Prognostic risk factors for pT4 colon cancer: A retrospective cohort study

TSUTOMU KUMAMOTO[1], SHIGEKI YAMAGUCHI[1], RYOSUKE NAKAGAWA[1], YOJI NAGASHIMA[2], FUMI MAEDA[1], KIMITAKA TANI[1], HIROKA KONDO[1], KURODO KOSHINO[1], YUKA KANEKO[1], YOSHIKO BAMBA[1], SHIMPEI OGAWA[1], YUJI INOUE[1] and MICHIO ITABASHI[1]

[1]Department of Surgery, Division of Colorectal Surgery; [2]Department of Surgical Pathology, Tokyo Women's Medical University, Tokyo 162-8666, Japan

Received October 4, 2022; Accepted November 10, 2022

DOI: 10.3892/ol.2022.13615

Abstract. The present study aimed to clarify the prognostic risk factors for pathological T4 (pT4) colon cancer and provide a basis for improved treatment in affected patients. The current retrospective cohort study included 83 consecutively enrolled patients who underwent curative surgery for primary pT4 colon cancer between January 2014 and December 2021 at Tokyo Medical Women's University (Tokyo, Japan). Oncological outcomes, including recurrence pattern, were compared between patients with pT4a and pT4b colon cancer. Independent risk factors associated with overall survival (OS) and relapse-free survival (RFS) were analyzed using a multivariate Cox regression model. The 3-year OS rates were 85.1 and 95.0% in the pT4a and pT4b groups (P=0.089) and 3-year RFS rates were 64.1 and 60.5% (P=0.589), respectively. Moreover, the 3-year peritoneal recurrence-free survival was 71.0 and 90.2% (P=0.085) in these groups, respectively. Independent risk factors for OS were histology (mucinous or poorly differentiated adenocarcinoma), tumor location (right-sided) and pN status (positive). The risk factors for RFS were histology and pN status. Patients with pT4b colon cancer and R_0 resection may not have a poorer prognosis compared with those with pT4a colon cancer. However, patients with pT4a colon cancer tended to have more peritoneal recurrence patterns. Histology and pN status were associated with OS and RFS, and right-sided colon cancer was also a risk factor for OS.

Correspondence to: Dr Tsutomu Kumamoto, Department of Surgery, Division of Colorectal Surgery, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku, Tokyo 162-8666, Japan
E-mail: kumamoto.tsutomu@twmu.ac.jp

Abbreviations: pT4, pathological T4; OS, overall survival; RFS, relapse-free survival; MVR, multivisceral en bloc resection; BMI, body mass index; CT, computed tomography; PET, positron emission tomography; IQR, interquartile range; HR, hazard ratio; CI, confidence interval

Key words: colon cancer, locally advanced cancer, multivisceral resection, pathological T4, prognostic factor, R0 resection

Introduction

Colorectal cancer is the fourth most common cancer, with 1.8 million cases worldwide as of 2017. It is also the second most common cause of cancer-related mortality, accounting for 896,000 deaths globally in 2017 (1). The depth of tumor invasion, which is classified into T status, is one of the poor prognostic factors, and T4 disease accounts for approximately 15% of all primary colon cancer (2,3). In the 7th edition of AJCC TNM classification in 2010, pathological T4 (pT4) was divided as tumor invasion through the visceral peritoneum (T4a) and to the adjacent organs or structures (T4b) (4) because a large study using National Cancer Data Base showed that pathological T4a (pT4a) had better 5-year survival rate than pathological T4b (pT4b) (5,6).

This classification is still applied today; however, there is no difference in the prognosis between pT4a and pT4b (7,8). A noteworthy point may be differences in the recurrence pattern between pT4a and pT4b colon cancer. The ratios of peritoneal recurrence were higher in pT4 colon cancer than in the other pT status colon cancer, ranging from 18.3 to 42.1% in previous studies (7-10). pT4a colon cancer had more frequent peritoneal recurrence than pT4b colon cancer (8). Conversely, R1 resection leads to some recurrence (especially locoregional recurrence) in pT4b colon cancer requiring multivisceral en block resection (MVR), and surgical technique also plays a role in prognosis (11). R1 resection is a poor prognostic factor for locally advanced colon cancer requiring MVR (12).

Poor prognostic factors for pT4 colon cancer remain incompletely elucidated. Understanding the oncological characteristics of pT4 colon cancer, including the tumor-specific differences between pT4a and pT4b colon cancer, can assist surgeons in providing the best possible treatment. Therefore, we investigated the prognostic risk factors for pT4 colon cancer in patients who underwent R0 resection. Toward this goal, we compared oncological outcomes, including overall survival (OS), relapse-free survival (RFS), and recurrence pattern, between patients with pT4 vs. pT4b colon cancer.

Additionally, the independent risk factors for pT4 colon cancer were examined.

Materials and methods

Patient selection criteria. Overall, 1,066 patients underwent surgery for primary colorectal cancer between 2014 and 2021 at Tokyo Women's Medical Hospital. Among these cases, 83 patients who underwent curative resection excluding emergency surgery and were diagnosed with pT4 colon cancer were enrolled. The patients with stage II-III cancer with lesions located between the cecum and rectosigmoid colon were included, but patients with stage IV colon cancer or R1 resection were excluded. En bloc MVR with complete mesocolic excision to achieve R0 resection was performed for patients with locally advanced colon cancer if tumors were invading or adhering to multiple organs or structures. The surgical approach included open, laparoscopic, and robotic surgery, and the most appropriate method was selected based on patient and tumor factors. A robotic approach was first used at our institution in 2017. The anastomosis in the minimally invasive surgery was not performed using the intra-corporeal functional end-to-end anastomosis technique. Conversion from the minimally invasive approach to an open approach was assigned to the open group. We collected medical data using the electronic medical records of these patients and analyzed them retrospectively. This study was approved by the Ethics Committee of Tokyo Women's Medical Hospital (Institutional Review Board number 5266).

Patient evaluation and perioperative treatment. Patient characteristics (age, sex, and body mass index [BMI]) were collected from the medical database. All patients were diagnosed with adenocarcinoma via biopsy and underwent colonoscopy and multidetector-row computed tomography (CT) or positron emission tomography (PET-CT) pre-operatively. Tumor status (tumor size, histology, pathological T stage and pathological N stage) and details concerning the surgical approach were obtained from the medical database. Pathological stage was determined according to the 8th edition of the TNM classification of malignant tumors (13). Regarding tumor location, the right colon was defined as the cecum and transverse colon, and the left colon was defined as the descending colon and the rectosigmoid colon.

Postoperative follow-up. Postoperative adjuvant chemotherapy was recommended for all patients based on their individual health status. Routine follow-up was performed every 3 months by consultation and included blood tests for tumor markers. Either CT or PET-CT was performed every 6 months. Additional examinations were performed in cases of suspected recurrence.

Statistical analysis. The baseline demographic information and long-term oncological outcomes (follow-up duration and recurrence site) were described and compared between the pT4a and T4b groups. Categorical data are presented as numbers and proportions and were compared between the two patient groups using Fisher's exact test. Continuous numerical variables are presented as median and interquartile range (IQR). The Mann-Whitney U test was used to compare the distribution of continuous numerical variables between the pT4a and pT4b groups. Patient characteristics (age, sex, BMI), tumor (tumor size, histology, tumor location, pT status, and pN status), and treatment-related variables (surgical approach, adjuvant chemotherapy) were used as potential risk factors for postoperative peritoneal recurrence, as described in previous studies (7,8). Factors of interest identified at the univariate level ($P<0.10$) were entered into a multivariate Cox regression model. The effects of these putative factors on recurrence risks are described as the hazard ratio (HR) and corresponding 95% confidence intervals (CIs). Statistical significance was set at a two-sided P-value of <0.05. Kaplan-Meier estimates were used to examine OS and RFS curves. The log-rank test was performed to compare long-term outcomes between the pT4a and pT4b groups. Among the patients with recurrence, OS with and without peritoneal recurrence, and with and without distant metastasis alone were also analyzed similarly. All statistical analyses were performed using SPSS version 24 (SPSS Inc., Chicago, IL, USA).

Results

Baseline demographics of patients. The baseline patient demographics, tumor characteristics, and treatment-related factors of the sample are summarized in Table I. There were no significant differences in patient characteristics, including age, sex, and BMI, between the pT4a group (n=62) and the pT4b group (n=21). Tumor size was, however, significantly larger in the pT4b group than in the pT4a group (P=0.033). The difference in the tumor location between the two groups was 37 cases (59.5%) (cecum: 6, ascending colon: 16, transverse colon: 15) vs. 8 cases (38.1%) (cecum: 2, ascending colon: 6) for the right-sided colon and 25 cases (40.3%) (descending colon: 4, sigmoid colon: 14, rectosigmoid colon: 7) vs. 13 cases (61.9%) (sigmoid colon: 11, rectosigmoid colon: 2) for the left-sided colon (P=0.128). The proportions of MVR were 4.8 and 100% in the pT4a and pT4b groups, respectively. The adjacent organs or structures resected for en bloc complete tumor resection were the peritoneum or abdominal wall (n=13), bladder (n=5), small intestine (n=4), other parts of the colon (n=3), duodenum (n=2), liver (n=1), ovary (n=1), gonadal vessels (n=1), omentum (n=1), and pararenal fat (n=1). Of these, it is in the pT4a group that there were the peritoneum or abdominal wall (n=3), omentum (n=1), and pararenal fat (n=1). Conversion from laparoscopy to open surgery was observed in one case. There were no significant differences in the surgical approach or use of postoperative adjuvant chemotherapy between the pT4a and pT4b groups.

Oncological outcomes including recurrence pattern. The oncological outcomes are summarized in Table II. The median (IQR) follow-up duration was comparable between the two groups (38.5 [15.8-55.0] months vs. 34 [14.5-58.5] months, P=0.917). Disease recurrence was observed in 17 (27.4%) and 8 (38.1%) patients in the pT4a and pT4b groups, respectively (P=0.413). Furthermore, peritoneal recurrence tended to occur more frequently in the pT4a group than in the pT4b group (19.4 vs. 9.5%, P=0.501), while distant metastasis ratio tended to be higher in the pT4b group than the pT4a group (11.3 vs. 28.6%, P=0.082). Five (71.4%) of the seven patients

Table I. Baseline patient demographics compared between the pT4a and pT4b groups.

Variables	Total (n=83)	pT status		P-value
		pT4a (n=62)	pT4b (n=21)	
Age, years	73.0 (62.0-77.0)	72.5 (61.0-77.3)	73.0 (66.0-78.0)	0.971
Sex, male/female n (%)	49 (52.4%)/34 (41.5%)	34 (54.8%)/28 (45.2%)	15 (71.4%)/6 (28.6%)	0.209
BMI, kg/m^2	21.6 (18.9-23.9)	21.8 (19.1-23.5)	21.3 (18.4-25.1)	0.773
Tumor size, cm	5.5 (4.5-7.0)	5.0 (4.1-7.0)	6.5 (5.5-8.3)	0.033
Site of tumor				0.128
Right-sided colon	45 (54.9%)	37 (59.7%)	8 (38.1%)	
Left-sided colon	38 (46.3%)	25 (40.3%)	13 (61.9%)	
Histology				0.200
Well/moderately	66 (79.5%)	47 (75.8%)	19 (90.5%)	
Mucinous	14 (16.9%)	13 (21.0%)	1 (4.8%)	
Poorly	3 (3.6%)	2 (3.2%)	1 (4.8%)	
pN status[a], n (%)				0.619
N0	45 (54.2%)	32 (51.6%)	13 (61.9%)	
N1	23 (27.7%)	19 (30.6%)	4 (19.0%)	
N2	15 (18.1%)	11 (17.7%)	4 (19.0%)	
Stent insertion before surgery, n (%)	15 (18.1%)	13 (20.1%)	2 (9.5%)	0.334
Approach, n (%)				0.234
Open	18 (21.7%)	11 (17.7%)	7 (33.3%)	
Laparoscopic	62 (74.7%)	49 (79.0%)	13 (61.9%)	
Robotic	3 (3.6%)	2 (3.2%)	1 (4.8%)	
MVR, n (%)	24 (28.9%)	3 (4.8%)	21 (100%)	
Adjuvant chemotherapy, n (%)	46 (55.4%)	33 (53.2%)	13 (61.9%)	0.613

[a]According to the TNM. Variables are described using medians and interquartile ranges. BMI, body mass index; MVR, multivisceral resection; pT4, pathological T4.

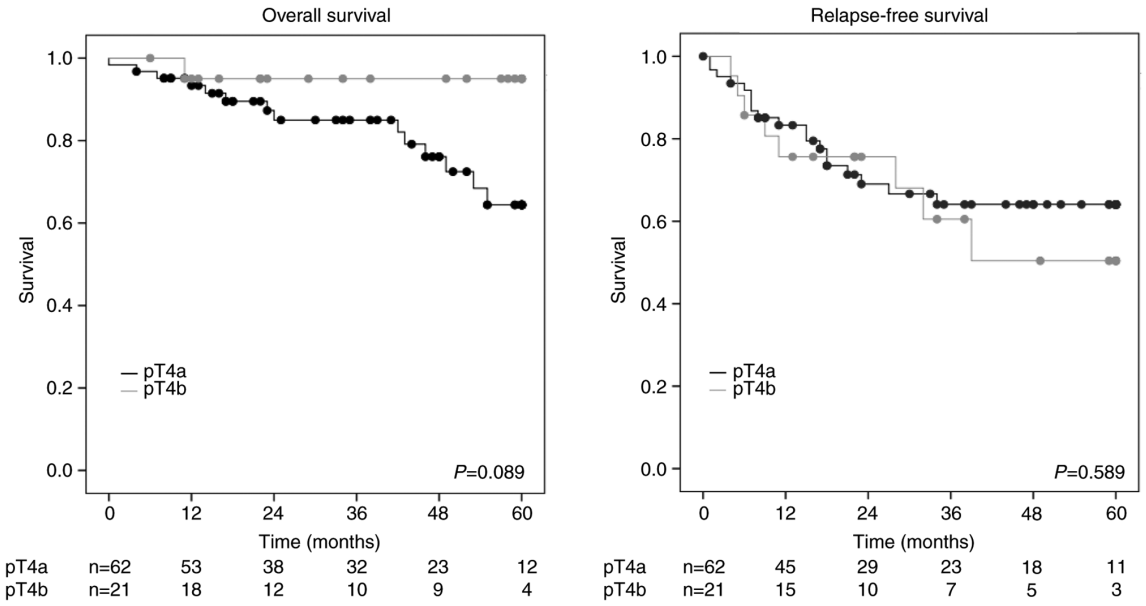

Figure 1. Overall survival and relapse-free survival in the pT4a and pT4b groups. pT4, pathological T4.

in the pT4b group who experienced recurrence were distant metastasis alone. The 3-year OS rates were 85.1% in the pT4a group and 95.0% in the pT4b group, respectively (P=0.089) (Fig. 1). The 3-year RFS rates were 64.1% in the pT4a

Table II. Oncological outcomes compared between the pT4a and pT4b groups.

Variables	Total (n=83)	pT4 status		P-value
		pT4a (n=62)	pT4b (n=21)	
Follow-up duration, months	38.0 (16.0-57.0)	38.5 (15.8-55.0)	34.0 (14.5-58.5)	0.917
Recurrent disease				
Overall, n (%)[a]	25 (30.1%)	17 (27.4%)	8 (38.1%)	0.413
Locoregional, n (%)	8 (9.6%)	6 (9.7%)	2 (9.5%)	1.000
Distant, n (%)	13 (15.7%)	7 (11.3%)	6 (28.6%)	0.082
Peritoneum, n (%)	14 (16.9%)	12 (19.4%)	2 (9.5%)	0.501
3-year overall survival	87.5%	85.1%	95.0%	0.089
3-year relapse-free survival	63.3%	64.1%	60.5%	0.589

[a]12 patients had some recurrent disease. Variables are described as medians and interquartile ranges. pT4, pathological T4.

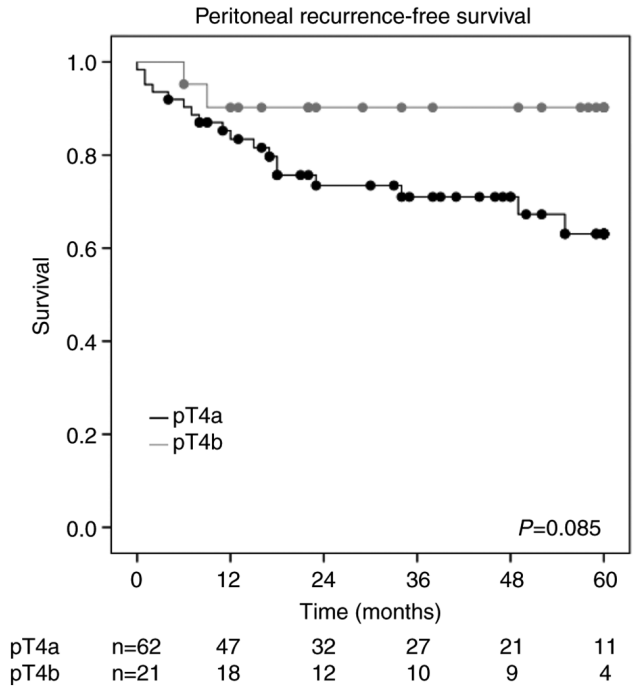

Figure 2. Peritoneal recurrence-free survival in the pT4a and pT4b groups. pT4, pathological T4.

group and 60.5% in the pT4b group, respectively (P=0.589) (Fig. 1). The 3-year peritoneal recurrence-free survival rate tended to be lower in the pT4a group than in the pT4b group (71.0 vs. 90.2%, P=0.085) (Fig. 2).

Risk factors for overall and recurrence-free survival. Table III presents the independent risk factors associated with OS and RFS. In univariate and multivariable analyses, OS was associated with mucinous or poorly differentiated adenocarcinoma (HR, 6.828; 95% CI, 2.173-21.456; P=0.001), right-sided colon cancer (HR, 4.290; 95% CI, 1.119-16.446; P=0.034), and pN status positive (HR, 5.060; 95% CI, 1.387-18.462; P=0.014). Conversely, poor prognostic factors were histologically confirmed mucinous or poorly differentiated adenocarcinoma (HR, 3.114; 95% CI, 1.375-7.052; P=0.006) and pN status positive (HR, 7.845; 95% CI, 2.706-22.745; P<0.001).

Discussion

This study investigated prognostic risk factors for pT4 colon cancer when radical resection was performed, including a comparison between the pT4a and pT4b groups. There were no statistical differences in OS and RFS between the pT4a and pT4b groups; however, there was a trend toward more disseminated recurrence in the pT4a group. Histology (mucinous or poorly differentiated adenocarcinoma) and pN status (positive) were associated with OS and RFS, and tumor location (right-sided) was an independent risk factor for OS in patients with pT4 colon cancer.

Before 2010, several studies had shown that tumor invasion through the visceral peritoneum is associated with a worse prognosis than invasion to the adjacent organs or structures (14-16). Subsequently, in the 7th edition of AJCC TNM classification (2010), pT4 was divided into pT4a and T4b4, since a large study using National Cancer Data Base showed pT4a had a better 5-year survival rate than pT4b (5). However, recent studies showed no difference between pT4a and pT4b, which is similar to our results (7,8). In our study, pT groups were not significantly associated with survival. Tumor location, histology, and pN status were associated with OS, and histology and pN status were risk factors for RFS. These findings are consistent with those of previous studies, which suggested that tumor location (right-sided), histology (mucinous or poor differentiated adenocarcinoma) and pN status were associated with a poorer prognosis (5,12,17,18), especially right-sided colon cancers characterized by mucinous histology, high microsatellite instability, and *BRAF* mutation carrier status (17,18).

Although pT4a colon cancer is expected to be more likely to cause peritoneal recurrence than pT4b colon cancer, studies have often failed to prove this with statistical significance. Our study also demonstrated a tendency for the pT4a group to be more prone to recurrence of peritoneal recurrence than the pT4b group (19.4 vs. 4.8%, P=0.168). At least one prior

Table III. Risk factors for overall survival and relapse-free survival in patients with pT4 colon cancer.

A, Overall survival

	Univariate		Multivariable	
Variables	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age (≥75 years old/<75 years old)	1.239 (0.449-3.417)	0.679		
Sex (male/female)	0.794 (0.288-2.191)	0.656		
BMI (≥22 kg/m^2/<22 kg/m^2)	0.625 (0.222-1.762)	0.374		
Tumor size (≥5 cm/<5 cm)	1.048 (0.357-3.077)	0.932		
Mucinous/Poorly (yes/no)	6.012 (2.134-16.937)	0.001	6.828 (2.173-21.456)	0.001
Location (right-sided/left-sided)	3.296 (0.929-11.694)	0.065	4.290 (1.119-16.446)	0.034
pT status[a] (T4a/4b)	4.893 (0.643-37.233)	0.125		
pN status[a] (N1-2/N0)	4.778 (1.347-16.941)	0.015	5.060 (1.387-18.462)	0.014
Stent insertion (yes/no)	1.721 (0.547-5.414)	0.354		
Approach (Laparoscopic or robotic/open)	0.767 (0.243-2.421)	0.651		
Adjuvant chemotherapy (yes/no)	0.909 (0.330-2.508)	0.909		

B, Relapse-free survival

	Univariate		Multivariable	
Variables	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age (≥75 years old/<75 years old)	0.537 (0.235-1.228)	0.141		
Sex (male/female)	1.128 (0.516-2.465)	0.763		
BMI (≥22 kg/m^2/<22 kg/m^2)	0.962 (0.452-2.048)	0.920		
Tumor size (≥5 cm/<5 cm)	0.910 (0.408-2.029)	0.818		
Mucinous/Poorly (yes/no)	3.328 (1.481-7.481)	0.004	3.114 (1.375-7.052)	0.006
Location (right-sided/left-sided)	1.525 (0.698-3.331)	0.290		
pT status[a] (T4a/4b)	0.797 (0.349-1.822)	0.591		
pN status[a] (N1-2/N0)	8.075 (2.789-23.374)	<0.001	7.845 (2.706-22.745)	<0.001
Stent insertion (yes/no)	1.074 (0.403-2.862)	0.887		
Approach (Laparoscopic or robotic/open)	1.118 (0.423-2.953)	0.822		
Adjuvant chemotherapy (yes/no)	1.156 (0.536-2.493)	0.712		

[a]According to the TNM. BMI, body mass index; CI, confidence interval; pT4, pathological T4.

study showed this effect could be due to a type II statistical error, and demonstrated that the pT4a group had more peritoneal recurrence than the pT4b group in the absence of this error (8). Interestingly, in our study, the pT4b group showed a trend toward more distant as opposed to peritoneal recurrence (11.3 vs. 28.6%, P=0.082). Peritoneal recurrence was associated with a poorer prognosis than was no peritoneal recurrence (P=0.009). However. the prognosis was poor in the presence of peritoneal recurrence, while distant metastasis alone was associated with a better prognosis than other recurrence patterns (P=0.039) (Fig. 2). Therefore, strategies that consider the recurrence pattern of pT4a vs. pT4b colon cancer are required for oncologists. A previous review of three large phase III randomized trials suggested that developing peritoneal recurrence led to poorer OS than other forms of recurrence (19).

A randomized controlled trial comparing open and laparoscopic surgery for colon cancer (JCOG0404) also found no significant differences in the rate of peritoneal recurrence between the two approaches (20). Conversely, a conflicting study showed an association between the laparoscopic approach and increased risk for peritoneal recurrence (21). We believe that it is important to avoid direct contact with the tumor as much as possible during laparoscopic surgery for pT4a, since the cancer cells are exposed on the surface of the serosa and may be disseminated by the surgical procedure. Conversely, it must be recommended that R0 resection with MVR is always required for patients in the pT4b group. The surgical approach should be selected according to the surgical-skill level of the institution and that of the surgeon to prevent R1 resection by the surgical procedure, as proposed in our previous study (12).

This study has some limitations. First, this was a retrospective study with a small sample size that included surgical data from a single institution. Second, this study had a selection bias for patients in terms of the surgical approach. However, this decision was based on the capacities of the research institution, which is in keeping with real-world clinical practice. Third, only a few patients received postoperative adjuvant chemotherapy. In contrast, the major strength of this study is its focus on patients with colon cancer who underwent R0 resection without primary involvement of the rectum. This is because locally advanced colon cancer is more prone to peritoneal recurrence than rectal cancer, and the treatment including surgical difficulty, is standardized. Finally, large-scale studies with multicenter designs would be required to generalize our findings.

In conclusion, our findings suggest that patients with pT4b colon cancer and R0 resection may not have a poorer prognosis compared to those with pT4a colon cancer. However, the possibility that patients with pT4a colon cancer had more peritoneal recurrence than those with pT4b colon cancer may have affected the survival rates. Histology (mucinous or poorly differentiated adenocarcinoma) and pN status (positive) were significant prognostic factors for OS and RFS, and tumor location (right-sided) was also associated with OS.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

The study concept and design were developed by TK and SY. Data collection was performed by TK, RN, YN, FM, KT, HK, KK, YK, YB, SO, YI and MI. The analysis was performed by TK. The manuscript was prepared by TK. The manuscript was supervised by SY. All authors reviewed the manuscript. TK and RN confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tokyo Women's Medical Hospital (Institutional Review Board number 5266). The committee waived the requirement for informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Dr Tsutomu Kumamoto, ORCID: 0000-0002-7177-9328.

References

1. Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, Abdelalim A, Abdoli A, Abdollahpour I, *et al*: Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the global burden of disease study. JAMA Oncol 5: 1749-1768, 2019.
2. Segelman J, Akre O, Gustafsson UO, Bottai M and Martling A: External validation of models predicting the individual risk of metachronous peritoneal carcinomatosis from colon and rectal cancer. Colorectal Dis 18: 378-385, 2016.
3. de Neree Tot Babberich MPM, Detering R, Dekker JWT, Elferink MA, Tollenaar RAEM, Wouters MWJM and Tanis PJ; Dutch ColoRectal Audit Group: Achievements in colorectal cancer care during 8 years of auditing in the Netherlands. Eur J Oncol 44: 1361-1370, 2018.
4. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A III: Colon and rectum. In: AJCC Cancer Staging Manual. 7th edition. Springer-Verlag, New York, NY, pp143-164, 2010.
5. Gunderson LL, Jessup JM, Sargent DJ, Greene FL and Stewart AK: Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol 28: 264-271, 2010.
6. Frankel WL and Jin M: Serosal surfaces, mucin pools, and deposits, oh my: Challenges in staging colorectal carcinoma. Mod Pathol 28 (Suppl 1): S95-S108, 2015.
7. Eom T, Lee Y, Kim J, Park I, Gwak G, Cho H, Yang K, Kim K and Bae BN: Prognostic factors affecting disease-free survival and overall survival in T4 colon cancer. Ann Coloproctol 37: 259-265, 2021.
8. Bastiaenen VP, Aalbers AGJ, Arjona-Sánchez A, Bellato V, van der Bilt JDW, D'Hoore AD, Espinosa-Redondo E, Klaver CEL, Nagtegaal ID, van Ramshorst B, *et al*: Risk of metachronous peritoneal metastases in patients with pT4a versus pT4b colon cancer: An international multicentre cohort study. Eur J Surg Oncol 47: 2405-2413, 2021.
9. Hompes D, Tiek J, Wolthuis A, Fieuws S, Penninckx F, Van Cutsem E and D'Hoore A: HIPEC in T4a colon cancer: A defendable treatment to improve oncologic outcome? Ann Oncol 23: 3123-3129, 2012.
10. van Santvoort HC, Braam HJ, Spekreijse KR, Koning NR, de Bruin PC, de Vries Reilingh TS, Boerma D, Smits AB, Wiezer MJ and van Ramshorst B: Peritoneal carcinomatosis in T4 colorectal cancer: Occurrence and risk factors. Ann Surg Oncol 21: 1686-1691, 2014.
11. Eveno C, Lefevre JH, Svrcek M, Bennis M, Chafai N, Tiret E and Parc Y: Oncologic results after multivisceral resection of clinical T4 tumors. Surgery 156: 669-675, 2014.
12. Kumamoto T, Toda S, Matoba S, Moriyama J, Hanaoka Y, Tomizawa K, Sawada T and Kuroyanagi H: Short- and long-term outcomes of laparoscopic multivisceral resection for clinically suspected T4 colon cancer. World J Surg 41: 2153-2159, 2017.
13. UICC: TNM Classification of Malignant Tumours. 8th edition. John Wiley & Sons Ltd., New York, NY, 2017.
14. Shepherd NA, Baxter KJ and Love SB: The prognostic importance of peritoneal involvement in colonic cancer: A prospective evaluation. Gastroenterology 112: 1096-1102, 1997.
15. Compton C, Fenoglio-Preiser CM, Pettigrew N and Fielding LP: American Joint Committee on cancer prognostic factors consensus conference: Colorectal working group. Cancer 8: 1739-1757, 2000.
16. Keshava A, Chapuis PH, Chan C, Lin BP, Bokey EL and Dent OF: The significance of involvement of a free serosal surface for recurrence and survival following resection of clinicopathological stage B and C rectal cancer. Colorectal Dis 9: 609-618, 2007.

17. Petrelli F, Tomasello G, Borgonovo K, Ghidini M, Turati L, Dallera P, Passalacqua R, Sgroi G and Barni S: Prognostic survival associated with left-sided vs right-sided colon cancer: A systematic review and meta-analysis. JAMA Oncol 3: 211-219, 2017.
18. Park JS, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, Lee WY and Chun HK: Prognostic comparison between mucinous and nonmucinous adenocarcinoma in colorectal cancer. Medicine (Baltimore) 94: e658, 2015.
19. Mayanagi S, Kashiwabara K, Honda M, Oba K, Aoyama T, Kanda M, Maeda H, Hamada C, Sadahiro S, Sakamoto J, *et al*: Risk factors for peritoneal recurrence in stage II to III colon cancer. Dis Colon Rectum 61: 803-808, 2018.
20. Saito S, Akagi T, Katayama H, Wakabayashi M, Inomata M, Yamamoto S, Ito M, Kinugasa Y, Egi H, Munakata Y, *et al*: Identification of patient subgroups with unfavorable long-term outcomes associated with laparoscopic surgery in a randomized controlled trial comparing open and laparoscopic surgery for colon cancer (Japan Clinical Oncology Group Study JCOG0404). Ann Gastroenterol Surg 5: 804-812, 2021.
21. Huynh C, Minkova S, Kim D, Stuart H and Hamilton TD: Laparoscopic versus open resection in patients with locally advanced colon cancer. Surgery 170: 1610-1615, 2021.