
Gender	
Male	225 (59%)
Female	159 (41%)
Age (years)	
Mean ± SD	68.0 ± 11.6
ECOG PS	
0	333 (87%)
1	37 (10%)
2-	14 (3%)
Location of tumor	
Colon	284 (74%)
Rectum	100 (26%)
Maximum diameter of CRC (mm)	
Mean ± SD	49.4 ± 21.9
Depth	
T3	289 (75%)
T4	95 (25%)
Obstruction	139 (36%)
Histological type[a]	
Diff. adenoca.	360 (94%)
Others	24 (6%)
Lymphatic invasion	57 (15%)
Venous invasion	282 (73%)
Perineural invasion	30 (8%)
Number of lymph nodes harvested	
< 12	57 (15%)
Preoperative lymphocyte count (/μl)	
Median (range)	1611 (200–8500)
Preoperative albumin (g/dl)	
Mean ± SD	3.7 ± 0.5
Preoperative hemoglobin (g/dl)	
Mean ± SD	12.0 ± 2.0
Preoperative CEA	
≤5 ng/ml	162 (53%)
>5 ng/ml	182 (47%)
Not evaluated	1 (0%)
Preoperative CA 19-9	
≤37 U/ml	326 (85%)
>37 U/ml	57 (15%)
Not evaluated	1 (0%)
Intraoperative blood transfusion	33 (9%)
Postoperative complications	
Any types (grade 2-)	94 (24%)
Anastomotic leakage	6 (2%)
Surgical site infections	33 (9%)

[a]Histology of major component was shown.
CEA: carcinoembryonic antigen; Diff. adenoca.: well or moderately differentiated adenocarcinoma; CRC: colorectal cancer; ECOG: Eastern Cooperative Oncology Group; PS: performance status; SD: standard deviation; CA: 19-9: carbohydrate antigen 19-9.

adjuvant chemotherapy use was 6.4 months (range 0.4–30.8 months).

Risk factors for recurrence

With a median follow-up period of 48.6 months, 52 patients (14%) developed recurrent disease. The estimated five-year RFS rate was 85.6% for all patients. We performed a univariate analysis using Cox's proportional hazards model in order to identify clinicopathological predictors of recurrence. Obstruction, T4, lymphocyte counts, and elevated CA 19-9 levels were associated with poorer RFS with a p-value less than .05 (Table 2). These parameters were subjected to multivariate analyses for recurrence. As shown in Table 3, T4 and elevated CA 19-9 levels were identified as independent predictive factors for recurrence [T4: HR 2.34, p = .0045; elevated CA 19-9 levels: HR 1.96, p = .045]. Moreover, the combination of T4 and elevated CA 19-9 showed a higher risk for recurrence with an unadjusted HR of 3.52 than T3 and/or normal CA 19-9 (p = .013, data not shown).

Benefits of adjuvant chemotherapy in high-risk stage II CRC

We compared RFS between patients with T4 CRC receiving adjuvant chemotherapy and those without chemotherapy. A Kaplan-Meier analysis revealed that the RFS curve for patients treated by adjuvant chemotherapy did not significantly differ from the curve for those without chemotherapy (five-year RFS rate: 60% vs. 76%, p = .28, Supplementary Figure 1).

Similar analyses were performed for CRC with the other independent risk factor, elevated CA 19-9 levels before surgery. The RFS curve for CRC patients with preoperative CA 19-9 elevations treated by adjuvant chemotherapy was inferior to that for those without chemotherapy, but the difference was not significant (five-year RFS rate: 44% vs. 77%, p = .11, Supplementary Figure 2).

Discussion

Pathological T4 has been the most frequently demonstrated predictive factor for recurrence in stage II CRC [13–16]. Consistent with the literature, T4 was identified as an independent factor that increased the risk of recurrence with the greatest significance in the present study. Moreover, elevated CA 19-9 levels before surgery was another independent risk factor for recurrence in stage II CRC. This tumor marker has not been extensively investigated as a predictive factor in curatively resected CRC. The Japanese Study Group for Postoperative Follow-up of Colorectal Cancer reported a positive correlation between elevated preoperative CA 19-9 levels and high recurrence rates in patients with stage II cancer of the colon and rectosigmoid operated on in the 1990s [17]. Our results reappraise the significance of this marker as a risk factor for recurrence.

A poor nutritional status such as a low 'prognostic nutrition index' calculated from serum albumin levels and lymphocyte counts reportedly has a negative impact on long-term survival in CRC [18,19]. As perioperative factors, it was suggested that anastomotic leakage increased the risk of local and systemic recurrence in CRC [20]. Moreover, previous studies showed that a poor prognosis was associated not only with overall postoperative infectious complications, but also with perioperative blood transfusion [21,22]. Based on these findings, we considered that preoperative lymphocyte counts, albumin and hemoglobin levels, intraoperative blood transfusion, and postoperative complications also need to be analyzed; however, these variables were not independently associated with recurrence in stage II CRC in the present study.

The benefits of adjuvant chemotherapy in stage II CRC have been investigated separately from the identification of risk factors for recurrence in most studies. A limited number of studies suggested T4, obstruction, lymphovascular invasion, high CEA levels and fewer dissected lymph nodes as specific parameters associated with survival benefits from adjuvant chemotherapy, although they were not concordantly listed

Table 2. Univariate analysis for recurrence in stage II CRC patients.

Variable		HR	95% CI	p-Value
Gender	Male (vs. Female)	0.68	0.39–1.17	.16
Age (years)	≥69 (vs. <69)	0.73	0.42–1.26	.26
ECOS PS	1 or more (vs. 0)	1.42	0.23–4.58	.65
Location of tumor	Rectum (vs. colon)	1.55	0.86–2.71	.14
Histological type[a]	Diff. adenoca. (vs. others)	0.80	0.33–2.64	.67
Obstruction	Present (vs. absent)	2.31	1.34–4.01	.003
Maximum diameter	≥50 mm (vs. <50 mm)	1.16	0.67–2.01	.59
Depth	T4 (vs. T3)	2.98	1.72–5.14	.0002
Lymphatic invasion	Present (vs. absent)	1.81	0.91–3.34	.09
Venous invasion	Present (vs. absent)	1.61	0.84–3.40	.15
Perineural invasion	Present (vs. absent)	1.43	0.50–3.27	.47
Harvested lymph nodes	<12 (vs. ≥12)	1.39	0.66–2.66	.36
Preoperative lymphocyte count (/μl)	<1611 (vs. >1611)	1.83	1.04–3.39	.037
Preoperative albumin	Low (vs. normal)	1.42	0.80–2.64	.23
Preoperative hemoglobin	Low (vs. normal)	1.09	0.62–1.94	.77
Preoperative CEA	Elevated (vs. normal)	1.29	0.75–2.24	.36
Preoperative CA 19-9	Elevated (vs. normal)	2.36	1.24–4.25	.011
Blood transfusion	Yes (vs. no)	1.11	0.39–2.54	.82
Overall postoperative complications	Grade 2–(vs. none/grade 1)	1.22	0.64–2.20	.53
Anastomotic leakage	Present (vs. absent)	2.54	0.42–8.17	.26
Surgical site infections	Present (vs. absent)	1.36	0.52–2.93	.50
Adjuvant chemotherapy	No (vs. yes)	0.84	0.39–2.19	.69

[a]Histology of major component was analyzed.
CRC: colorectal cancer; ECOG: Eastern Cooperative Oncology Group; Diff. adenoca.: well or moderately differentiated adenocarcinoma; PS: performance status; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: confidence interval; HR: hazard ratio.

Table 3. Multivariate analysis for recurrence in stage II CRC.

Variable		HR	95% CI	p-Value
Obstruction	Present (vs. absent)	1.69	0.95–3.01	.074
Depth	T4 (vs. T3)	2.34	1.31–4.15	.0045
Preoperative lymphocyte count (/μl)	<1611 (vs. >1611)	1.46	0.81–2.73	.21
Preoperative CA 19-9	Elevated (vs. normal)	1.96	1.02–3.58	.045

CA 19-9: carbohydrate antigen 19-9; CI: confidence interval; CRC: colorectal cancer; HR: hazard ratio (Cox Proportional Hazards Model).

[5,14,15,17,23]. However, several studies including a meta-analysis reported that adjuvant chemotherapy did not markedly improve survival in high-risk stage II CRC [5,24,25]. Hence, the benefits of adjuvant chemotherapy in stage II CRC remain debatable. Our study failed to show improvements in RFS in the identified high-risk patients by adjuvant chemotherapy. There are several possibilities that may explain these results; our cohort comprised an insufficient number of patients receiving adjuvant chemotherapy to permit a statistically meaningful analysis. Furthermore, stage II CRC patients who received adjuvant chemotherapy may have more aggressive features than non-recipients ('selection bias'). More intensified regimens such as oxaliplatin-including chemotherapy may be required to improve the prognosis of high-risk stage II CRC. Inversely, adjuvant chemotherapy may have no impact or even exert detrimental effects on high-risk stage II patients. Hoshino et al. reported a nomogram for predicting recurrence in stage II CRC, where adjuvant chemotherapy was not an independent factor [26]. In our patients with T4 or high preoperative CA 19-9 levels, postoperative RFS rates deteriorated slightly with the use of adjuvant chemotherapy. In this regard, a recent population-based study suggested that adjuvant chemotherapy was associated with increases in recurrence and all-cause mortality in stage II colon cancer patients [27]. The Japanese Study Group for Postoperative Follow-up of Colorectal Cancer also showed that survival rates were significantly worse in patients with only one risk factor who received adjuvant chemotherapy than in those who did not [17]. Furthermore, Böckelman et al. argued the importance of quality of diagnostic work-up and follow-up that substantially influenced disease-free survival (DFS) in CRC in a meta-analysis [28]. Therefore, further investigations will be required in order to clarify which patients with stage II CRC will obtain survival benefits by what type of adjuvant chemotherapy.

Our study contains several limitations due to its retrospective nature. As the indications for adjuvant chemotherapy were not decided by criteria, there was a potential bias in selecting patents treated by chemotherapy as described above. Four different chemotherapeutic regimens were implemented in a small number of patients, and their administration periods varied. Our analyses did not contain details about side effects under treatment. Furthermore, we did not perform analyses using molecular biomarkers such as oncogenes, tumor suppressor genes, microsatellite and chromosomal instabilities, and micro-RNAs; information on the *RAS* gene status was not available in most patients, partly because the cost of the gene analysis was not covered by national health insurance until 2015 in Japan.

To conclude, in addition to pathological T4, elevated CA 19-9 levels were identified as a significant risk factor for recurrence in curatively resected stage II CRC. However, our results and previous findings collectively suggest that identifying CRC patients who may benefit from adjuvant treatment is still a big challenge.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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