

Tumor Marker Index Based on CEA and CA19-9 as a Prognostic Biomarker in Resectable Colon Cancer

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Abstract


Background/Aim: Despite curative resection, the prognosis after surgery for colon cancer varies considerably even among patients within the same TNM stage. There is a need for reliable biomarkers to complement the TNM classification. In pancreatic cancer, tumor markers have been reported as indicators of biological resectability. We therefore focused on tumor markers in colon cancer and investigated the prognostic significance of the tumor marker index (TMI).

Patients and Methods: We retrospectively reviewed patients with colon cancer (cecum to rectosigmoid) who underwent curative resection at our institution between 2011 and 2023. Among them, 361 patients without missing clinical or laboratory data were included. TMI was defined as the product of preoperative serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels. Patients were stratified into low- and high-TMI groups based on cutoff values determined by receiver operating characteristic (ROC) curve analysis with recurrence as the outcome. Three-year recurrence-free survival (3y-RFS), local recurrence-free survival (3y-LRFS), and distant metastasis-free survival (3y-DMFS) were compared between groups.

Results: The optimal TMI cutoff value was 64, with 226 cases classified into the low-TMI group and 135 cases into the high-TMI group. The 3y-RFS rate was significantly higher in the low-TMI group than in the high-TMI group (94.0% vs. 88.4%, $p=0.023$). Similarly, the 3y-LRFS rate was significantly better in the low-TMI group (97.7% vs. 95.2%, $p=0.044$). In contrast, there was no significant difference in 3y-DMFS between the low- and high-TMI groups (95.4% vs. 91.4%, $p=0.103$).

Conclusion: TMI was associated with postoperative recurrence patterns in curatively resected colon cancer. TMI may serve as a simple and clinically useful biomarker to complement TNM staging and improve risk stratification after curative surgery.

Keywords: Colon cancer, tumor marker, CEA, CA19-9, overall survival, recurrence-free survival.

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Introduction

Although curative resection remains the cornerstone of treatment for colon cancer, postoperative outcomes vary widely even among patients with the same pathological stage. The TNM classification, while indispensable, does not fully capture the biological heterogeneity of colon cancer, and additional prognostic biomarkers are required to refine postoperative risk stratification and guide surveillance strategies.

In pancreatic cancer, serum tumor markers such as carbohydrate antigen 19-9 (CA19-9) have been widely used not only for diagnosis and monitoring but also as indicators of biological aggressiveness and resectability. These findings suggest that tumor markers may reflect intrinsic tumor biology beyond anatomical extent. However, the clinical utility of combined tumor marker indices in colon cancer has not been fully established.

Carcinoembryonic antigen (CEA) and CA19-9 are routinely measured tumor markers in colorectal cancer. While each marker alone has limited prognostic accuracy, combining these markers may enhance their predictive value. In this study, we focused on the tumor marker index (TMI), defined as the product of CEA and CA19-9, and investigated its prognostic significance in patients undergoing curative resection for colon cancer.

Patients and Methods

Patients. This retrospective study included consecutive patients with colon cancer (from the appendix to the rectosigmoid) who underwent curative resection at our institution between January 2011 and December 2023. Patients with incomplete clinical data, missing preoperative tumor marker measurements, or non-curative resection were excluded. A total of 361 patients were eligible for analysis. The Review Board of the Tokyo Medical University Hospital approved the study (T2025-0157).

Tumor marker assessment and definition of TMI. Preoperative serum levels of CEA and CA19-9 were measured according

to institutional standards. TMI was calculated as the product of CEA and CA19-9 values ($\text{CEA} \times \text{CA19-9}$).

Determination of cutoff value. The optimal cutoff value for TMI was determined using receiver operating characteristic (ROC) curve analysis, with postoperative recurrence as the outcome variable. The cutoff value corresponding to the maximum Youden index was selected.

Outcomes and follow-up. The primary outcome was recurrence-free survival (RFS). Secondary outcomes included local recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS). Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test.

Statistical analysis. Continuous variables are summarized as medians with ranges, and categorical variables as frequencies and percentages. Survival outcomes were compared between the low- and high-TMI groups. A p -value <0.05 was considered statistically significant.

Results

Patient characteristics. Among the 361 patients, 226 were classified into the low-TMI group and 135 into the high-TMI group based on the cutoff value of 64 (Table I). There were no significant differences between the two groups in terms of age or sex distribution. Preoperative serum CEA, CA19-9, and TMI levels were significantly higher in the high-TMI group (all $p < 0.001$).

With regard to tumor characteristics, the distributions of pathological T category, N category, and pathological stage differed significantly between the two groups, with more advanced disease observed in the high-TMI group ($pT: p=0.009$; $pN: p<0.001$; $pStage: p=0.004$). In contrast, tumor location, histological subtype, lymphatic invasion, venous invasion, surgical approach, and the number of harvested lymph nodes were comparable between the groups. Postoperative recurrence occurred significantly more frequently in the high-TMI group ($p=0.025$), whereas

Table I. Baseline clinicopathological characteristics according to tumor marker index (TMI).

		Low-TMI (n=226)	High-TMI (n=135)	p-Value
Sex (%)	Female	93 (41.2)	55 (40.7)	1
Age (median)		68	70	0.41
Preoperative CA19-9		8.52 (6.01)	41.86 (81.79)	<0.001
Preoperative CEA		3.60 (4.43)	14.48 (19.95)	<0.001
Location (%)	Appendix	1 (0.4)	2 (1.5)	0.678
	Cecum	15 (6.6)	10 (7.4)	
	Ascending colon	57 (25.2)	33 (24.4)	
	Transverse colon	28 (12.4)	11 (8.1)	
	Discending colon	17 (7.5)	8 (5.9)	
	Sigmoid colon	73 (32.3)	49 (36.3)	
	Rectosigmoid colon	33 (14.6)	22 (16.3)	
	Sigmoid colon + Cecum	1 (0.4)	0 (0.0)	
	Ascending colon + Sigmoid colon	1 (0.4)	0 (0.0)	
Approach (%)	Male	133 (58.8)	80 (59.3)	0.31
	OPEN	41 (18.1)	32 (23.7)	
	LAP	183 (81.0)	103 (76.3)	
	RALS	2 (0.9)	0 (0.0)	
pT (%)	1	20 (8.8)	2 (1.6)	0.01
	2	11 (4.9)	3 (2.3)	
	3	157 (69.5)	95 (71.4)	
	4	38 (16.8)	33 (24.8)	
pN (%)	0	137 (60.6)	57 (42.9)	<0.001
	1	64 (28.3)	43 (32.3)	
	2	20 (8.8)	30 (22.2)	
	3	5 (2.2)	3 (2.3)	
pStage (%)	1	19 (8.6)	5 (3.8)	0.004
	2	115 (51.8)	52 (39.1)	
	3	88 (39.6)	76 (57.1)	
Lymphatic invasion (%)	0	72 (31.8)	29 (21.8)	0.498
	1	102 (45.1)	61 (46.0)	
	2	41 (18.1)	35 (26.3)	
	3	11 (4.9)	8 (6.0)	
Venous invasion (%)	0	62 (27.4)	26 (19.5)	
	1	91 (40.3)	55 (41.4)	
	2	57 (25.2)	40 (30.1)	
	3	16 (7.1)	12 (9.0)	
Histology (%)	tub1	46 (19.8)	18 (13.5)	0.326
	tub2	153 (67.5)	96 (72.3)	
	por	12 (5.3)	4 (3.1)	
	muc	7 (3.0)	10 (7.6)	
	Others	8 (3.4)	5 (4.9)	
Number of harvested lymph nodes		23	22	0.53
Recurrence (%)	No	198 (87.6)	106 (78.5)	0.025
	Yes	28 (12.4)	29 (21.5)	
Pattern of recurrence (%)	No	197 (87.2)	106 (78.5)	0.099
	LR	8 (3.5)	9 (6.7)	
	DM	20 (8.8)	17 (12.6)	
	Both	1 (0.4)	3 (2.2)	
Tumor marker index (median)		22.62	694.68	<0.001

CA19-9: Carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; DM: distant metastasis; LR: local recurrence.

the distribution of recurrence patterns (local recurrence, distant metastasis, or both) did not differ significantly between groups.

Among the 361 patients, 226 were classified into the low-TMI group and 135 into the high-TMI group based on the cutoff value of 64. Baseline clinicopathological

characteristics were comparable between groups (Table I).

Survival outcomes. The 3y-RFS rate was significantly higher in the low-TMI group than in the high-TMI group [94.0% (95%CI=90.0-96.5%) vs. 88.4% (95%CI=81.5-92.8%), $p=0.023$] (Figure 1). Similarly, the low-TMI group demonstrated significantly better 3y-LRFS [97.7% (95%CI=94.5-99.0%) vs. 95.2% (95%CI=89.5-97.8%), $p=0.044$] (Figure 2). In contrast, although the 3y-DMFS tended to be higher in the low-TMI group, the difference did not reach statistical significance [95.4% (95%CI=91.5-97.5%) vs. 91.4% (95%CI=84.9-95.1%), $p=0.103$] (Figure 3).

Discussion

Despite curative resection, prognosis after surgery for colon cancer remains heterogeneous, even among patients within the same TNM stage. Although TNM classification is essential for anatomical staging, it does not fully reflect tumor biology, host-tumor interactions, or occult micrometastatic disease. Consequently, there is an unmet need for biomarkers that complement TNM staging and improve postoperative risk stratification in patients with colon cancer (1-3).

In pancreatic cancer, serum tumor markers – particularly CA19-9 – have been widely investigated as indicators of biological aggressiveness and so-called “biological resectability”. Previous studies have demonstrated that elevated preoperative CA19-9 levels are associated with early recurrence and poor survival, even after technically curative resection (4, 5). These findings have influenced treatment strategies in pancreatic cancer, supporting the concept that biological factors should be considered alongside anatomical criteria. Based on this background, we hypothesized that tumor markers may similarly reflect tumor biology in colon cancer.

CEA is the most established tumor marker in colorectal cancer and is routinely used for postoperative

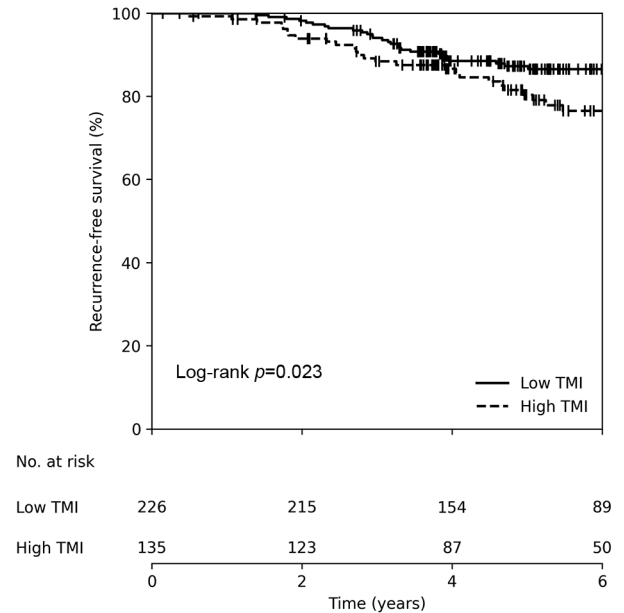


Figure 1. Recurrence-free survival according to tumor marker index (TMI) in patients with colon cancer.

surveillance. However, its sensitivity and specificity for predicting recurrence are limited when used alone (6). CA19-9, although less emphasized in colorectal cancer, has been reported to correlate with advanced disease stage, tumor burden, and unfavorable prognosis (7, 8). Several studies have suggested that combining CEA and CA19-9 improves prognostic accuracy compared with either marker alone (9, 10).

In this study, we focused on the TMI, calculated as the product of preoperative CEA and CA19-9 values, as a composite biomarker reflecting tumor biology. The rationale for this approach is that simultaneous elevation of both markers may indicate a biologically aggressive phenotype characterized by enhanced invasiveness or residual microscopic disease. Indeed, our results demonstrated that a high TMI was significantly associated with inferior recurrence-free survival and local recurrence-free survival following curative resection.

Notably, although high TMI was associated with worse 3-year RFS and LRFS, no statistically significant difference was observed in distant metastasis-free survival. This

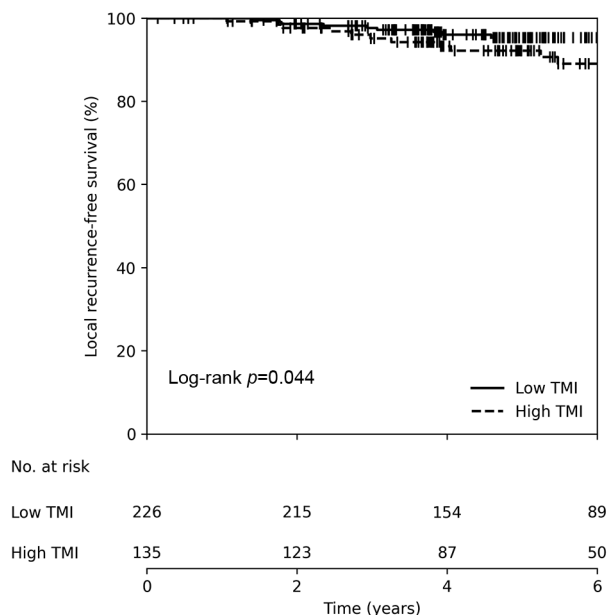


Figure 2. Local recurrence-free survival according to tumor marker index (TMI) in patients with colon cancer.

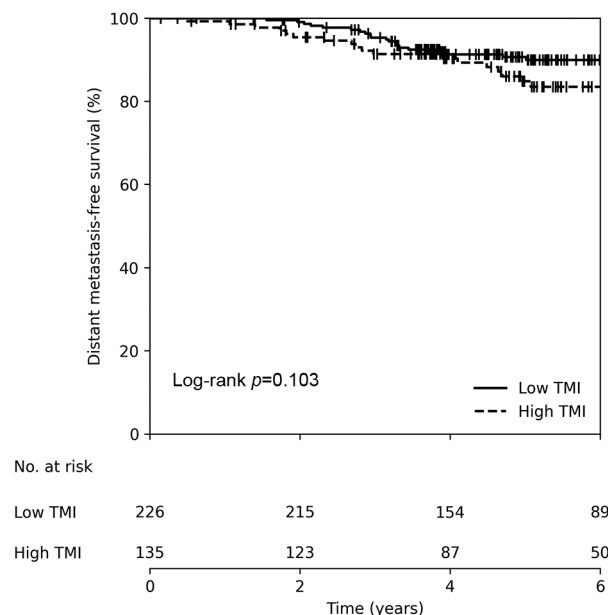


Figure 3. Distant metastasis-free survival according to tumor marker index (TMI) in patients with colon cancer.

finding may suggest that TMI is more closely related to local tumor aggressiveness or locoregional disease control rather than systemic metastatic potential. Alternatively, the effect of adjuvant chemotherapy may have attenuated differences in distant recurrence between groups. Similar discrepancies between local and distant recurrence have been reported in previous studies evaluating tumor markers in colorectal cancer (9, 11).

The discriminatory ability of TMI for predicting recurrence, as assessed by ROC analysis, was modest, with an AUC of approximately 0.57. While this value indicates limited predictive power when used in isolation, it is important to emphasize that TMI is derived from inexpensive, routinely measured serum markers. Therefore, TMI should be regarded as a complementary biomarker rather than a standalone prognostic tool. When combined with TNM staging and other clinicopathological factors, TMI may contribute to more refined postoperative risk stratification.

From a clinical perspective, TMI offers several advantages. It can be calculated easily from standard

preoperative laboratory data without additional cost or specialized testing. Incorporating TMI into clinical practice may help identify patients at higher risk of recurrence who could benefit from intensified surveillance or tailored adjuvant treatment strategies, particularly among patients with intermediate-stage disease.

Study limitations. First, its retrospective design and single-institution setting introduce potential selection bias. Second, treatment strategies and adjuvant chemotherapy regimens may have varied over the long study period. Third, the cutoff value for TMI was derived from a single cohort and requires external validation. Future prospective, multicenter studies are warranted to validate the prognostic value of TMI and clarify its role in personalized treatment strategies for colon cancer.

Conclusion

TMI, calculated from preoperative CEA and CA19-9 levels, is a potential prognostic biomarker in curatively resected

colon cancer. Incorporating TMI into postoperative risk stratification may improve individualized surveillance and management strategies beyond conventional TNM staging.

Conflicts of Interest

The Authors have no conflicts of interest associated with this study.

Authors' Contributions

T.K. and J.M. conceptualized the study; J.M. developed the methodology; T.K. and J.M. performed the formal analysis; T.K. and J.M. provided the resources; T.K. and J.M. wrote and prepared the original draft; J.M. and Y.N. wrote, reviewed, and edited the manuscript; and J.M. and Y.N. supervised the study.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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