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ORIGINAL SCIENTIFIC REPORT

Impact of Primary Tumor Resection on Mortality in Patients with Stage IV Colorectal Cancer with Unresectable Metastases: A Multicenter Retrospective Cohort Study

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Abstract

Background Primary tumor resection (PTR) before commencing systemic chemotherapy in patients with stage IV colorectal cancer and unresectable metastases (mCRC) remains controversial. This study aimed to assess whether PTR before systemic chemotherapy is associated with mortality in mCRC patients, after adjusting for confounding factors, such as the severity of the primary tumor and metastatic lesions.

Methods We analyzed hospital-based cancer registries from nine designated cancer hospitals in Fukushima Prefecture, Japan. Patients were divided into two groups (PTR and non-PTR), based on whether PTR was performed as initial therapy for mCRC or not. The primary outcome was all-cause mortality. Kaplan–Meier survival analysis was performed, and survival estimates were compared using the log-rank test. Adjusted hazard ratios were calculated using Cox regression to adjust for confounding factors. All tests were two-sided; P-values < 0.05 were considered statistically significant.

Results Between 2008 and 2015, 616 mCRC patients were included (PTR: 414 [67.2%]; non-PTR: 202 [32.8%]). The median follow-up time was 18.0 (interquartile range [IQR]: 8.4–29.7) months, and 492 patients (79.9%) died during the study period. Median overall survival in the PTR and non-PTR groups was 23.9 (IQR: 12.2–39.9) and 12.3 (IQR: 6.2–23.8) months, respectively ($P < 0.001$, log-rank test). PTR was significantly associated with improved overall survival (adjusted hazard ratio: 0.51; 95% confidence interval: 0.42–0.64, $P < 0.001$).

Conclusions PTR before systemic chemotherapy in patients with mCRC was associated with improved survival.

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Introduction

Among colorectal cancer (CRC) cases, the proportion of patients with stage IV CRC has been estimated to be around 15–25% [1–3]. Although complete resection of the primary tumor and metastatic lesions is a radical treatment for these patients, almost all patients have unresectable distant metastases and therefore receive systemic chemotherapy[4]. Despite progress in systemic chemotherapy, which now includes targeted molecular agents, improvements in survival rates have been unsatisfactory[5].

Primary tumor resection (PTR) before systemic chemotherapy in patients with stage IV CRC with unresectable metastases (mCRC) is controversial. PTR improves the quality of life (QOL) and reduces the side effects of systemic chemotherapy as well as the risk of complications, such as bleeding, obstruction, and perforation that may occur due to the primary tumor[6, 7]. However, PTR prolongs the introduction of systemic chemotherapy with further delays if complications arise[8, 9].

Several randomized controlled trials (RCTs) have been conducted to investigate the effects of PTR in mCRC patients. However, one study required a reduction in the sample size as managing accumulating cases became difficult, and to date, all RCTs remain incomplete [10–15]. Moreover, the overall condition of these participants is better, with limited progression of the primary lesion and severity of distant metastases. These cases are, therefore, different from the cases in clinical practice where it is difficult to decide whether PTR should be performed. Although some observational studies have been conducted, these studies could not adjust for some important confounding factors, such as symptoms from the primary tumor, depth of tumor invasion, severity of regional lymph node metastases, and pattern and severity of distant metastases[16, 17].

This study aimed to assess whether PTR before systemic chemotherapy is associated with mortality in patients with mCRC, when adjusted for confounding factors, including severity of the primary tumor and metastatic lesions.

Materials and methods

Study design and cohort development

This was a multicenter, retrospective cohort study. All nine designated cancer hospitals across Fukushima Prefecture, Japan, participated. First, we extracted data of patients with stage IV CRC, defined based on the International Classification of Diseases for Oncology, Third Edition (ICD-O3) topographical codes: C18.0, C18.2–C18.9, C19.9, C20.9, from each hospital-based cancer registry. We extracted data on age, sex, primary tumor site, and degree of differentiation. Second, we extracted data from medical records and administrative data on patients' clinical and demographic characteristics, including the Charlson comorbidity index (CCI), clinical symptoms, clinical staging (cTNM stage) (based on the TNM classification system (version 7) of the American Joint Committee on Cancer), Barthel index (a measure of activities of daily living (ADLs)), and type of treatment. Two gastrointestinal surgeons (MH and HK), who were blinded to the survival outcome, reviewed the medical records and computed tomography (CT) images before initial treatment in this cohort and made the diagnosis based on cTNM staging, metastatic pattern, and clinical symptoms of the primary tumor. Anonymized datasets acquired from individual hospitals were merged into a single dataset.

Patients were included if they fulfilled the following criteria: consecutive adult patients ($\geq$ 18 years old) seen between 2008 and 2015, with histologically confirmed colorectal adenocarcinomas or intraoperatively diagnosed with stage IV CRC.

The exclusion criteria were as follows: metastasectomy for metastatic disease, best supportive care in main treatment for mCRC, perforation due to the primary tumor, emergency surgery, and absence of data on treatment strategy.

Definition of PTR and non-PTR

Patients who underwent PTR as initial treatment were classified into the PTR group, and the rest of the patients comprised the non-PTR group. Patients who underwent palliative surgery, such as colostomy and bypass, as initial treatment were also classified into the non-PTR group.

Outcomes

The primary endpoint was overall survival (OS), which was calculated as the number of days from the date of CRC diagnosis until death. Patients were censored if they were lost to follow-up or were still alive on December 31, 2017.

Covariates and categorization

Several demographic and clinical variables were included in the analysis, such as sex, age at diagnosis ($<$ 75, $\geq$ 75 years), period of diagnosis (2008–2009, 2010–2012, 2013–2015), primary tumor site (right colon cancer, RCC: tumors located in the cecum, ascending colon, hepatic flexure, or transverse colon; left colon

cancer, LCC: tumors located within the splenic flexure, descending colon, sigmoid colon or recto-sigmoid junction; rectal cancer: tumor located between rectum and anus), and degree of tumor differentiation (well or moderately differentiated, poorly or undifferentiated). The CCI was used to assess patients' comorbidities at first admission for CRC-related hospitalization and was classified into three categories based on the CCI scores (0, 1–2, $\geq$ 3)[18]. The Barthel index was used to measure patients' ADLs on admission and discharge after the first hospitalization. This index uses a scale of 0–100 and is classified into two categories (0–60, 61–100) for analysis [19]. Patients with obstruction or melena due to the primary tumor were defined as having clinical symptoms. Melena was defined as anemia requiring transfusion or bleeding that required medical intervention. Obstruction was defined as the inability of a colonoscope to pass through the primary lesion and/or the presence of obstructive symptoms (fullness, nausea, or vomiting).

Based on the 7th edition of the TNM classification [20], we classified patients into two categories (T1–3, and T4a or T4b) in terms of the T factor, and two categories (N0–1, N2) for the N factor. Based on the Japanese Classification of Colorectal Carcinoma [21], we distinguished the following types of metastases: liver metastases (hepatic tumors [HT], H1: $\leq$ 5 HT and HT size $\leq$ 5 cm; H2: $\geq$ 5 HT or HT size $\geq$ 5 cm; H3: $\geq$ 5 HT and HT size $\geq$ 5 cm) and pulmonary metastases (lung tumors [LT], PUL1: $<$ 3 LT in one lung or two LTs in both lungs; PUL2: $\geq$ 3 LTs in both lungs; carcinomatous pleurisy; or mediastinal lymph node metastases). Additionally, we described the remaining metastatic patterns as follows: peritoneal dissemination (presence or absence), distal lymph node metastases (presence or absence), other organ metastases: bone, brain, ovary, and others (presence or absence), and number of metastatic organs (1 or $\geq$ 2).

Regarding treatment, in addition to the presence or absence of PTR, we described the number of days from the date of diagnosis to the introduction of systemic chemotherapy and classified the systemic chemotherapy regimen as follows: 5-fluorouracil (5-FU) (none, oral, or infusion), oxaliplatin (OX) or irinotecan (IRI) (none, OX, or IRI), and molecular target drug (none, anti-vascular endothelial growth factor [VEGF] drug, or anti-epidermal growth factor receptor [EGFR] drug).

Statistical analyses

Patient characteristics are reported as descriptive statistics, with continuous variables expressed as medians and interquartile ranges (IQR) and categorical variables expressed as counts and percentages. Univariate analyses were employed to compare the variables between the two groups, in which categorical variables were compared with the Fisher's exact test, and continuous variables were compared with the Mann–Whitney U test. We described missing values and applied complete case analysis in the main analysis. For sensitivity analysis, we applied multiple imputations using the chained equation method for participants with one or more missing covariates. Twenty multiple imputed datasets were created, and the estimates from each dataset were combined using Rubin's rule [22].

Survival analysis was performed using the Kaplan–Meier method, and survival estimates were compared using the log-rank test. The association between PTR and overall survival (OS) was analyzed using Cox proportional hazards regression models for all-cause mortality, adjusted for confounding and prognostic factors (age at diagnosis, sex, CCI, period of diagnosis, ADLs, clinical symptoms due to primary tumor, degree of tumor differentiation, T-stage, N-stage, liver metastases, lung metastases, peritoneal dissemination, distal lymph node metastases, other organ metastases, and number of metastatic organs). We carried out the following subgroup analyses: clinical symptoms due to the primary tumor (absence or presence) and the location of the primary tumor (colon cancer or rectal cancer). Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. All significance tests were 2-sided, and P values < 0.05 were considered statistically significant. Statistical analyses were performed using STATA version 16.0 software (STATA Corporation, College Station, TX, USA).

Results

We identified 1,262 patients diagnosed with stage IV CRC, between 2008 and 2015, and excluded 478 patients based on the exclusion criteria. Moreover, 168 patients were excluded because of missing covariates: 109 without Barthel index data, 43 without data on the degree of differentiation, and 16 lacked data concerning the primary tumor site. As a result, 616 patients were included in the main analysis (Fig. 1). The PTR group had 414 patients (67.2%), and the non-PTR group had 202 (32.8%) patients. The median follow-up time was 18.0 months (IQR, 8.4–29.7), and 492 patients (79.9%) died during the study period. In the PTR group, 61 patients (14.7%) did not receive systematic chemotherapy following PTR. Twenty-seven patients (13.4%) in the non-PTR group did not receive systematic chemotherapy following palliative surgery.

Patient demographics and clinical characteristics are summarized in Table 1. The median age was 69 (IQR: 60–76) years. A total of 394 patients (64.0%) exhibited clinical symptoms from the primary tumor. A higher percentage of patients exhibited clinical symptoms in the PTR

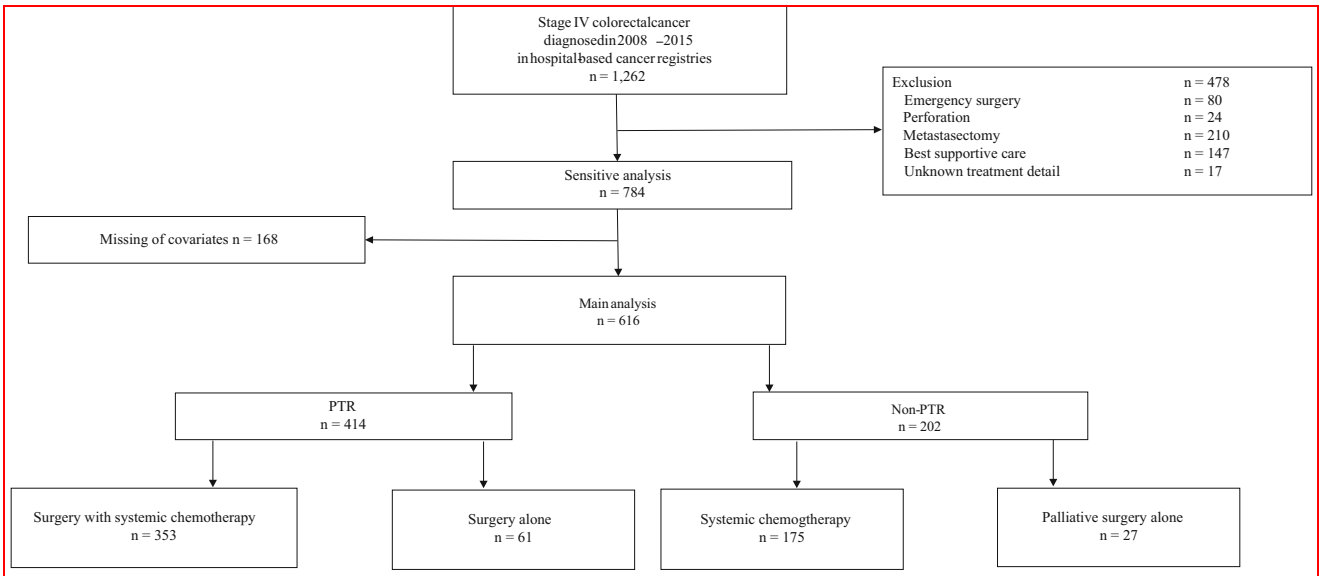

Fig. 1 Overview of patient selection. Abbreviation: PTR = primary tumor resection

group (PTR: 69.8%; non-PTR group: 52.0%). Only one metastatic organ was more frequently reported in the PTR group (264 [63.8%]) than in the non-PTR group (103 (51.0%)). The incidences of various parameters in the non-PTR and PTR groups were as follows: rectal cancer (non-PTR: 74 [36.6%], PTR: 73 [17.6%]); T4 stage (non-PTR: 139 [68.8%], PTR: 265 [64.0%]); H3 or severe liver metastases (non-PTR: 73 [36.1%], PTR: 83 [20.0%]); PUL2 or severe lung metastases (non-PTR: 57 [28.2%], PTR: 77 [18.6%]); distal lymph node metastases (non-PTR: 76 [37.6%], PTR: 93 [22.5%]); other organ metastases (non-PTR: 17 [8.4%], PTR: 15 [3.6%]); and peritoneal dissemination (non-PTR: 21.8%, PTR: 28.3%).

Table 2 shows the distribution of systemic chemotherapy regimens in the two groups and surgical treatment in the non-PTR group. The median number of days from diagnosis to introduction of systemic chemotherapy was 49 and 28 days in the PTR and non-PTR groups, respectively. Among the non-PTR group, 97 patients (48.0%) underwent palliative surgery before commencing systemic chemotherapy, and 23 patients (11.4%) underwent primary tumor resection during systemic chemotherapy.

OS analysis was performed using the Kaplan–Meier method (Fig. 2). The median OS was 23.9 (IQR: 12.2–39.9) months and 12.3 (IQR: 6.2–23.8) months for the PTR and non-PTR groups, respectively ($P < 0.001$, log-rank test).

The effect of PTR on survival benefit was estimated using Cox proportional hazards regression models for all-cause mortality with complete case analysis (Table 3). The adjusted HR of the PTR group was 0.51 (95% CI: 0.42–0.64, $P < 0.001$), compared with the non-PTR group. Sensitivity analysis with multiple imputation methods revealed similar results for the PTR (HR = 0.49; 95% CI: 0.41–0.59, $P < 0.001$) (Supplemental material).

Figure 3 shows adjusted HRs for OS from the subgroup analysis performed on clinical symptoms due to primary tumor and the location of primary tumor. In each aspect, the PTR group was associated with better prognosis when compared with the non-PTR group.

Discussion

This retrospective cohort study evaluated the effectiveness of PTR before systemic chemotherapy in mCRC patients, and adjusted for confounding factors, including severity of the primary tumor and metastatic lesions. PTR before systemic chemotherapy for mCRC was associated with improved prognosis. A previous report from Japan revealed an association between PTR and prognosis in mCRC patients (HR: 0.46; 95% CI: 0.32–0.66), which demonstrated similar results to those found in our study [16]. It is noteworthy that molecular targeted drugs contribute to improved prognosis in mCRC patients [23], and the former study included patients diagnosed between 1997 and 2007, before molecular targeted drugs had been introduced in Japan. Meanwhile, our study included patients who could already receive molecular targeted drugs as standard treatment. Similar results obtained in our study suggest that PTR contributes to improved prognosis in mCRC patients regardless of the systemic chemotherapy regimen employed. The reason for the favorable prognosis associated with PTR may be the prevention of potential

Table 1 Patients' characteristics

	Total (n = 616)		PTR (n = 414)		Non-PTR (n = 202)		P value
Age in year, median (IQR)	69	(60–77)	69	(60–77)	67	(60–74)	0.14
Sex, n (%)							0.66
Male	383	(62.2%)	260	(62.8%)	123	(60.9%)	
Female	233	(37.8%)	154	(37.2%)	79	(39.1%)	
CCI, n (%)							0.15
0	325	(52.8%)	207	(50.0%)	118	(58.4%)	
1, 2	240	(39.0%)	170	(41.1%)	70	(34.7%)	
≥ 3	51	(8.3%)	37	(8.9%)	14	(6.9%)	
Birthel index, n (%)							0.10
100–61	547	(88.8%)	374	(90.3%)	173	(85.6%)	
60–0	69	(11.2%)	40	(9.7%)	29	(14.4%)	
Symptoms form primary tumor, n (%)							< 0.001
Absence	222	(36.0%)	125	(30.2%)	97	(48.0%)	
Presence	394	(64.0%)	289	(69.8%)	105	(52.0%)	
Period of diagnosis, n (%)							0.063
2008–2009	145	(23.5%)	109	(26.3%)	36	(17.8%)	
2010–2012	230	(37.3%)	149	(36.0%)	81	(40.1%)	
2013–2015	241	(39.1%)	156	(37.7%)	85	(42.1%)	
Location of primary tumor, n (%)							< 0.001
RCC	236	(38.3%)	166	(40.1%)	70	(34.7%)	
LCC	233	(37.8%)	175	(42.3%)	58	(28.7%)	
Rectal cancer	147	(23.9%)	73	(17.6%)	74	(36.6%)	
Differentiation, n (%)							0.78
Well/ moderate	551	(89.5%)	369	(89.1%)	182	(90.1%)	
Poor/ undifferentiated	65	(10.6%)	45	(10.9%)	20	(9.9%)	
T-stage, n (%)							0.28
T1-3	212	(34.4%)	149	(36.0%)	63	(31.2%)	
T4a, b	404	(65.6%)	265	(64.0%)	139	(68.8%)	
N-stage, n (%)							0.086
N0, 1	294	(47.7%)	208	(50.2%)	86	(42.6%)	
N2	322	(52.3%)	206	(49.8%)	116	(57.4%)	
Liver metastases, n (%)							< 0.001
H0	189	(30.7%)	133	(32.1%)	56	(27.7%)	
H1	119	(19.3%)	95	(22.9%)	24	(11.9%)	
H2	152	(24.7%)	103	(24.9%)	49	(24.3%)	
H3	156	(25.3%)	83	(20.0%)	73	(36.1%)	
Lung metastases, n (%)							0.024
PUL0	433	(70.3%)	301	(72.7%)	132	(65.3%)	
PUL1	49	(8.0%)	36	(8.7%)	13	(6.4%)	
PUL2	134	(21.8%)	77	(18.6%)	57	(28.2%)	
Peritoneal dissemination, n (%)							0.097
Absence	455	(73.9%)	297	(71.7%)	158	(78.2%)	
Presence	161	(26.1%)	117	(28.3%)	44	(21.8%)	
Distal lymph node metastases, n (%)							< 0.001
Absence	447	(72.6%)	321	(77.5%)	126	(62.4%)	
Presence	169	(27.4%)	93	(22.5%)	76	(37.6%)	
Other organ metastases, n (%)							0.019
Absence	584	(94.8%)	399	(96.4%)	185	(91.6%)	

Table 1 continued

	Total (n = 616)		PTR (n = 414)		Non-PTR (n = 202)		P value
Presence	32	(5.2%)	15	(3.6%)	17	(8.4%)	
Number of metastatic organ, n (%)							0.003
1	367	(59.6%)	264	(63.8%)	103	(51.0%)	
> = 2	249	(40.4%)	150	(36.2%)	99	(49.0%)	

Abbreviations: *PTR* primary tumor resection, *IQR* interquartile ranges, *CCI* Charlson comorbidity index, *RCC* right colon cancer, *LCC* left colon cancer

Table 2 Detail of treatment among patients

	Total (n = 616)		PTR (n = 414)		Non-PTR (n = 202)		P value
Days from diagnosis to treatment, median (IQR)	42	(30–62)	49	(36–70)	28	(13–42)	< 0.001
5-FU, n (%)							
None	91	(14.8%)	63	(15.2%)	28	(13.9%)	0.001
Infusion	319	(51.8%)	195	(47.1%)	124	(61.4%)	
Oral	206	(33.4%)	156	(37.7%)	50	(24.8%)	
OX or IRI, n (%)							
None	157	(25.5%)	111	(26.8%)	46	(22.8%)	0.23
OX	435	(70.6%)	284	(68.6%)	151	(74.8%)	
IRI	24	(3.9%)	19	(4.6%)	5	(2.5%)	
Molecular target drug, n (%)							
None	341	(55.4%)	239	(57.7%)	102	(50.5%)	0.15
Anti-VEGF drug	228	(37.0%)	148	(35.7%)	80	(49.6%)	
Anti-EGFR drug	47	(7.6%)	27	(6.5%)	20	(9.9%)	
Palliative surgery, n (%)							
Absence					105	(52.0%)	
Presence					97	(48.0%)	
PTR during systemic chemotherapy, n (%)							
Absence					179	(88.6%)	
Presence					23	(11.4%)	

Abbreviations: *PTR* primary tumor resection, *IQR* interquartile ranges, *5-FU* 5-fluorouracil, *OX* oxaliplatin, *IRI* irinotecan, *VEGF* vascular endothelial growth factor, *EGFR* epidermal growth factor receptor

complications associated with the primary tumor during systemic chemotherapy.

Our study classified the severity of liver and lung metastases before treatment using CT scans, based on the Japanese Classification of Colorectal Carcinoma [21]. Additionally, our study investigated T and N factors with CT scans before treatment, which was lacking in a previous report [24]. In the non-PTR group, a higher percentage of patients had rectal cancer and T4b, for which it is difficult to perform PTR. Additionally, a higher percentage of non-PTR patients had H3, PUL2, distal lymph node metastases, and other organ metastases, which are poorer prognostic factors, as compared to PTR patients. These factors were biased between the groups, contributing to the need for decision-making for treatment and to the overall prognosis. Therefore, they could be important confounding factors.

Postoperative complications or delays in introducing systemic chemotherapy due to PTR could also be important

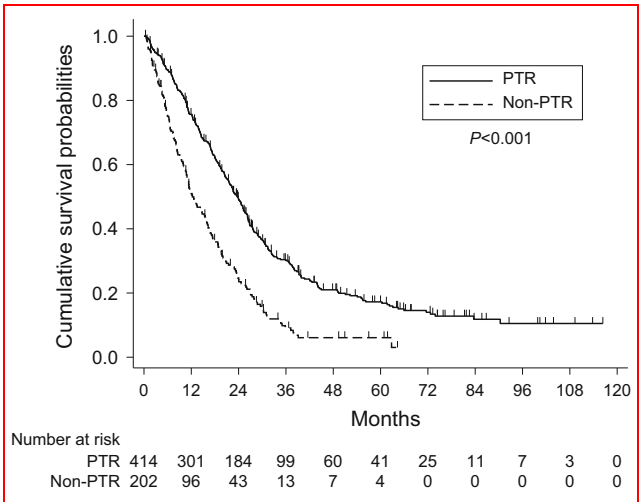

Fig. 2 Overall survival according to PTR and non-PTR groups. Abbreviation: PTR = primary tumor resection

factors that significantly impact prognosis. In our study, the time taken from making a diagnosis to introduction of systemic chemotherapy was 21 days longer in the PTR group than that in the non-PTR group. Additionally, 14.7% of the PTR group did not receive systemic chemotherapy. These results could be influenced by postoperative complications, which were lacking in our study. The incidence of postoperative complications in CRC is reported as 8–10% [25]. In particular, stage IV CRC had a higher incidence of postoperative complications than other stages of CRC, owing to the overall poor condition of patients [26]. In our study, a certain proportion of postoperative complications occurred in the PTR group. Despite this, our study showed an association between PTR and improved prognosis. In the future, it will be important to identify patients at high risk of postoperative complications and select low-risk surgical procedures for such patients.

To our knowledge, this is the first retrospective cohort study to assess whether PTR before systemic chemotherapy is associated with mortality in mCRC patients, after adjusting for confounding factors, such as severity of the primary tumor and metastatic lesion (based on the 7th edition of TNM classification and Japanese Classification of Colorectal Carcinoma). Although some RCTs are currently in progress, these have not been completed because of difficulties in gathering cases. Since patients with mCRC are often treated across various clinical departments, i.e., surgery, oncology, palliative care, etc., it is difficult to extract data of patients with stage IV CRC. Hospital-based cancer registries, which include almost all patients treated in the hospital and the registries of all designated cancer hospitals are in the same format, are useful to extract the data of patients with stage IV CRC and to conduct real-world and multicenter cohort studies. Additionally, the combination of hospital-based cancer registries and clinical records helped to overcome the limitations of depending on hospital-based cancer registries alone, which could lack certain information, such as severity of the primary tumor and metastatic lesions. Therefore, the results of our study could help clinicians to decide whether PTR before systemic chemotherapy is associated with mortality in mCRC patients.

There are several limitations to our study. First, unmeasured confounding factors could exist as a result of the doctor's preferences and are difficult to measure. Second, although patients were enrolled from 2008 to 2015, treatment strategies, including intensive chemotherapeutic regimens and molecular analysis (RAS, BRAF, and MSI), have changed significantly. Thus, our study may not be fully reflective of the current medical practice. Third, there were missing data of covariates in 21.4% of cases. We described the missing values and applied multiple imputation methods to compensate for them in the sensitivity analysis. The findings in the main analysis and the sensitivity analysis were similar. Fourth, measurement bias could exist in the evaluation of peritoneal dissemination, since a higher percentage of patients in the PTR group had peritoneal dissemination, although the difference was not statistically significant. In mCRC, peritoneal dissemination is the poorest prognostic factor in the metastatic pattern [27]. A small amount of peritoneal dissemination that could not be identified in the images was identified during intraoperative findings in all patients in the PTR group.

Conclusions

PTR before systemic chemotherapy for unresectable mCRC was associated with improved survival. Pragmatic clinical trials involving mCRC patients, for whom surgeons would find it difficult to determine whether to perform PTR in clinical practice, are required.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00268-021-06233-x.

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Declerations

Ethical statement The study was conducted in accordance with the Declaration of Helsinki and relevant local laws and regulations**.** The

Table 3 Hazard ratios of all-cause mortality using Cox proportional hazards regression models with complete case analysis

	Unadjusted			Adjusted		
	HR	95% CI	*p* value	HR	95% CI	*p* value
PTR or non-PTR						
Non-PTR	(reference)			(reference)		
PTR	0.51	(0.42–0.61)	< 0.001	0.51	(0.42–0.64)	< 0.001
Age						
< 75	(reference)			(reference)		
≥ 75	1.28	(1.05–1.55)	0.013	1.53	(1.25–1.88)	< 0.001
Sex						
Male	(reference)			(reference)		
Female	1.08	(0.90–1.29)	0.43	1.11	(0.91–1.34)	0.31
CCI						
0	(reference)			(reference)		
1, 2	0.98	(0.81–1.18)	0.85	1.05	(0.86–1.27)	0.66
≥ 3	1.16	(0.83–1.62)	0.38	1.04	(0.72–1.49)	0.84
Symptoms from primary tumor						
Absence	(reference)			(reference)		
Presence	1.16	(0.97–1.40)	0.110	1.16	(0.94–1.42)	0.16
Barthel index						
100–61	(reference)			(reference)		
60–0	1.78	(1.35–2.35)	< 0.001	1.69	(1.26–2.26)	< 0.001
Period of diagnosis						
2008–2009	(reference)			(reference)		
2010–2012	0.97	(0.77–1.21)	0.78	0.87	(0.69–1.10)	0.24
2013–2015	0.94	(0.75–1.19)	0.61	0.77	(0.60–0.98)	0.033
Primary site						
RCC	(reference)			(reference)		
LCC	0.92	(0.75–1.12)	0.41	0.87	(0.70–1.09)	0.22
Rectal cancer	0.91	(0.72–1.14)	0.41	0.78	(0.59–1.02)	0.068
Differentiation						
Well/ moderate	(reference)			(reference)		
Poor/ undifferentiated	1.23	(0.93–1.64)	0.150	1.24	(0.91–1.70)	0.17
T-stage						
T1-3	(reference)			(reference)		
T4a, b	1.41	(1.17–1.70)	< 0.001	1.24	(1.00–1.53)	0.048
N-stage						
N0, 1	(reference)			(reference)		
N2	1.40	(1.17–1.67)	< 0.001	1.27	(1.04–1.56)	0.021
Liver metastasis						
H0	(reference)			(reference)		
H1	1.02	(0.78–1.33)	0.89	1.12	(0.82–1.55)	0.47
H2	1.79	(1.40–2.29)	< 0.001	2.14	(1.54–2.97)	< 0.001
H3	2.27	(1.78–2.89)	< 0.001	2.34	(1.70–3.22)	< 0.001
Lung metastasis						
PUL0	(reference)			(reference)		
PUL1	0.96	(0.68–1.35)	0.82	1.00	(0.67–1.50)	0.99
PUL2	1.24	(1.00–1.54)	0.045	1.33	(1.01–1.76)	0.04
Peritoneal dissemination						
Absence	(reference)			(reference)		

Table 3 continued

	Unadjusted			Adjusted		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Presence	1.17	(0.95–1.42)	0.14	1.39	(1.06–1.83)	0.016
Distal lymph node metastasis						
Absence	(reference)			(reference)		
Presence	1.15	(0.95–1.40)	0.16	1.12	(0.88–1.43)	0.37
Other organ metastasis						
Absence	(reference)			(reference)		
Presence	1.83	(1.22–2.74)	0.003	1.85	(1.19–2.88)	0.007
Number of metastatic organ						
1	(reference)			(reference)		
≥ 2	1.74	(1.46–2.09)	< 0.001	1.06	(0.77–1.46)	0.72

Abbreviations: *RCC* right colon cancer, *LCC* left colon cancer, *IQR* interquartile range, *CCI* Charlson comorbidity index, *CI* confidence interval, *HR* hazard ratio

H1: ≤ 5 hepatic tumours (HT) and HT size ≤ 5 cm; H2: ≥ 5 HT or HT size ≥ 5 cm; H3: ≥ 5 HT and HT size ≥ 5

PUL1: < 3 lung tumours (LT) in one lung, or two LTs in both lungs; PUL2: ≥ 3 LTs in both lungs, carcinomatous pleurisy, or mediastinum lymph node metastasis

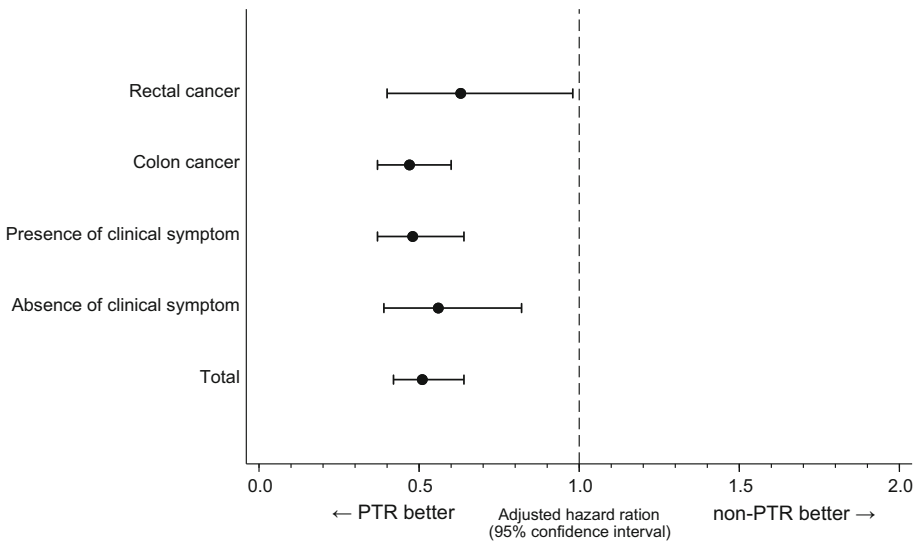

Fig. 3 Adjusted hazard ratios for overall survival from the subgroup analysis. Abbreviation: PTR = primary tumor resection

study protocol was approved by the institutional review board of all participating hospitals (UMIN000033718).

Informed consent The institutional review board waived the requirement for informed consent in accordance with the Japanese government's Ethical Guidelines for Medical and Health Research Involving Human Subjects, which allow for the opt-out approach.

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