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ORIGINAL ARTICLE

Prognostic significance of doubling time in patients undergoing radical surgery for metachronous peritoneal metastases of colorectal cancer

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Abstract

Purpose The doubling times of tumor volume and tumor markers are associated with the prognosis of liver or lung metastases from colorectal cancer (CRC). However, no studies have assessed peritoneal metastases. Therefore, we aimed to elucidate the association between doubling time and the prognosis of patients who underwent radical surgery for metachronous peritoneal metastases of CRC.

Methods We calculated the tumor doubling times (TDT) of peritoneal metastases and serum carcinoembryonic antigen-doubling times (CEA-DT) in 33 consecutive patients who underwent radical surgery for metachronous peritoneal metastases between January 2006 and April 2017. The impact of short TDT and CEA-DT on overall survival (OS) and relapse-free survival (RFS) was retrospectively reviewed.

Results In long TDT (> 137 days) group, the 5-year OS rate was 74.1% and median OS time was 6.6 years. In long CEA-DT (> 102 days) group, the 5-year OS rate was 50.0% and median OS time was 5.6 years. Conversely, in short TDT (≤ 137 days) and CEA-DT (≤ 102 days) group, the 5-year OS rates and median OS times were both 0.0% and 3.2 years, respectively. In the multivariate analysis, short TDT was an independent risk factor for poor RFS ($P = 0.006$) and OS ($P = 0.010$). Similarly, short CEA-DT was also a poor risk factor for RFS ($P < 0.001$) and OS ($P = 0.012$).

Conclusions Short TDT and CEA-DT are independent risk factors for poor OS and RFS after surgery for metachronous peritoneal metastases of CRC. TDT and CEA-DT should be considered when selecting candidates for surgical resection.

Keywords Doubling time · Peritoneal metastases · Colorectal cancer · Prognosis

Introduction

Metachronous peritoneal metastasis is observed in 2.1–4.2% of patients who have undergone surgery for colorectal cancer (CRC) [1–3]. Peritoneal metastasis is associated with a poor prognosis. The median survival of patients with peritoneal metastasis who are treated with systemic chemotherapy is 12.7–16.3 months [4, 5]. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have improved the prognosis of patients with peritoneal metastasis [6, 7], with a median survival of up to 19.2–30.1 months [8–11].

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However, surgical resection can be invasive, and the morbidity rates of CRS with HIPEC are very high [8, 12, 13]. Moreover, in highly advanced cases, CRS may not improve the prognosis because of the high rate of recurrence [14]. Therefore, the decision to operate must be carefully considered based on coexisting diseases, the difficulty of surgical resection, and the risk of recurrence.

The ability of cancer cells to proliferate may be a risk factor for tumor recurrence. Because cancer cells grow exponentially, the tumor doubling time (TDT) has been used as an indicator of the growth rate. TDT was first proposed by Collins et al. [15, 16] to predict the growth rate of pulmonary metastases from CRC. The doubling time (DT) of tumor markers has also been evaluated as an indicator of tumor growth. TDT and the tumor marker DT are associated with the prognosis in various cancers, including CRC. In patients with liver or lung metastases of CRC [17–23], short TDT and short carcinoembryonic antigen (CEA)-DT are considered to be risk

factors for a poor prognosis. In patients with local recurrence of rectal cancer, short CEA-DT is considered to be a risk factor for a poor prognosis [24, 25]. However, there have been no studies of peritoneal metastases of CRC.

Therefore, we aimed to elucidate the association between TDT of peritoneal metastases or CEA-DT and the prognosis of patients who underwent radical surgery for metachronous peritoneal metastases of CRC.

Methods

Patient selection

In total, 35 consecutive patients who underwent radical surgery for metachronous peritoneal metastases after primary curative surgery for CRC at The University of Tokyo Hospital (Tokyo, Japan) between January 2006 and April 2017 were retrospectively reviewed. Between January 2006 and April 2017, a total of 2195 patients underwent primary curative surgery for CRC. Metachronous peritoneal metastases were evaluated according to the criteria of the Japan Society for Cancer of the Colon and Rectum (JSCCR) [26]: P1, peritoneal metastasis only to the adjacent peritoneum; P2, a few metastases to the distant peritoneum; and P3, diffuse metastases to the distant peritoneum. Peritoneal cancer index (PCI) scores of P1, P2, and P3 seemed to be in the range of 1–6, 4–20, and > 10, respectively [27]. P1 and P2 were selected as candidates for surgical resection. DT was not considered while deciding the treatment method. Radical surgery was defined as resection of all peritoneal metastases that could be detected macroscopically without total peritonectomy or HIPEC. As for rectal cancer, it is sometimes difficult to discriminate peritoneal metastases from local recurrence. Therefore, recurrences in the pelvic floor, except for anastomotic and lateral lymph node recurrences, were also included as recurrences that were considered to be peritoneal metastases. Two of the 35 patients were excluded because neither TDT nor CEA-DT could be calculated, which means tumor diameter and serum CEA could be measured only one time. Finally, 33 patients were identified. The study protocol was approved by the Ethics Committee of The University of Tokyo (approval number: 3252-(7)). Because this was retrospective study, informed consent was replaced by the obligation of information and the right of the participants to opt out.

Patient follow-up

The median follow-up time was 2.8 years (range, 0.9–7.4 years). Blood sampling, computed tomography (CT), and colonoscopy were performed after radical surgery for metachronous peritoneal metastases. Generally, blood sampling was performed every 3 months, CT every 6 months, and colonoscopy every 12 months. When serum CEA levels were elevated or there was the possibility of recurrence, blood sampling and CT were performed more frequently.

Measurements of DT

DT was calculated as the growth rate of metachronous peritoneal metastasis during the chemotherapy- and radiotherapy-free interval. TDT was calculated by measuring the tumor diameter by CT. The CT slice thickness was 5.0 mm. TDT and CEA-DT were calculated as described below and in previous studies [17–19, 22–25, 28].

$$\mathrm{TDT} = t \cdot \log 2 / [3 \cdot \log Dt / D0]$$

(t, interval between two measurements; Dt, tumor diameter at second measurement; D0, tumor diameter at first measurement)

$$\mathrm{CEA{-}DT} = t \cdot \log 2 / [\log Ct / C0]$$

(t, interval between two measurements; Ct, serum CEA level at second measurement; C0, serum CEA level at first measurement)

In cases where there were two or more metastatic lesions, the largest lesion was selected to calculate TDT. The most frequent site we measured was pelvic region (central, 6.1%; right upper, 3.0%; epigastrium, 3.0%; left upper, 3.0%; left flank, 6.1%; left lower, 15.2%; pelvis, 42.4%; right lower, 12.1%; right flank, 9.1%). When the tumor diameter was measured by CT at three or more time points, TDT could be calculated from the slope of regression lines of the tumor growth curves (Fig. 1). This also applied to serum CEA levels [29]. In one patient, the tumor diameter was difficult to measure due to the indistinct border of the lesion. This patient was excluded

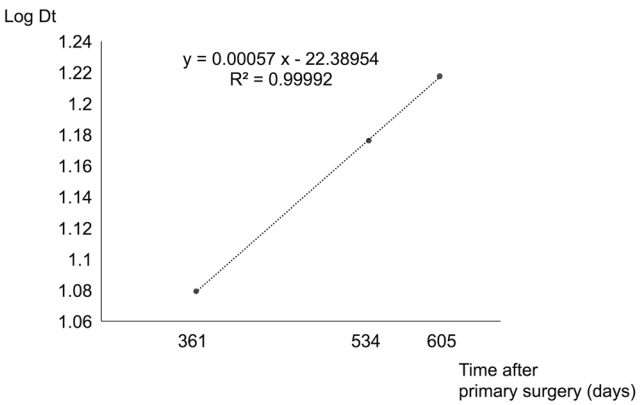

Fig. 1 Sample of linear regression of the common logarithm of tumor diameter and time. Slope of the regression line = log2/3·TDT (TDT = t·log2/[3·log$D$t/D0]). The TDT of this patient was 176 days. D0, tumor diameter at first measurement; Dt, tumor diameter at second measurement; R^2, determination coefficient; t, interval between two measurements; TDT, tumor doubling time

from the evaluation of TDT. Therefore, TDT was calculated in 32 patients. CEA-DT was calculated in patients with serial elevations in serum CEA levels of > 5.0 ng/ml. The serum CEA level was measured only once in one patient and was not elevated in 10 patients. Therefore, CEA-DT was calculated in 22 patients.

Statistical analyses

The statistical significance of the association between DT and patient characteristics was determined using Fisher's exact test, Wilcoxon's rank-sum test, and analysis of variance. Overall survival (OS) and relapse-free survival (RFS) rates after surgery for metachronous peritoneal metastases of CRC were calculated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses of the risk factors for OS and RFS after surgery for metachronous peritoneal metastases of CRC were performed using the Cox proportional hazards models. Only the variables with $P < 0.10$ from the univariate analysis were included in the multivariate analysis. In the multivariate analysis, TDT and CEA-DT were analyzed separately, due to the strong association between them. In the analysis of OS, all patients ($n = 33$) who underwent radical surgery for metachronous peritoneal metastases were included. In the analysis of RFS, only patients ($n = 26$) with R0 resection for metachronous peritoneal metastases were included, which excluded 7 patients who had undergone R1 resection. All statistical analyses were conducted using JMP Pro 13 (SAS Institute Inc., Cary, NC, USA). P values < 0.05 were considered statistically significant.

Results

Patient characteristics

The patient characteristics are summarized in Table 1. In total, 33 consecutive patients (25 men and 8 women) were identified. The median age was 64 years (range, 40–77 years). The median TDT and CEA-DT were 137 days (range, 30–523 days) and 102 days (range, 20–529 days), respectively. Serum CEA levels were high (> 5.0 ng/ml) in 17 patients before primary surgery. Although CEA levels decreased after surgery in most patients with high CEA levels, two patients still had high (> 5.0 ng/ml) CEA levels. Peritoneal metastases could be detected when CEA levels were accelerated first time after primary surgery in 16 patients among 23 patients with elevated CEA levels. Adjuvant systemic chemotherapy after surgery for metachronous peritoneal metastases of CRC was performed by 5-fluorouracil (5FU) plus oxaliplatin in 13 patients and 5FU monotherapy in 9 patients.

Regression analysis

TDT and CEA-DT were calculated from the regression lines of the tumor growth curves for 14 and 17 patients, respectively. The median determination coefficients (R^2) for TDT and CEA-DT were 0.99521 (0.90202–0.99992) and 0.95492 (0.85504–0.99765), respectively. R^2 was significantly higher for TDT than for CEA-DT ($P = 0.007$).

Association between TDT and CEA-DT

Both TDT and CEA-DT were calculated for 21 patients. The Spearman's correlation coefficient for the comparison between TDT and CEA-DT was 0.8834 ($P < 0.001$) (Fig. 2).

Association between DT and patient characteristics

Patients were stratified into two groups according to TDT: short TDT group (TDT ≤ 137 days; $n = 16$) and long TDT group (TDT > 137 days; $n = 16$). Associations between TDT and patient characteristics are summarized in Table 2. Patients were also stratified into three groups according to CEA-DT: short CEA-DT group (CEA-DT ≤ 102 days; $n = 11$), long CEA-DT group (CEA-DT > 102 days; $n = 11$), and no elevation group ($n = 10$). Associations between CEA-DT and patient characteristics are summarized in Table 3. Cutoff values were determined according to the median TDT and CEA-DT. Short TDT was associated with male sex ($P = 0.037$), short (≤ 1 year) disease-free interval (DFI) from the primary surgery ($P = 0.032$), and short CEA-DT ($P < 0.001$).

Patient prognosis

In total, the 5-year OS rate was 35.2% and the median OS was 4.2 years. The 2- and 5-year RFS rates were 43.1% and 25.2%, respectively; the median RFS time was 1.3 years. OS and RFS curves after surgery for metachronous peritoneal metastases of CRC according to TDT and CEA-DT are shown in Fig. 3a–d. All patients in short TDT group developed recurrence within 2 years and none of the patients survived beyond 5 years. The median OS time was 3.2 years. In long TDT group, the 2-year RFS and 5-year OS rates were 76.2% and 74.1%, respectively. The median OS time was 6.6 years. Similarly, in short CEA-DT group, all patients developed recurrence within 2 years and none of the patients survived beyond 5 years. The median OS time was 3.2 years. For patients with long CEA-DT and no elevation, the 2-year RFS rates were 57.1% and 64.8%, whereas the 5-year OS rates were 50.0% and 64.3%, respectively. The median OS time of patients in long CEA-DT group was 5.6 years. The prognosis of patients with long CEA-DT or no elevation was significantly better than that of patients with short CEA-DT.

Table 1 Patient characteristics

Characteristics	
Total number	33
Sex (male/female)	25/8
Age, median (range)	64 (40–77)
BMI, median (range)	21.7 (15.5–36.4)
Primary lesion	
Site (colon/rectum)	12/21
T stage (T1–3/T4)	16/17
N stage (N0/N1/N2)	15/13/5
pStage (II/III/IV)	14/15/4
Vascular invasion (present/absent/unknown)	28/4/1
Lymph invasion (present/absent/unknown)	14/18/1
Histologic differentiation (well/moderate/unknown)	13/19/1
Perforation (present/absent)	0/33
Ileus (present/absent)	3/30
Circumferential resection margin (negative/positive)	33/0
Serum CEA level (> 5.0 ng/ml/≤ 5.0 ng/ml)	17/16
Metachronous peritoneal lesion	
Disease-free interval[a] (≤ 1/> 1 year)	17/16
Disease-free interval, median (range)	1.0 year (0.4–4.1)
Interval until elevation of CEA level, median (range)	1.1 years (0.4–2.8)
TDT, median (range)	137 days (30–523)
CEA-DT, median (range)	102 days (20–529)
Preoperative therapy (CRT/chemotherapy/none)	3/10/20
Concurrent metastasis (present/absent)	5/28
Postoperative therapy (chemotherapy/none)	22/11
Curability (R0/R1)	26/7
PCI, average (range)	3.1 (2–10)

[a] Time interval from the date of surgery for the primary lesion to the date of recurrence

BMI, body mass index; *CEA-DT*, carcinoembryonic antigen-doubling time; *CRT*, chemoradiotherapy; *PCI*, peritoneal cancer index; *pStage*, pathological Stage; *TDT*, tumor doubling time

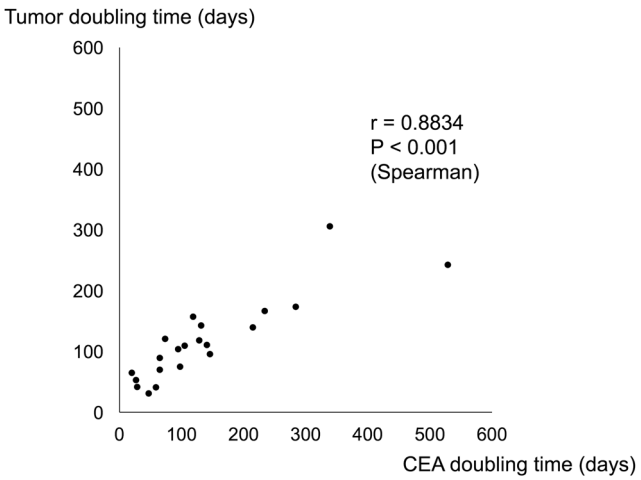

Fig. 2 Association between TDT and CEA-DT. CEA-DT, carcinoembryonic antigen-doubling time; TDT, tumor doubling time

Univariate and multivariate analyses

The univariate and multivariate analyses of the risk factors for OS and RFS after surgery for metachronous peritoneal metastases of CRC are shown in Table 4. In these analyses, patients were divided in two groups based on CEA-DT according to their prognosis from Kaplan-Meier survival curves: short CEA-DT and long CEA-DT/no elevation (Fig. 3c, d). In the univariate analysis, male sex, short TDT, and short CEA-DT were significant risk factors for poor RFS, and short TDT and short CEA-DT were significant risk factors for poor OS. In the multivariate analysis, short TDT was an independent risk factor for poor RFS (hazard ratio, 6.55; 95% confidence interval, 1.66–36.75; $P = 0.006$) and OS (hazard ratio, 9.51; 95% confidence interval, 1.67–84.01; $P = 0.010$). Similarly, short CEA-DT was also an independent risk factor for poor RFS

Table 2 Association between tumor doubling time and patient characteristics

	TDT > 137 days	TDT ≤ 137 days	*P* value
Total number	16	16	
Sex			
Male	9	15	0.037*
Female	7	1	
Age, median (range)	66(40–77)	62 (47–75)	0.180
Primary lesion			
Site			
Colon	5	7	0.716
Rectum	11	9	
Vascular invasion			
+	12	16	0.101
−	4	0	
Lymph invasion			
+	9	5	0.285
−	7	11	
Histologic differentiation			
Well	7	6	1.000
Moderate	9	10	
Tumor depth			
T2, T3	11	5	0.076
T4	5	11	
Lymph node metastasis			
+	7	11	0.285
−	9	5	
Distant metastasis			
+	2	2	1.000
−	14	14	
Metachronous peritoneal lesion			
Disease-free interval[a]			
≤ 1 year	5	12	0.032*
> 1 year	11	4	
CEA-DT			
≤ 102 days	0	10	< 0.001*
> 102 days	7	4	
No elevation	9	1	
Concurrent metastasis			
+	2	3	1.000
−	14	13	
PCI			
≤ 3	13	12	1.000
> 3	3	4	

* $P < 0.05$

[a] Time interval from the date of surgery for the primary lesion to the date of recurrence

CEA-DT, carcinoembryonic antigen-doubling time; *PCI*, peritoneal cancer index; *TDT*, tumor doubling time

(hazard ratio, 20.37; 95% confidence interval: 4.45–125.84; $P < 0.001$) and OS (hazard ratio, 5.80; 95% confidence interval, 1.48–28.46; $P = 0.012$).

Table 3 Association between CEA doubling time and patient characteristics

	No elevation	CEA-DT > 102 days	CEA-DT ≤ 102 days	*P* value
Total number	10	11	11	
Sex				
Male	7	7	10	0.357
Female	3	4	1	
Age, median (range)	66 (47–77)	64 (40–75)	62 (51–76)	0.923
Primary lesion				
Site				
Colon	1	5	7	0.050
Rectum	9	6	4	
Vascular invasion				
+	7	10	10	0.184
−	3	1	0	
Lymph invasion				
+	4	5	4	1.000
−	6	6	6	
Histologic differentiation				
Well	6	4	2	0.200
Moderate	4	7	8	
Tumor depth				
T2, T3	7	6	2	0.053
T4	3	5	9	
Lymph node metastasis				
+	5	7	5	0.747
−	5	4	6	
Distant metastasis				
+	2	1	1	0.664
−	8	10	10	
Metachronous peritoneal lesion				
Disease-free interval[a]				
≤ 1 year	4	4	9	0.079
> 1 year	6	7	2	
Concurrent metastasis				
+	2	1	2	0.850
−	8	10	9	
PCI				
≤ 3	9	9	7	0.439
> 3	1	2	4	

* $P < 0.05$

[a] Time interval from the date of surgery for the primary lesion to the date of recurrence

CEA-DT, carcinoembryonic antigen-doubling time; *PCI*, peritoneal cancer index; *TDT*, tumor doubling time

Discussion and conclusions

In the present study, the median TDT and CEA-DT for peritoneal metastases of CRC were 137 days (range, 30–523 days) and 102 days (range, 20–529 days), respectively. Previously, in patients with lung metastases [16, 30], mean TDT by

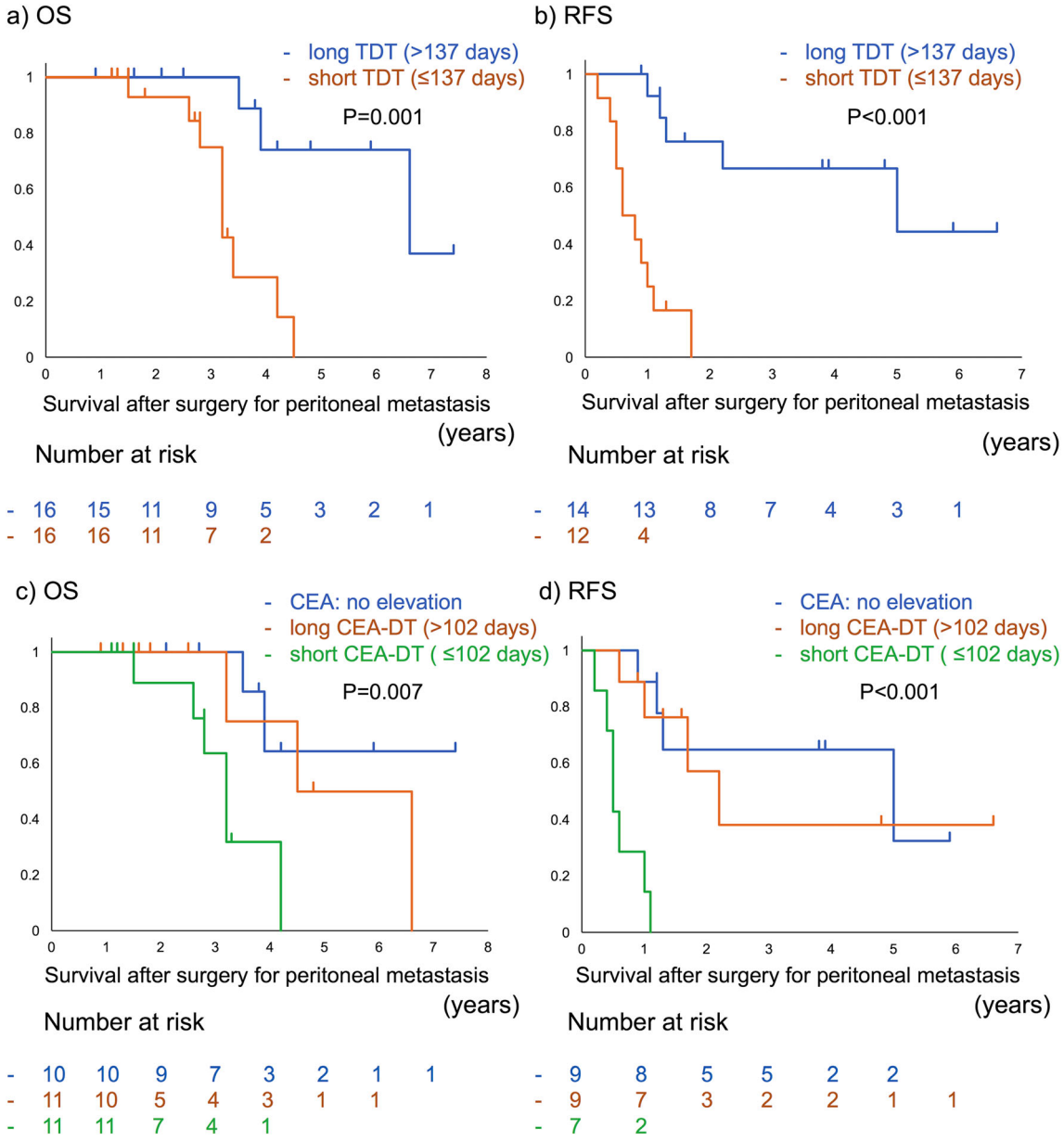

Fig. 3 Survival curves after surgery for metachronous peritoneal metastases of CRC are shown. **a** OS and **b** RFS curves stratified by TDT and **c** OS and **d** RFS curves stratified by CEA-DT. CEA-DT, carcinoembryonic antigen-doubling time; CRC, colorectal cancer; OS, overall survival; RFS, relapse-free survival; TDT, tumor doubling time

Roentgen was reported to be approximately 100 days (range, 109–116 days). In patients with liver metastases [19, 20, 31], mean DT was reported to be 60.1–111.1 days. DT was slightly longer in patients with peritoneal metastases. Peritoneal tumors have a poor blood supply [32], which may explain their longer DT compared to tumors in other organs. Peritoneal metastasis is a known risk factor for a poor prognosis. This may be due to the ineffectiveness of chemotherapy [33] or difficulty of diagnosis [34, 35], rather than the rapid growth of the tumor.

The risk of recurrence is an important consideration in determining the treatment for peritoneal carcinomatosis. Goéré et al. [14] reported that among patients with a peritoneal cancer index (PCI) of > 17, CRS and intraperitoneal chemotherapy did not improve the prognosis because of the high rate of recurrence after surgical resection. In patients with a high risk of recurrence, the efficacy of surgery may be limited. Long TDT, no elevation in CEA level, and long CEA-DT were associated with a better prognosis in the present study. Conversely, all patients with short TDT and short CEA-DT developed recurrence within 2 years, and none of the patients survived beyond 5 years after surgery for metachronous peritoneal metastases. Thus, for patients with long TDT, no elevation in CEA level and long CEA-DT, resection of localized

Table 4 Univariate and multivariate analyses of risk factors in survival after surgery for metachronous peritoneal metastases of CRC

Factors	OS HR (95% CI)	*P* value	RFS HR (95% CI)	*P* value
Univariate analyses				
Sex (male/female)	3.02 (0.57–55.40)	0.223	6.77 (1.34–123.16)	0.016*
Age (≤ 65/> 65 years)	1.27 (0.38–4.85)	0.703	1.42 (0.52–4.00)	0.489
BMI (≤ 25/> 25 kg/m^2)	1.21 (0.35–5.58)	0.772	1.57 (0.50–6.87)	0.466
Primary lesion				
Site (colon/rectum)	1.41 (0.37–4.68)	0.595	1.50 (0.50–4.19)	0.450
Vascular invasion (±)	1.60 (0.30–29.36)	0.636	3.92 (0.78–71.08)	0.108
Lymph invasion (±)	0.84 (0.22–2.70)	0.781	0.83 (0.28–2.25)	0.724
Histologic differentiation (moderate/well)	1.81 (0.53–6.46)	0.337	1.27 (0.46–3.79)	0.653
Tumor depth (T4/T2, T3)	1.15 (0.36–3.72)	0.811	2.18 (0.80–6.19)	0.126
Lymph metastasis (±)	3.21 (0.95–12.48)	0.061	2.66 (0.91–8.95)	0.075
Distant metastasis (±)	2.48 (0.36–10.84)	0.308	1.17 (0.18–4.38)	0.838
Metachronous peritoneal lesion				
Disease-free interval[a] (≤ 1/> 1 year)	2.69 (0.79–10.54)	0.114	1.90 (0.68–5.49)	0.218
TDT (≤ 137/> 137 days)	9.10 (2.23–61.23)	0.001*	10.45 (3.12–47.58)	< 0.001*
CEA-DT	7.09 (1.76–35.26)	0.006*	13.42 (3.59–64.03)	< 0.001*
(≤ 102/> 102 days, no elevation)				
Concurrent metastasis (±)	1.94 (0.50–6.33)	0.313	1.06 (0.24–3.34)	0.924
Preoperative therapy (±)	0.95 (0.25–3.03)	0.929	1.12 (0.38–3.03)	0.822
Postoperative therapy (±)	0.64 (0.19–2.45)	0.485	2.55 (0.80–11.23)	0.118
Curability (R1/R0)	2.03 (0.44–7.12)	0.330	–	–
PCI (> 3/≤ 3)	1.93 (0.50–6.43)	0.313	1.45 (0.33–4.60)	0.585
Multivariate analyses ver.1				
Sex (male/female)	–	–	2.65 (0.33–54.03)	0.372
Primary lesion				
Lymph metastasis (±)	0.94 (0.20–4.66)	0.935	1.45 (0.44–5.48)	0.550
Metachronous peritoneal lesion				
TDT (≤ 137/> 137 days)	9.51 (1.67–84.01)	0.010*	6.55 (1.66–36.75)	0.006*
Multivariate analyses ver.2				
Sex (male/female)	–	–	4.52 (0.72–88.86)	0.116
Primary lesion				
Lymph metastasis (±)	2.44 (0.65–10.01)	0.185	5.53 (1.55–24.55)	0.008*
Metachronous peritoneal lesion				
CEA-DT (≤ 102/> 102 days, no elevation)	5.80 (1.48–28.46)	0.012*	20.37 (4.45–125.84)	< 0.001*

* $P < 0.05$

[a] Time interval from the date of surgery for the primary lesion to the date of recurrence

BMI, body mass index; *CEA-DT*, carcinoembryonic antigen-doubling time; *CI*, confidence interval; *CRC*, colorectal cancer; *HR*, hazard ratio; *OS*, overall survival; *PCI*, peritoneal cancer index; *RFS*, relapse-free survival; *TDT*, tumor doubling time

peritoneal metastasis is recommended. However, for patients with short TDT and short CEA-DT, the efficacy of surgery may be limited and the decision to operate must be considered carefully. TDT and CEA-DT may be useful indicators for selecting candidates for surgical resection.

Regression lines were drawn when the tumor diameters or serum CEA levels were measured at three or more time points. Both R^2 values were exceedingly high. Therefore, two measurements may be sufficient to accurately determine TDT from these results. Although the R^2 value for CEA level was lower than that for the tumor volume, there was a strong significant association between TDT and CEA-DT. Moreover, long CEA-DT and no elevation in CEA level were associated with a better prognosis. CT is a standard tool for evaluating peritoneal carcinomatosis [36]. Technological advances in CT have improved its sensitivity up to 60.0–91.0% [34, 35, 37, 38]. However, for lesions < 10.0 mm in diameter, the sensitivity reduces to 9.1–28.0% [34, 35]. It can be difficult to assess the size of small tumors. However, CEA-DT can be evaluated easily within a short time interval in the majority of patients. Therefore, when the evaluation of TDT is difficult, CEA-DT is a useful prognostic determinant.

Takakura et al. [39] reported that a short DFI was a risk factor for survival after surgery for pulmonary metastasis from CRC and that the DFI may reflect oncological characteristics, such as TDT. Given the significant association between the DFI and TDT in this study, the DFI may also be a useful marker of tumor growth. However, in the present study, a short DFI was not a risk factor for a poor prognosis; furthermore, it is difficult to determine the DFI accurately because it depends on the timing of the follow-up CT. Therefore, we concluded that TDT and CEA-DT may be better prognostic factors.

This study has several limitations. First, the CT slice thickness was 5.0 mm. If the CT slice thickness was < 5.0 mm, tumor diameters might be measured more accurately. Second, the number of patients were small to determine the definitive cutoff points for DT, like 137 days or 102 days, about prognosis. Therefore, further studies with larger sample sizes are needed. Nonetheless, based on our results, we believe that TDT and CEA-DT are associated with prognosis.

In conclusion, short TDT and CEA-DT are independent risk factors for poor OS and RFS after surgery for metachronous peritoneal metastases of CRC. TDT and CEA-DT should be considered when selecting candidates for surgical resection.

Authors' contribution HM established the study concept and design, acquired the data, and drafted the manuscript. All co-authors contributed to this study, especially as described below in all criteria. KM established the study concept and design and revised the manuscript. HN, HN, KH, and SI revised the manuscript. KK maintained the databases and revised the manuscript. TT, TN, YS, and KS analyzed and interpreted the data.

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Compliance with ethical standards

The study protocol was approved by the Ethics Committee of The University of Tokyo (approval number: 3252-(7)).

Conflict of interest The authors declare that they have no conflict of interest.

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