Primary tumor resection improves prognosis of unresectable carcinomas of the transverse colon including flexures with pulmonary metastasis: a cohort study

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Purpose **Studies of unresectable colorectal cancer pulmonary metastasis (CRPM) have rarely analyzed patient prognosis from the perspective of colonic subsites. This study aimed to evaluate the effects of primary tumor resection (PTR) on the prognosis of patients with unresectable pulmonary metastases of transverse colon cancer pulmonary metastasis (UTCPM), hepatic flexure cancer pulmonary metastasis (UHFPM), and splenic flexure cancer pulmonary metastasis (USFPM).**

Methods **Patients were identified from the Surveillance, Epidemiology, and End Results database between 2000 and 2018. The Cox proportional hazards regression models were used to identify prognostic factors of overall survival (OS) and cause-specific survival (CSS). The Kaplan–Meier analyses and log-rank tests were conducted to assess the effectiveness of PTR on survival.**

Results **This study included 1294 patients: 419 with UHFPM, 636 with UTCPM, and 239 with USFPM. Survival analysis for OS and CSS in the PTR groups, showed that there were no statistical differences in the the UHFPM, UTCPM, and USFPM patients. There were statistical differences in the UHFPM, UTCPM, and USFPM patients for OS and CSS. Three non-PTR subgroups showed significant statistical differences for OS and CSS.**

Conclusion **We confirmed the different survival rates of patients with UTCPM, UHFPM, and USFPM and proved for the first time that PTR could provide survival benefits for patients with unresectable CRPM from the perspective of the colonic subsites of the transverse colon, hepatic flexure, and splenic flexure.** ***European Journal of Cancer Prevention*** **33: 95–104 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.**

European Journal of Cancer Prevention 2024, **33**:95–104

Keywords: cohort study, colorectal cancer pulmonary metastasis, Cox models, hepatic flexure, primary tumor resection, SEER, splenic flexure, transverse colon

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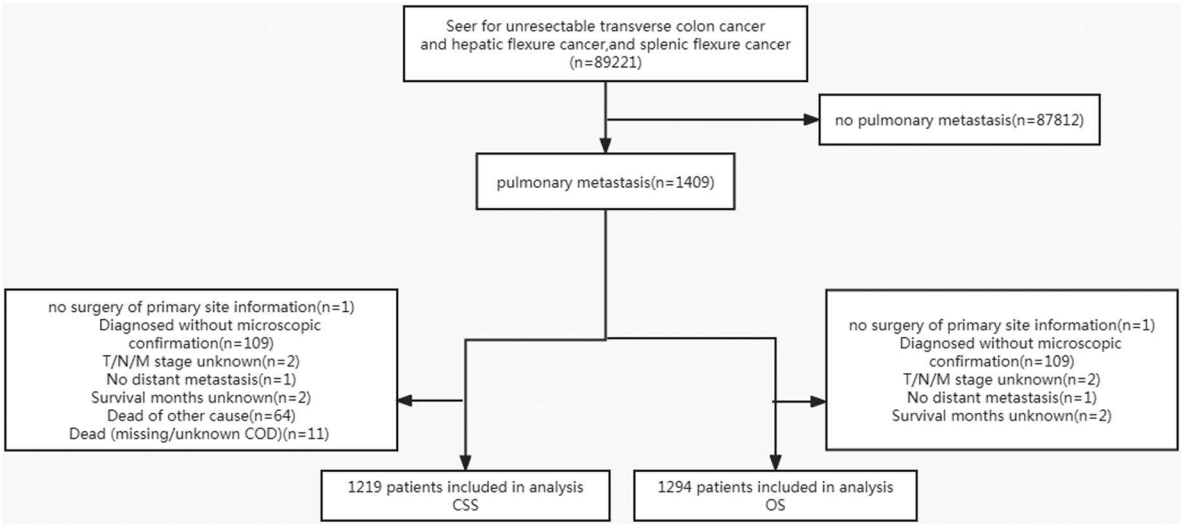
Received 7 June 2023 **Accepted** 15 August 2023.

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer death worldwide (Bray *et al*., 2018; Dekker *et al*., 2019; Keum and Giovannucci, 2019; Siegel *et al*., 2020a, 2020b; Sponholz *et al*., 2021). In patients with CRC, the lungs are the second most frequently affected sites of metastasis, after the liver (Hwang *et al*., 2010; Labianca *et al*., 2010; Mitry *et al*., 2010; Zeng *et al*., 2017; Feng *et al*., 2019). The incidence of CRC continues to increase each year. Approximately 30–40% of CRC patients are diagnosed with metastatic CRC, and another 30% will develop metastatic CRC later in life (Mitry *et al*., 2010; Nordholm-Carstensen *et al*., 2014; Ge *et al*., 2019; Ottaiano *et al*., 2020). In recent years, the widespread use of chest computed tomography scans has resulted in a continuous increase in the number of CRC patients who are diagnosed with pulmonary metastases. The lung is an ideal metastatic target for hematogenously disseminated cancer cells, given that lung parenchyma cells are very close to the pulmonary intravascular space, and it is a nutrient-rich environment, where the blood supply and the partial pressure of oxygen are guaranteed (Krishnan *et al*., 2006). However, compared with other distal metastases, lung metastases have relatively slower growth and better overall survival (OS) (Khattak *et al*., 2012; Prasanna *et al*., 2018).

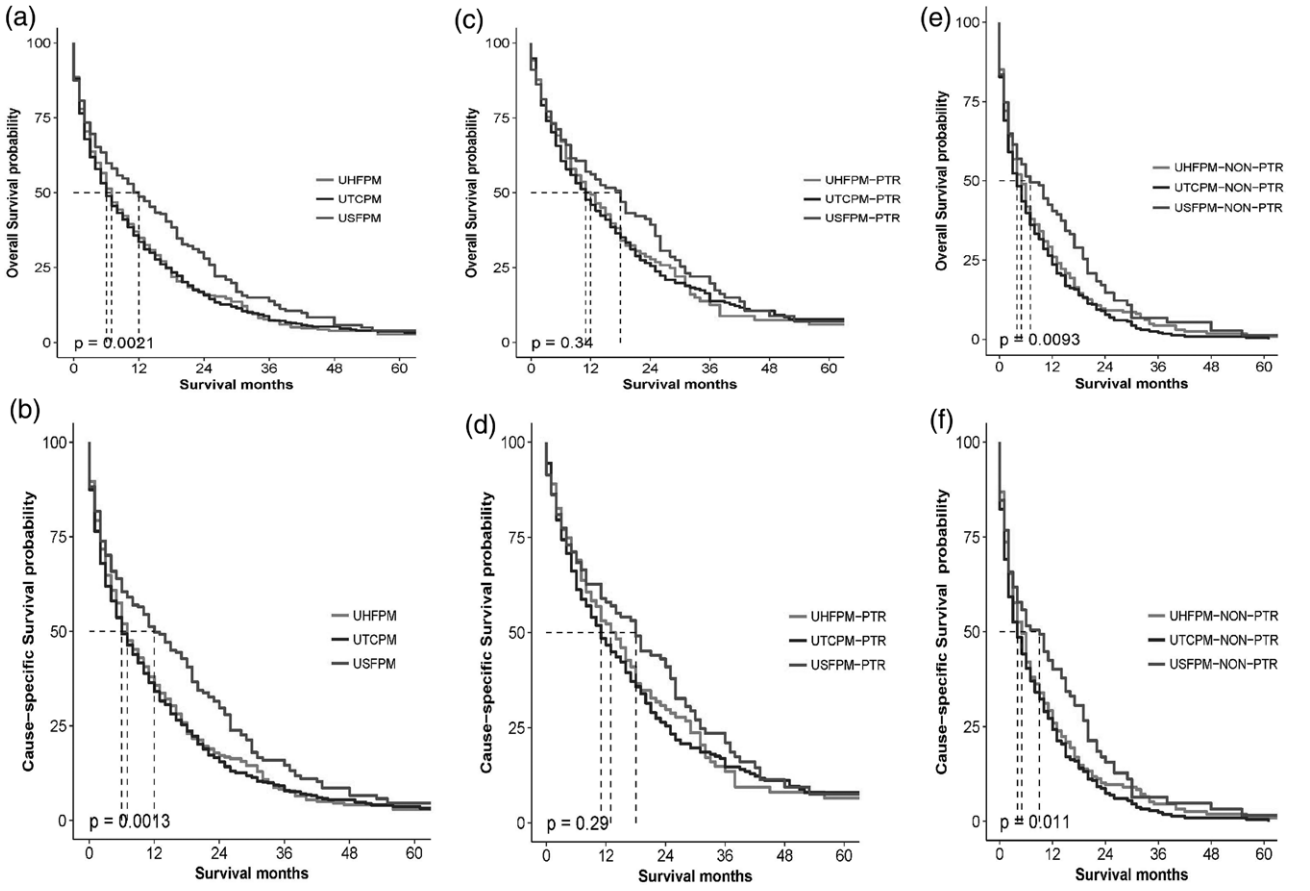
The ideal surgical treatment for patients with CRC pulmonary metastasis (CRPM) seems to be complete surgical resection of pulmonary metastases at the time of primary tumor resection (PTR) (Tampellini *et al*., 2012; Vatandoust *et al*., 2015; Tarantino *et al*., 2017; Zhang *et al*., 2017; van Rooijen *et al*., 2018; Wang *et al*., 2018; Benson *et al*., 2021). However, in most patients who initially

Fig. 1



The flowchart of the study.

Fig. 2



Kaplan–Meier survival analysis for OS and CSS of total cohort (a and b), PTR cohort (c and d) and non-PTR cohort (e and f). CSS, cause-specific survival; OS, overall survival; PTR, primary tumor resection.

have lung metastases, there is widespread distribution and large number of lung metastases. Furthermore, in a minority of patients, there is the location or size of the metastatic lesions, or that the metastatic lesions are close to the hilus of the lung or important blood vessels or organs. That is the reason for unresectable pulmonary metastases. However, at the time of diagnosis, CRC patients are unable to undergo surgical resection because of pulmonary metastasis. For these patients, growing evidence has shown that PTR could prolong the survival of patients with unresectable CRPcM.

In addition to the many known risk factors affecting the long-term survival of patients with metastatic colon cancer, recent studies have shown that primary tumor location is also an important prognostic factor (Price *et al.*, 2015; Sasaki *et al.*, 2016; Creasy *et al.*, 2017; Buisman *et al.*, 2020; Treska *et al.*, 2020). As a junctional site between the right and left colon, their anatomopathological features have not been fully elucidated. Because of this complexity, it seems that this colon segment can not be simply classified as the right colon or the left colon, and pulmonary metastasis from cancer of this colon segment is more complex than other colon segments. Therefore, it was necessary to conduct targeted research for unresectable CRPM of this colon segment. This study aimed to investigate the prognosis of unresectable pulmonary metastases from the perspective of the colonic subsites of the transverse colon, hepatic flexure, and splenic flexure in relation to PTR.

Materials and methods

Data source and selection

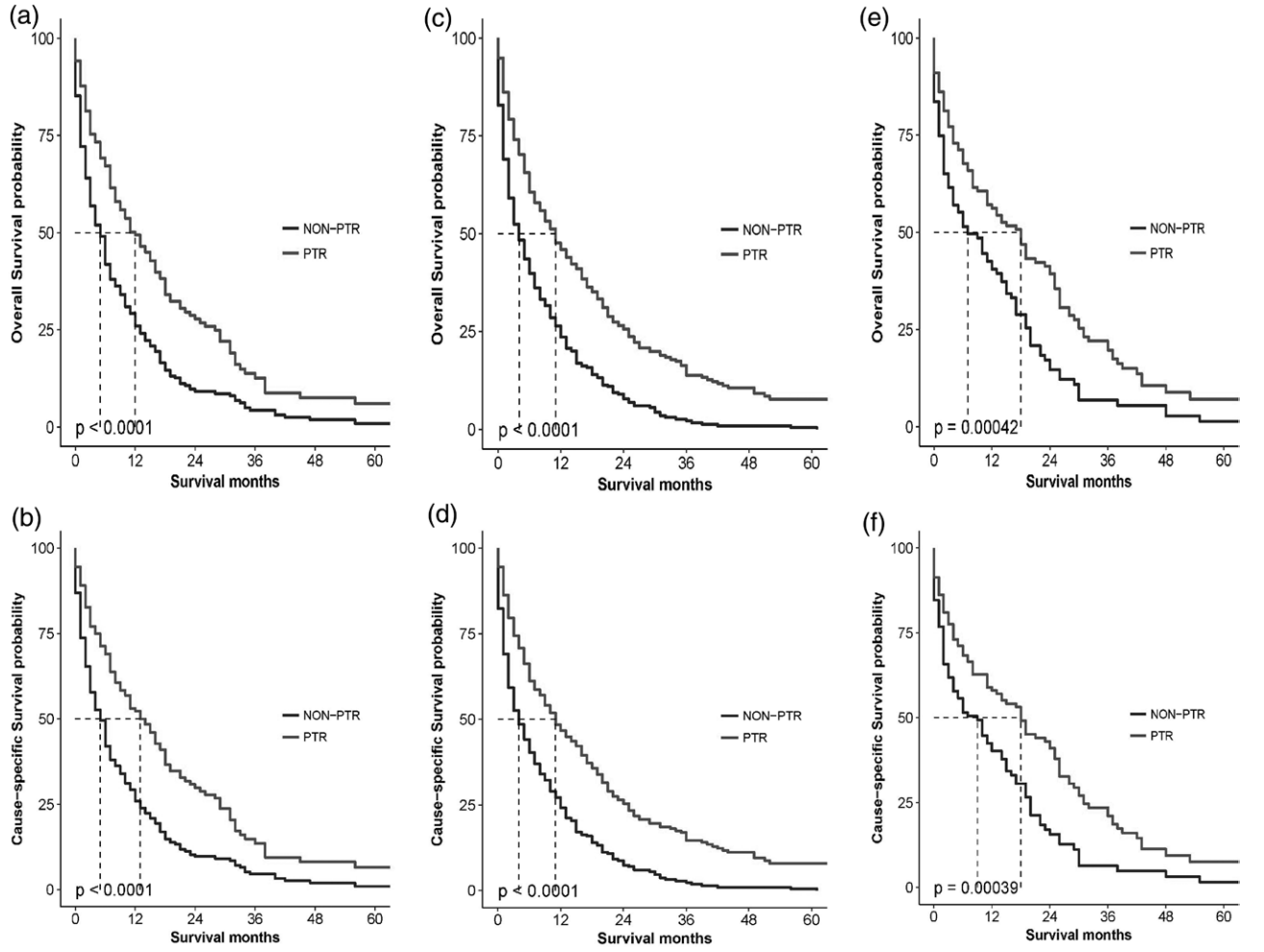
The Surveillance, Epidemiology, and End Results (SEER) 18 regions database (Incidence-SEER 18 Regs Research Data [with additional treatment fields], November 2020 Sub [2000–2018 varying]) was used to identify patients with unresectable carcinomas of the transverse colon, including flexures with pulmonary metastases. The selection criteria included: (1) ICD-O-3 site codes: hepatic flexure, transverse colon, and

Table 1 Baseline characteristics of UHFPM, UTCPM and USFPM patients

Variables	Total (n = 1294)	UHFPM (n = 419)	UTCPM (n = 636)	USFPM (n = 239)	*P*-value
					0.009
Age, n (%)					
≤64	525 (40.6)	158 (37.7)	250 (39.3)	117 (49)	
65–76	396 (30.6)	144 (34.4)	200 (31.4)	52 (21.8)	
≥77	373 (28.8)	117 (27.9)	186 (29.2)	70 (29.3)	
Gender, n (%)					0.918
Female	613 (47.4)	196 (46.8)	305 (48)	112 (46.9)	
Male	681 (52.6)	223 (53.2)	331 (52)	127 (53.1)	
Race, n (%)					0.516
White	896 (69.2)	299 (71.4)	442 (69.5)	155 (64.9)	
Black	267 (20.6)	82 (19.6)	130 (20.4)	55 (23)	
Other	131 (10.1)	38 (9.1)	64 (10.1)	29 (12.1)	
Marital status, n (%)					0.962
Married	605 (46.8)	198 (47.3)	295 (46.4)	112 (46.9)	
Unmarried/Unknown	689 (53.2)	221 (52.7)	341 (53.6)	127 (53.1)	
T stage, n (%)					0.002
T1 + T2 + T3 + Tis	468 (36.2)	139 (33.2)	247 (38.8)	82 (34.3)	
T4	330 (25.5)	92 (22)	159 (25)	79 (33.1)	
Unknown	496 (38.3)	188 (44.9)	230 (36.2)	78 (32.6)	
N stage, n (%)					0.214
N0	428 (33.1)	156 (37.2)	195 (30.7)	77 (32.2)	
N1 + N2	653 (50.5)	194 (46.3)	338 (53.1)	121 (50.6)	
Unknown	213 (16.5)	69 (16.5)	103 (16.2)	41 (17.2)	
PTR, n (%)					0.002
NO	740 (57.2)	263 (62.8)	361 (56.8)	116 (48.5)	
YES	554 (42.8)	156 (37.2)	275 (43.2)	123 (51.5)	
Chemotherapy, n (%)					0.402
Yes	748 (57.8)	242 (57.8)	359 (56.4)	147 (61.5)	
No/Unknown	546 (42.2)	177 (42.2)	277 (43.6)	92 (38.5)	
Grade, n (%)					0.094
I + II	573 (44.3)	186 (44.4)	264 (41.5)	123 (51.5)	
III + IV	268 (20.7)	85 (20.3)	135 (21.2)	48 (20.1)	
Unknown	453 (35.0)	148 (35.3)	237 (37.3)	68 (28.5)	
Tumor size, n (%)					0.004
≤5 cm	256 (19.8)	89 (21.2)	120 (18.9)	47 (19.7)	
> 5 cm	272 (21.0)	63 (15)	145 (22.8)	64 (26.8)	
Unknown	766 (59.2)	267 (63.7)	371 (58.3)	128 (53.6)	
CEA, n (%)					0.949
Negative	135 (10.4)	40 (9.5)	70 (11)	25 (10.5)	
Positive	811 (62.7)	264 (63)	395 (62.1)	152 (63.6)	
Unknown	348 (26.9)	115 (27.4)	171 (26.9)	62 (25.9)	

CEA, carcinoembryonic antigen; PTR, primary tumor resection; UHFPM, unresectable hepatic flexure cancer pulmonary metastasis; USFPM, unresectable splenic flexure cancer pulmonary metastasis; UTCPM, unresectable transverse colon cancer pulmonary metastasis.

Fig. 3



Kaplan–Meier Survival analysis for OS and CSS between the PTR and non-PTR groups in UHFPM (a and b), UTCPM (c and d) and USFPM (e and f) patients. CSS, cause-specific survival; OS, overall survival; PTR, primary tumor resection; UHFPM, unresectable hepatic flexure cancer pulmonary metastasis; USFPM, unresectable splenic flexure cancer pulmonary metastasis; UTCPM, unresectable transverse colon cancer pulmonary metastasis.

splenic flexure; (2) ICD-O-3 behavior codes: malignant; (3) diagnostic confirmation: positive histology, positive exfoliative cytology, and no positive histology; Positive laboratory test/marker study; (4) ICD-O-3 histologic type codes: 8000, 8010, 8012, 8013, 8041, 8070, 8140, 8210, 8240, 8246, 8255, 8261, 8263, 8480, 8481, 8490, 8510, 8560, 8574, and 9100; 5) complete information of surgery of primary site; 6) vital status: alive or dead. The exclusion criteria were as follows: (1) incomplete information on surgery at the primary site; (2) unknown T/N/M stage; (3) diagnosis without microscopic confirmation; and (4) unknown survival months (Fig. 1).

All patients were divided into three major cohorts: UHFPM, UTCPM, and USFPM. All patients in every cohort were then divided into two groups according to whether they received PTR. The data from the SEER database were publicly available; therefore, this study did not require approval from the ethics review committee.

Statistical analysis

All data were analyzed using the statistical software packages R 3.3.2 (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.7.1 [18]. Chi-squared test was used to compare categorical variables across the UTCPM, UHFPM, and USFPM groups. OS and cause-specific survival (CSS) were compared using the Kaplan–Meier curves. The multivariate Cox regression analysis was performed to identify factors associated with survival. Subgroup analysis was performed using the Kaplan–Meier curves. Statistical significance was set at $P \leq 0.05$.

OS and CSS were the primary endpoints. OS was defined as the time from diagnosis to death from every cause, and

Table 2 Univariate analysis for OS of UHFPM, UTCPM and USFPM patients

	UHFPM		UTCPM		USFPM	
Variables	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age						
≤64	Reference		Reference		Reference	
65–76	1.19 (0.92–1.52)	0.18	1.05 (0.86–1.29)	0.636	0.96 (0.67–1.39)	0.835
≥77	1.47 (1.14–1.91)	0.003	1.68 (1.37–2.07)	< 0.001	1.57 (1.14–2.17)	0.006
Gender						
Female	Reference		Reference		Reference	
Male	1.08 (0.88–1.34)	0.452	0.93 (0.78–1.1)	0.377	1.18 (0.89–1.56)	0.252
Race						
White	Reference		Reference		Reference	
Black	0.92 (0.71–1.2)	0.551	0.97 (0.78–1.19)	0.758	0.77 (0.54–1.09)	0.135
Other	0.83 (0.57–1.19)	0.307	0.91 (0.69–1.2)	0.508	0.86 (0.54–1.35)	0.503
Marital status						
Married	Reference		Reference		Reference	
Unmarried/Unknown	1.17 (0.95–1.44)	0.147	1.21 (1.02–1.43)	0.028	1.41 (1.06–1.86)	0.017
T stage						
T4	Reference		Reference		Reference	
Unknown	1.09 (0.83–1.43)	0.522	1.33 (1.07–1.66)	0.009	0.97 (0.69–1.37)	0.878
T1 + T2 + T3 + Tis	0.69 (0.52–0.93)	0.013	0.71 (0.57–0.88)	0.002	0.61 (0.44–0.86)	0.005
N stage						
N0	Reference		Reference		Reference	
Unknown	1.29 (0.94–1.78)	0.115	1.58 (1.2–2.07)	< 0.001	0.85 (0.55–1.29)	0.441
N1 + N2	0.89 (0.71–1.12)	0.308	0.99 (0.82–1.19)	0.886	0.69 (0.51–0.94)	0.02
Chemotherapy						
Yes	Reference		Reference		Reference	
No/Unknown	2.83 (2.28–3.5)	< 0.001	3.02 (2.54–3.59)	< 0.001	3 (2.25–4)	< 0.001
Grade						
I + II	Reference		Reference		Reference	
III + IV	1.43 (1.1–1.88)	0.009	1.85 (1.48–2.3)	< 0.001	1.52 (1.07–2.17)	0.021
Unknown	1.22 (0.96–1.56)	0.109	1.67 (1.37–2.04)	< 0.001	1.34 (0.95–1.88)	0.098
Tumor size						
≤5 cm	Reference		Reference		Reference	
> 5 cm	1.49 (1.07–2.07)	0.017	1.6 (1.24–2.06)	< 0.001	1.14 (0.77–1.69)	0.508
Unknown	1.25 (0.97–1.61)	0.09	1.87 (1.48–2.35)	< 0.001	1.17 (0.82–1.69)	0.384
CEA						
Negative	Reference		Reference		Reference	
Positive	1.4 (0.96–2.05)	0.082	1.7 (1.27–2.28)	< 0.001	1.66 (1.02–2.7)	0.041
Unknown	1.61 (1.07–2.42)	0.023	2.06 (1.5–2.82)	< 0.001	1.4 (0.83–2.36)	0.211

OS, overall survival; PTR, primary tumor resection; UHFPM, unresectable hepatic flexure cancer pulmonary metastasis; USFPM, unresectable splenic flexure cancer pulmonary metastasis; UTCPM, unresectable transverse colon cancer pulmonary metastasis.

CSS was defined as the date from the first diagnosis to death caused by this disease.

Results

Baseline characteristics of the patients

Based on the inclusion criteria, this study included a cohort of 1294 unresectable CRPM: 419 with UHFPM, 636 cases with UTCPM, and 239 with USFPM. A total of 156 patients with UHFPM, 275 with UTCPM, and 123 with USFPM underwent PTR.

Of all patients, 71.2% of the patients were aged <76 years, and the majority were White (69.2%). Approximately 44.3% of the patients had grade I–II tumors. Most patients (62.7%) had CEA Positive. Table 1 summarizes baseline patient characteristics.

Kaplan–Meier survival analysis

Of the 1294 patients recruited, 1101(356 UHFPM, 547 UTCPM, and 198 USFPM) had died by the end of the last follow-up, and 1026 (335 UHFPM, 512 UTCPM, and 179 USFPM) had died of UHFPM, UTCPM, and USFPM, respectively.

Survival analysis for OS and CSS in the PTR groups, showed that there were no statistical differences in the the UHFPM, UTCPM, and USFPM patients ($P > 0.05$). There were statistical differences in the UHFPM, UTCPM, and USFPM patients for OS and CSS ($P < 0.05$). Three non-PTR subgroups showed significant statistical differences for OS and CSS ($P < 0.05$) (Fig. 2).

For UHFPM, UTCPM, and USFPM patients, the OS rate of PTR vs. non-PTR groups was ($P < 0.001$). Survival analysis for CSS between the PTR and non-PTR groups is the same. The results of the survival analysis for all patients are shown in Fig. 3.

Prognostic factors

Univariate and multivariate Cox regression analyses of the OS of patients with UHFPM, UTCPM, and USFPM were performed (Tables 2 and 3).

T stage, Chemotherapy, Grade, Tumor size, and CEA were strong predictors of OS. In univariate analysis for OS of UHFPM, UTCPM and USFPM patients (Table 2). Compared with Patients aged ≤64 years, 65–76 years patients in the UHFPM patients for OS hazard ratio were

Table 3 Multivariate analysis for OS of UHFPM, UTCPM and USFPM patients

	UHFPM		UTCPM		USFPM	
Variables	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age						
≤64	Reference		Reference		Reference	
65–76	0.93 (0.71–1.22)	0.613	1.11 (0.9–1.36)	0.344	0.97 (0.64–1.45)	0.866
≥77	1.13 (0.86–1.48)	0.392	1.22 (0.98–1.53)	0.081	1.09 (0.75–1.61)	0.646
Gender						
Female	Reference		Reference		Reference	
Male	1.18 (0.94–1.48)	0.164	0.99 (0.83–1.17)	0.867	1.36 (0.99–1.87)	0.059
Race						
White	Reference		Reference		Reference	
Black	0.93 (0.7–1.23)	0.601	1.12 (0.9–1.4)	0.317	0.71 (0.49–1.03)	0.073
Other	1.03 (0.7–1.51)	0.887	0.98 (0.73–1.3)	0.864	0.55 (0.34–0.9)	0.018
Marital status						
Married	Reference		Reference		Reference	
Unmarried/Unknown	1.18 (0.93–1.5)	0.168	0.88 (0.74–1.06)	0.177	1.13 (0.83–1.54)	0.422
T stage						
T4	Reference		Reference		Reference	
Unknown	0.84 (0.6–1.18)	0.312	0.99 (0.75–1.32)	0.97	0.88 (0.55–1.41)	0.592
T1 + T2 + T3 + Tis	0.63 (0.47–0.86)	0.003	0.73 (0.58–0.92)	0.007	0.54 (0.37–0.8)	0.002
N stage						
N0	Reference		Reference		Reference	
Unknown	1.08 (0.77–1.51)	0.665	1.12 (0.84–1.49)	0.446	0.62 (0.38–1.03)	0.063
N1 + N2	1.17 (0.9–1.51)	0.237	1.42 (1.15–1.75)	0.001	0.94 (0.62–1.43)	0.778
Chemotherapy						
Yes	Reference		Reference		Reference	
No/Unknown	2.79 (2.21–3.53)	<0.001	3.7 (3.03–4.52)	<0.001	4.15 (2.92–5.9)	<0.001
Grade						
I + II	Reference		Reference		Reference	
III + IV	1.59 (1.19–2.11)	0.001	2.07 (1.64–2.62)	<0.001	1.67 (1.12–2.48)	0.012
Unknown	0.96 (0.73–1.26)	0.764	1.32 (1.06–1.65)	0.013	1.07 (0.71–1.62)	0.752
Tumor size						
≤5 cm	Reference		Reference		Reference	
> 5 cm	1.29 (0.92–1.83)	0.144	1.77 (1.35–2.31)	<0.001	1.19 (0.79–1.79)	0.408
Unknown	0.95 (0.71–1.27)	0.741	1.49 (1.13–1.96)	0.004	1 (0.63–1.58)	0.998
CEA						
Negative	Reference		Reference		Reference	
Positive	1.11 (0.74–1.66)	0.628	1.65 (1.22–2.23)	0.001	3.42 (1.88–6.23)	<0.001
Unknown	1.1 (0.71–1.71)	0.668	1.81 (1.3–2.51)	<0.001	2.62 (1.44–4.77)	0.002

OS, overall survival; PTR, primary tumor resection; UHFPM, unresectable hepatic flexure cancer pulmonary metastasis; USFPM, unresectable splenic flexure cancer pulmonary metastasis; UTCPM, unresectable transverse colon cancer pulmonary metastasis.

19% increase. Patients with more advanced disease (T stages T4), more positive lymph nodes involved (N1 and N2), and the higher the grade (Grade III + IV)were more likely to Shorten OS.

Multivariate analysis for OS of UHFPM patients, predictors of worse OS were high grade III + IV tumor (HR, 1.59; 95% CI, 1.19–2.11), larger tumor size > 5 cm (HR, 1.29; 95% CI, 0.92–1.83), CEA positive (HR, 1.11;95% CI, 0.74–1.66), more positive nodes involved N1–2 (HR, 1.17; 95%CI, 0.9–1.51), and older age ≥77 years (HR, 1.13; 95% CI, 0.86–1.48) (Table 3).

The common prognostic factors for UHFPM, UTCPM, and USFPM patients included grade (I + II vs. III + IV), T stage (T1 + T2 + T3 + TIS vs. T4), and chemotherapy (No/Unknown vs. yes). N stage (N0 vs. N1 + N2) was a prognostic factor for USFPM patients but not for UHFPM and UTCPM patients.

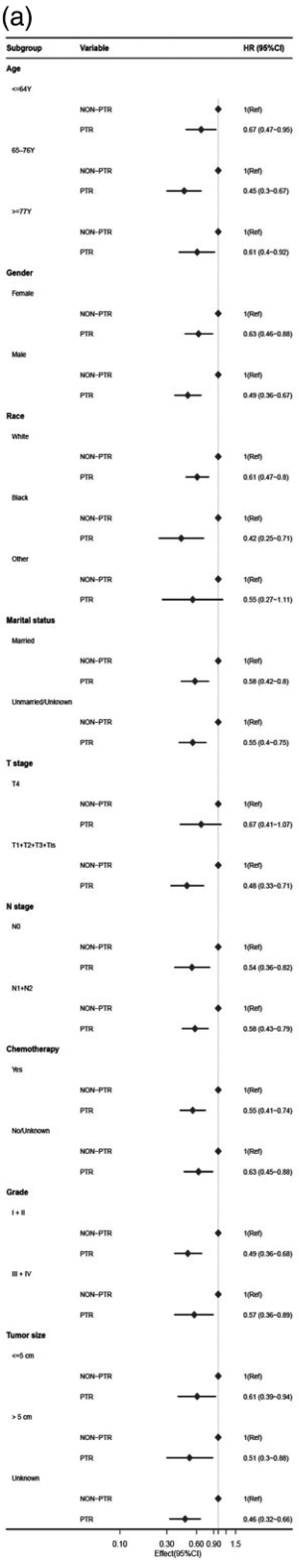
Subgroup analyses for OS and CSS

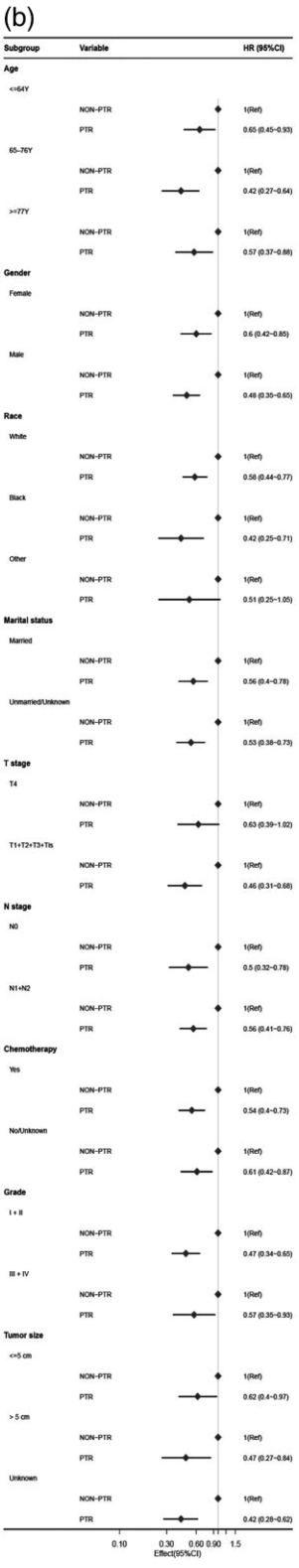
Subgroup analyses for OS and CSS were performed in prespecified subgroups using forest plots, and the prespecified stratification factor was whether PTR was performed. For the UHFPM group, the forest plot showed that all subgroups appeared to have protective factors against OS and CSS (Fig. 4). In the UTCPM group, the forest plot showed that the PTR was a protective factor against OS and CSS (Fig. 5). In the USFPM group, the forest plot showed that PTR was a protective factor against OS and CSS. All the subgroups included age, sex, race, marital status, T stage, N stage, chemotherapy, and tumor grade (Fig. 6). We validated the results all subgroups for OS and CSS and found that they were stable in all subgroups without interaction.

Discussion

Pulmonary metastasis is the most common extra-abdominal manifestation of advanced CRC [32,33].(Vatandoust *et al*., 2015; Zeng *et al*., 2017) Previously, the effect of tumor location on the prognosis of patients with unresectable metastatic CRC was compared between two groups mostly according to 'right colon and left colon' (Zhang *et al*., 2017; Ge *et al*., 2019; Wang *et al*., 2019; Ergun *et al*., 2020; Tharin *et al*., 2020; Yang *et al*., 2020). However, as a junctional site between the right and left colons, the lymphatic drainage and vascular supply of

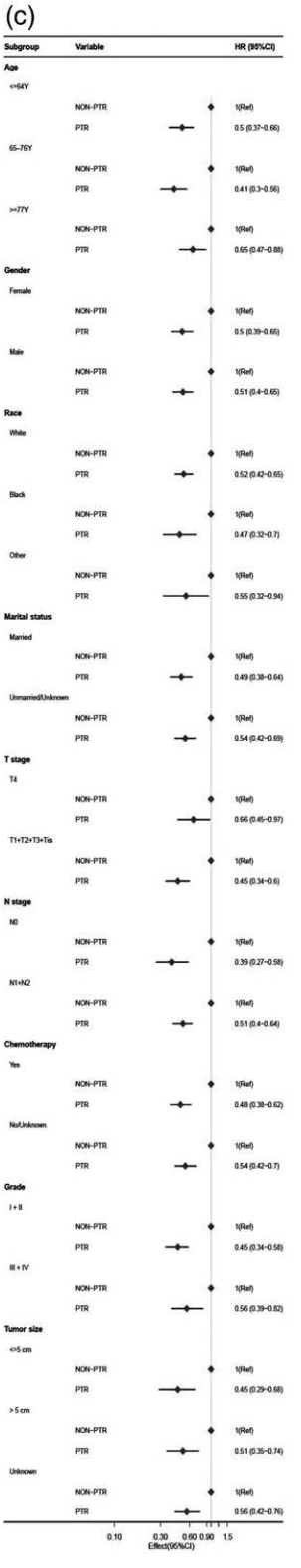
Fig. 4

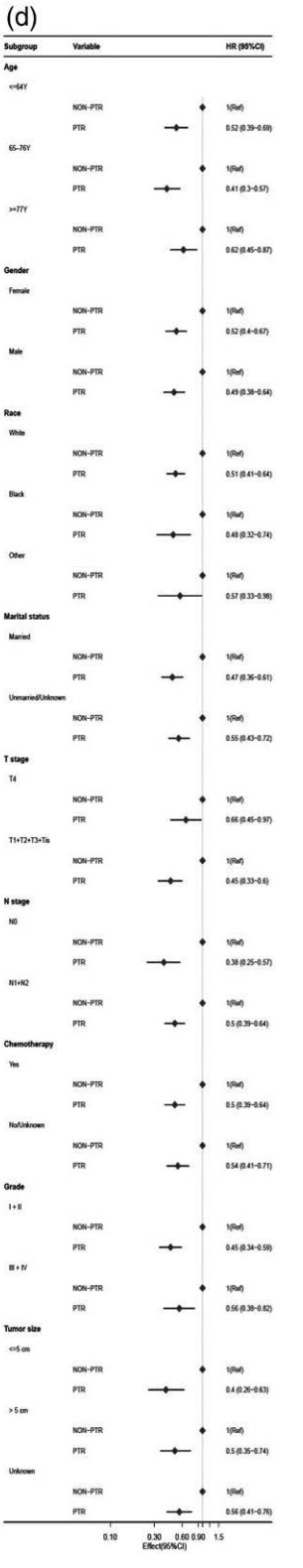




Forest plot for UHFPM patients in the subgroup analysis of OS (a) and CSS (b). UHFPM, unresectable hepatic flexure cancer pulmonary metastasis.

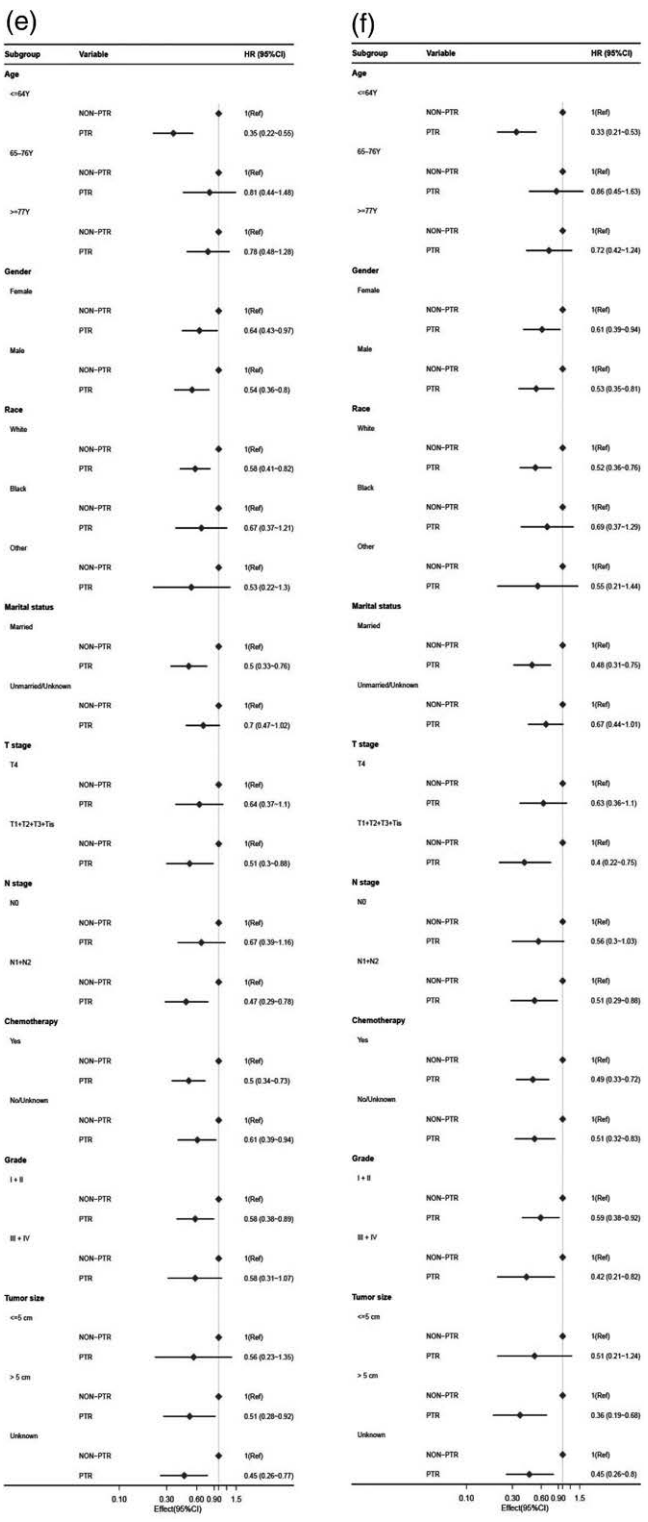
Fig. 5





Forest plot for UTCPM patients in the subgroup analysis of OS (c) and CSS (d). UTCPM, unresectable transverse colon cancer pulmonary metastasis.

Fig. 6



Forest plot for USFPM patients in the subgroup analysis of OS (e) and CSS (f). USFPM, unresectable splenic flexure cancer pulmonary metastasis.

the transverse colon, including flexures, lie between the right and left anatomical territories, and their anatomopathological features have not yet been fully elucidated. Because of its complexity, this colonic segment cannot be simply classified as the right or left colon (Glebov *et al*., 2003; Benedix *et al*., 2011, 2012; Ghazi *et al*., 2012; Yamauchi *et al*., 2012; Zhang *et al*., 2015; Loree *et al*., 2018; Xi *et al*., 2019). An increasing number of studies have proven that a simple classification into right- and left-sided CRC cannot represent the complexity of this tumor entity and have put forward the importance of research from the perspective of colonic subsites (Wray *et al*., 2009; Benedix *et al*., 2011, 2012; Yamauchi *et al*., 2012; Bhangu *et al*., 2013; Loree *et al*., 2018). As a continuum from the right to the left colon, complex blood supply and lymphatic drainage cause the transverse colon, including the flexures of the most complex colon segment in the whole colon; however, few studies have examined pulmonary metastasis from cancer of this colon segment. To the best of our knowledge, this was the first study to investigate the prognosis of patients with unresectable CRPM and the effect of PTR on survival in the colonic subsites of the transverse colon, hepatic flexure, and splenic flexure.

We found that for the total cohort, the OS of UHFPM, UTCPM, and USFPM patients were discrepant. For patients undergoing PTR, there was no difference in prognosis of UHFPM, UTCPM, and USFPM. For patients without PTR, there was a difference in the prognoses for UHFPM, UTCPM, and USFPM. In response to these results, we propose the following possible explanations: first, there are different embryonic sources of these three colonic subsites; in the embryologic development of the distal intestine, the hepatic flexure originates from the midgut, and the splenic flexure originates from the hindgut. One study found that the embryonic origin is involved in the prognosis of metastatic CRC (Loupakis *et al*., 2015). This may explain why the OS rates of the UHFPM, UTCPM, and USFPM groups were different, which may be due to the complex oncological characteristics of 2/3 of the transverse colon originating from the midgut and 1/3 from the hindgut. The splenic flexure is supplied by branches of the inferior mesenteric artery. The hepatic flexure is mainly supplied by branches of the superior mesenteric artery (Arru *et al*., 2007; Konopke *et al*., 2009).

For the first time, we analyzed the effect of PTR on the survival of patients with unresectable CRPM at three colonic subsites: the transverse colon, hepatic flexure, and splenic flexure. We found that PTR was a common factor for UHFPM, UTCPM, and USFPM, and that PTR could prolong the OS and CSS of patients. We speculated that there were several possible reasons why PTR could improve patient survival: first, the increased survival rate after PTR may be attributed to the reduction of primary

tumor burden; second, PTR reduced potential CRC-related complications, such as acute bleeding, perforation, and obstruction, which could cause higher surgical mortality and morbidity (Stillwell *et al.*, 2010; Clancy *et al.*, 2014); third, PTR destroyed the angiogenic environment, favoring unresectable pulmonary metastasis growth.

In this study, the SEER database was used to analyze the effects of PTR on the survival of patients with UTCLM, UHFLM, and USFLM. However, this study had some limitations. First, the SEER database did not provide some surgical information, such as operation time, blood loss, and postoperative complications. Second, chemotherapy is an important treatment method for patients with unresectable CRPM. The SEER database did not provide specific chemotherapy regimens, dosage, curative time, side-effects, and effect, which may affect the decision of surgical efficacy to a certain extent; third, since the SEER database did not provide details of the number, location, and size of metastases of individual organs, we were unable to further analyze the effects of different tumor burden on the choice of surgical strategy for patients with UTCPM, UHFPM, and USFPM; fourth, due to the lack of more detailed information on gene mutation status in the SEER database, we did not further analyze the effects of different gene mutation states on PTR and adjuvant chemotherapy for patients with UTCPM, UHFPM, and USFPM; finally, there was a selective bias in the retrospective study. Future studies can focus on the gene mutation analysis of different colon subsites (Natsume *et al.*, 2018; Bennouna *et al.*, 2019; Hsu *et al.*, 2019; Chen *et al.*, 2020; Kalantzis *et al.*, 2020; Martin *et al.*, 2020; Huang *et al.*, 2021).

Conclusion

In summary, we proved that PTR could provide survival benefits for patients with unresectable CRPM from the perspective of colonic subsites of transverse colon, hepatic flexure, and splenic flexure. In addition, we need to further build our own database to collect gene mutation analysis of different colon subsites, it should be considered to guide treatment for unresectable CRPM.

Acknowledgements

We would like to thank the Surveillance, Epidemiology, and End Results Program (National Cancer Institute) for developing the SEER database.

Wenhua Xiao, Liang Peng, Huixia Zhao, and Hui Li contributed to the study conception design. Huixia Zhao, Guangze Song, Ruliang Wang, Na Guan, and Chao Yun contributed to acquisition and analysis of data. Huixia Zhao, Guangze Song, Jingwen Yang, and Jin-Bao Ma contributed to the interpretation of data. Draft and revision of the manuscript: All authors. All the authors have read and approved the final version of the manuscript.

The data supporting the results of this study are available in the SEER 18 regions database [Incidence-SEER 18 Regs Research Plus Data, Nov 2020 Sub (2000–2018 varying)] https://seer.cancer.gov/data/.

Conflicts of interest

There are no conflicts of interest.

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