


Article

Primary Tumor Resection Provides Survival Benefits for Patients with Synchronous Brain Metastases from Colorectal Cancer

Xiaofei Cheng¹, Yanqing Li², Dong Chen¹, Xiangming Xu¹, Fanlong Liu^{1,*} and Feng Zhao^{3,*} 

¹ Department of Colorectal Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China; xfcheng@zju.edu.cn (X.C.); cdking@zju.edu.cn (D.C.); zjxxm1974@163.com (X.X.)

² Department of Pathology, The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou 310009, China; 2512074@zju.edu.cn

³ Department of Radiation Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

* Correspondence: fanlong_liu@zju.edu.cn (F.L.); zju_zhaofeng@zju.edu.cn (F.Z.)

Abstract: Background: Brain metastases (BMs), particularly synchronous brain metastases, in colorectal cancer (CRC) patients are uncommon. The survival benefit of primary tumor resection (PTR) in patients with metastatic colorectal cancer is controversial. Whether PTR can bring survival benefits to patients with BMs of CRC has not been reported. Methods: From 2010 to 2016, 581 CRC patients with BMs from the Surveillance, Epidemiology, and End Results (SEER) database were divided into PTR and non-PTR groups. The log-rank test was used to compare the survival distributions. The Kaplan-Meier method was used to estimate survival. By controlling additional prognostic factors, a Cox proportional multivariate regression analysis was used to estimate the survival benefit of PTR. Results: The median overall survival for CRC patients with synchronous BMs was 3 months, with a 1-year survival rate of 27.2% and a 2-year survival rate of 12.8%. The PTR group contained 171 patients (29.4%), whereas the non-PTR group had 410 patients (70.6%). Patients who underwent PTR had a 1-year survival rate of 40.2% compared to 21.7% in those who did not ($p < 0.0001$). Cox proportional analysis showed that patients ≥ 60 years (hazard ratio [HR] 1.718, 95% confidence interval [CI] 1.423–2.075, $p < 0.0001$) had a shorter OS than patients < 60 years of age. OS was better in CEA-negative than in CEA-positive patients (HR 0.652, 95% CI 0.472–0.899, $p = 0.009$). Patients in whom the primary tumor was removed had considerably improved prognoses (HR 0.654, 95% CI 0.531–0.805, $p < 0.0001$). Subgroup analysis revealed that the PTR group achieved a survival advantage except for patients with CEA negative. Conclusions: Patients with synchronous BMs from CRC may benefit from primary tumor resection (PTR). Age, CEA level, and PTR were independent prognostic risk factors for CRC patients with synchronous BMs.

Keywords: colorectal cancer (CRC); brain metastases (BMs); survival; prognosis factors; primary tumor resection (PTR)



Citation: Cheng, X.; Li, Y.; Chen, D.; Xu, X.; Liu, F.; Zhao, F. Primary Tumor Resection Provides Survival Benefits for Patients with Synchronous Brain Metastases from Colorectal Cancer. *Diagnostics* **2022**, *12*, 1586. <https://doi.org/10.3390/diagnostics12071586>

Academic Editors: Lucía Inglada-Pérez and José Perea

Received: 3 June 2022

Accepted: 27 June 2022

Published: 29 June 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Colorectal cancer (CRC) is the main cause of cancer-related death globally, with mortality rates of 45%, 35%, and 47.8% in Europe, the United States, and worldwide, respectively [1]. The main cause of disease progression and death for CRC patients is metastasis, which is present in ~25% of patients at the time of diagnosis and develops in another 25% later in life [2]. The most frequent sites of metastasis in CRC are the liver and lungs. Brain metastases (BMs) are rare, with an incidence of only 0.3–9% [3]. However, the prevalence of BMs may be rising over time, owing to improved CRC diagnosis at an earlier stage, thorough follow-up, and higher patient survival as a result [4]. Furthermore, brain or cerebral imaging is not usually suggested in clinical recommendations concerning

metastatic CRC at risk, which means that BMs are commonly detected only when symptoms arise, which is typically late in the disease process. Headaches, nausea, and hemiparesis are common symptoms of BMs, and they contribute to a poor quality of life [5]. As a result, CRC BMs cannot be dismissed as a minor clinical issue that requires little attention.

The prognosis of patients with BMs from CRC is very poor, as the median survival is only 2–9.6 months [6–8]. Age, Karnofsky performance status (KPS), extracerebral metastases, and BMs number are predictive variables for OS in retrospective investigations [9–12]. CRC BMs patients with negative CEA levels had a 3-month survival advantage, implying that a positive CEA level is related to a poor OS [6,13]. The prognosis of CRC BMs is also affected by the location of the underlying tumor. Compared to patients with left-sided CRC, those with right-sided CRC develop BMs much earlier and have a significantly worse prognosis [14]. The treatment of metastatic CRC has altered substantially in recent years, owing mostly to the development of targeted treatments and immunotherapy. While there is no consensus on how to treat patients with CRC BMs, their care is similar to that of patients with other solid tumors. It is based on criteria such as the patient's performance status, the underlying tumor's features, and the number/location of the brain lesions [15]. The goal of treatment is typically palliative, and alternatives include surgical excision, stereotactic radiosurgery (SRS), whole-brain radiation therapy (WBRT), or combinations of these [12,16].

Primary tumor resection (PTR) is controversial in CRC patients with unresectable metastases [17]. PTR enhances the quality of life and minimizes the negative effects of systemic chemotherapy and the risk of complications from the initial tumor, including bleeding, blockage, and perforation [18]. On the other hand, PTR delays the beginning of systemic chemotherapy, with additional delays if complications emerge [19]. Many physicians choose younger and healthier patients for surgical resection of primary tumors based on their clinical experience. Given the low incidence of BMs from CRC, no relevant reports suggest whether these patients can benefit from PTR.

The goal of this study was to evaluate the survival of individuals with synchronous CRC BMs who had their primary tumor surgically removed with that of patients who did not undergo surgery. To the best of our knowledge, this was the first study of the effect of PTR on their survival from CRC BMs.

2. Material and Methods

2.1. Study Population

Synchronous BMs were defined as brain metastases present at the time of CRC diagnosis. Data on synchronous BMs were obtained from patients registered between 2010 and 2016 in the National Cancer Institute's SEER database, which was accessible at <https://seer.cancer.gov/> (accessed on 15 November 2021). The following clinicopathological variables were included: age (<60, ≥60 years); race (Black, White, other); gender (female, male); tumor grade (well/moderately differentiated, poorly differentiated/undifferentiated, unknown); histological type (adenocarcinoma, other); surgery at the primary site (PTR, non-PTR); carcinoembryonic antigen (CEA) level (negative, positive, unknown); T stage (T0/T1, T2, T3, T4, unknown); N stage (N0, N1, N2, unknown); M stage (M1a, M1b, unknown) and survival time. The primary tumor location was classified according to CRC subtype, which included right colon cancer (RCC: cecum, ascending colon, hepatic flexure, and transverse colon), left colon cancer (LCC: splenic flexure, descending colon, and sigmoid colon), and rectal cancer (RC: rectosigmoid junction and rectum). The presence of bone, lung, and liver metastases at diagnosis was recorded in the SEER database as the number of extracranial metastases.

Patients were followed from the time of CRC diagnosis until the last follow-up, death, or trial conclusion, whichever came first. Patients with unidentified BMs were excluded from the study, as were those in whom BMs were detected 6 months after CRC diagnosis or during autopsy. The candidate selection technique is depicted in detail in Figure 1.

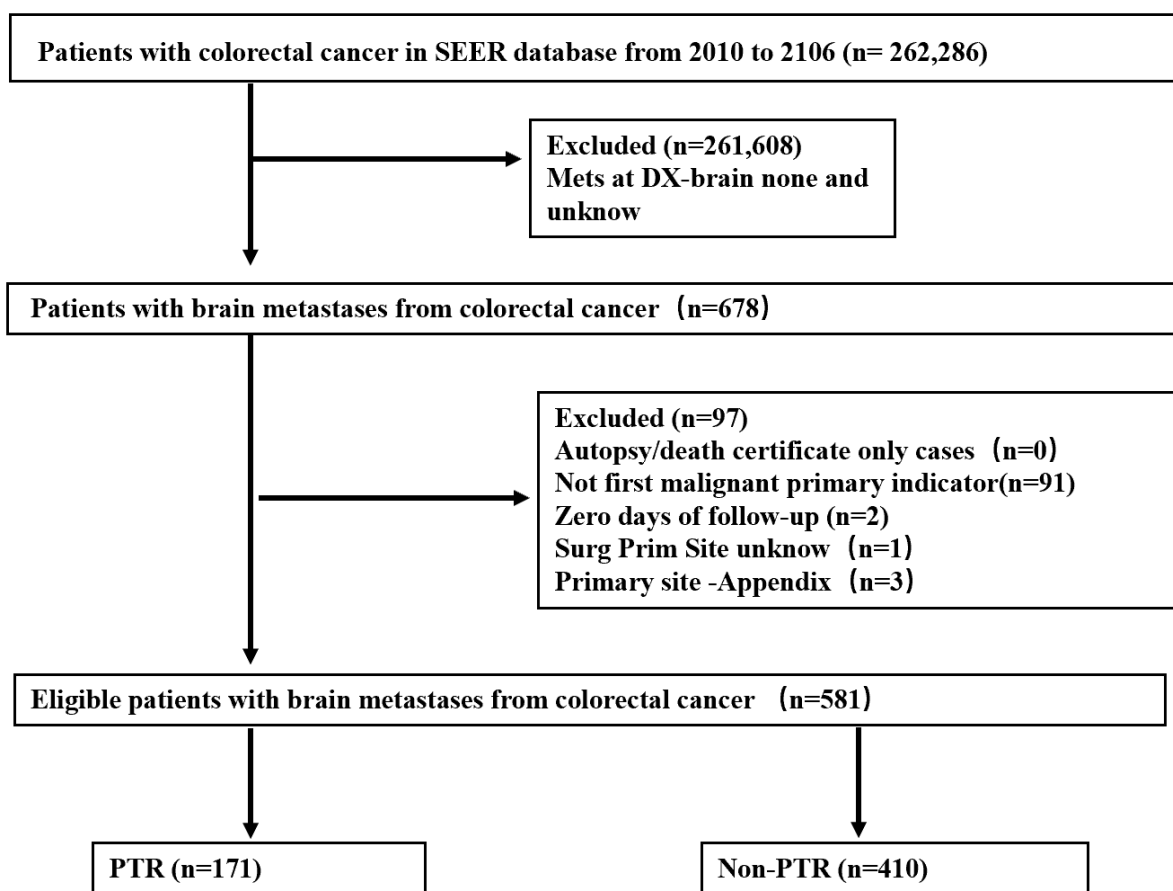


Figure 1. Flow diagram of eligible CRC patients with BMs who had their primary tumor surgically resected or did not have surgery.

2.2. Statistical Analysis

The chi-square test and Fisher's exact test were used to compare categorical variables that were given as a number with a percentage. The Kaplan-Meier method and log-rank test were used to generate survival curves. The prognostic variables of patients with brain metastases were determined using Cox proportional hazards models. Univariately significant variables were incorporated into a multivariate analysis to identify independent prognostic factors. A p -value < 0.05 was considered statistically significant. SPSS version 25 and Graph Pad Prism 8 were used to execute all statistical procedures.

3. Results

3.1. Patient Characteristics

Between 2010 and 2016, among 262,286 patients diagnosed with CRC, synchronous BMs were detected in 678, corresponding to an incidence of 0.26%. After rigorous screening, 581 CRC patients with BMs were included (Figure 1). The PTR group contained 171 patients (29.4%), whereas the non-PTR group had 410 patients (70.6%). In terms of primary tumor location, tumor grade, extrahepatic disease, T-stage, N-stage, and CEA, there was a substantial difference between the two groups. Some patients in the non-PTR group had uncertain T-stage, N-stage, or tumor differentiation, which accounted for a significant fraction of the total. Additionally, we discovered that the PTR group had a higher proportion of patients with RCC, M1a, and CEA negative. Of 581 patients, 206 (35.5%) had RCC, 115 (19.8%) had LCC, 170 (29.3%) had RC, and in 90 (15.5%) the CRC type was unknown. Among the total cohort of 581 patients with synchronous BMs, 410 (70.6%) had extracranial metastasis. The patient characteristics are presented in detail in Table 1.

Table 1. Baseline Characteristics of Patients Between the PTR group and the non-PTR group.

Variable	Total (n = 581)		Non-PTR (n = 410)		PTR (n = 171)		p Value
Age (yr)							
<60	225	(37.8)	161	(39.3)	64	(37.4)	0.678
≥60	356	(61.3)	249	(60.7)	107	(62.6)	
Race							
Black	67	(11.5)	49	(12.0)	18	(10.5)	0.682
White	470	(80.9)	328	(80.0)	142	(83.0)	
Other	44	(7.6)	33	(8.0)	11	(6.4)	
Gender							
Female	275	(47.3)	196	(47.8)	79	(46.2)	0.724
Male	306	(52.7)	214	(52.2)	92	(53.8)	
Primary tumor site							
RCC	206	(35.5)	115	(28.0)	91	(53.2)	<0.0001
LCC	115	(19.8)	70	(17.1)	45	(26.3)	
RC	170	(29.3)	142	(34.6)	28	(16.4)	
Unknown	90	(15.5)	83	(20.2)	7	(4.1)	
Histology							
Adenocarcinoma	505	(86.9)	357	(87.1)	148	(86.5)	0.865
Other	76	(13.1)	53	(12.9)	23	(13.5)	
Tumor grade							
Well/moderately	222	(38.2)	129	(31.5)	93	(54.4)	<0.0001
Poorly/undifferentiated	137	(23.6)	69	(16.8)	68	(39.8)	
Unknown	222	(38.2)	212	(51.7)	10	(5.8)	
T stage							
T0/T1	64	(11.0)	61	(14.9)	3	(1.8)	<0.0001
T2	20	(3.4)	12	(2.9)	8	(4.7)	
T3	132	(22.7)	44	(10.7)	88	(51.5)	
T4	100	(17.2)	35	(8.5)	65	(38.0)	
Tx	265	(45.6)	258	(62.9)	7	(4.1)	
N stage							
N0	192	(33.0)	154	(37.6)	38	(22.2)	<0.0001
N1	162	(27.9)	105	(25.6)	57	(33.3)	
N2	90	(15.5)	17	(4.1)	73	(42.7)	
Nx	137	(23.6)	134	(32.7)	3	(1.8)	
M stage							
M1a	106	(18.2)	55	(13.4)	51	(29.8)	<0.0001
M1b	410	(70.6)	309	(75.4)	101	(59.1)	
M1x	65	(11.2)	46	(11.2)	19	(11.1)	
CEA							
Positive	309	(53.2)	222	(54.1)	87	(50.9)	<0.0001
Negative	64	(11.0)	32	(7.8)	32	(18.7)	
Unknown	208	(35.8)	156	(38.0)	52	(30.4)	

Abbreviations: PTR, primary tumor resection; RCC, right colon cancer; LCC, left colon cancer; RC, rectal cancer.

3.2. Survival and Prognostic Factors

Patients with CRC and synchronous BMs had a median OS of 3 months, with a 1-year survival rate of 27.2% and a 2-year survival rate of 12.8%. Patients who underwent primary tumor resection had a 1-year survival rate of 40.2% compared to 21.7% in those who did not ($p < 0.0001$; Figure 2A). Median survival was 9 months in the PTR group, compared with 4 months in the non-PTR group. A comparison of OS by age (<60 and ≥60 years) showed that median survival times were 9 months and 3 months, respectively. The difference in OS between the two groups was statistically significant ($p < 0.0001$; Figure 2B). The 1-year survival rate in the CEA-positive group was 26.7%, much lower than that of the CEA-negative group (42%); the difference was statistically significant ($p = 0.0003$; Figure 2C). Patients without extracranial metastasis also had better outcomes than those with extracranial metastasis ($p = 0.001$; Figure 2D)

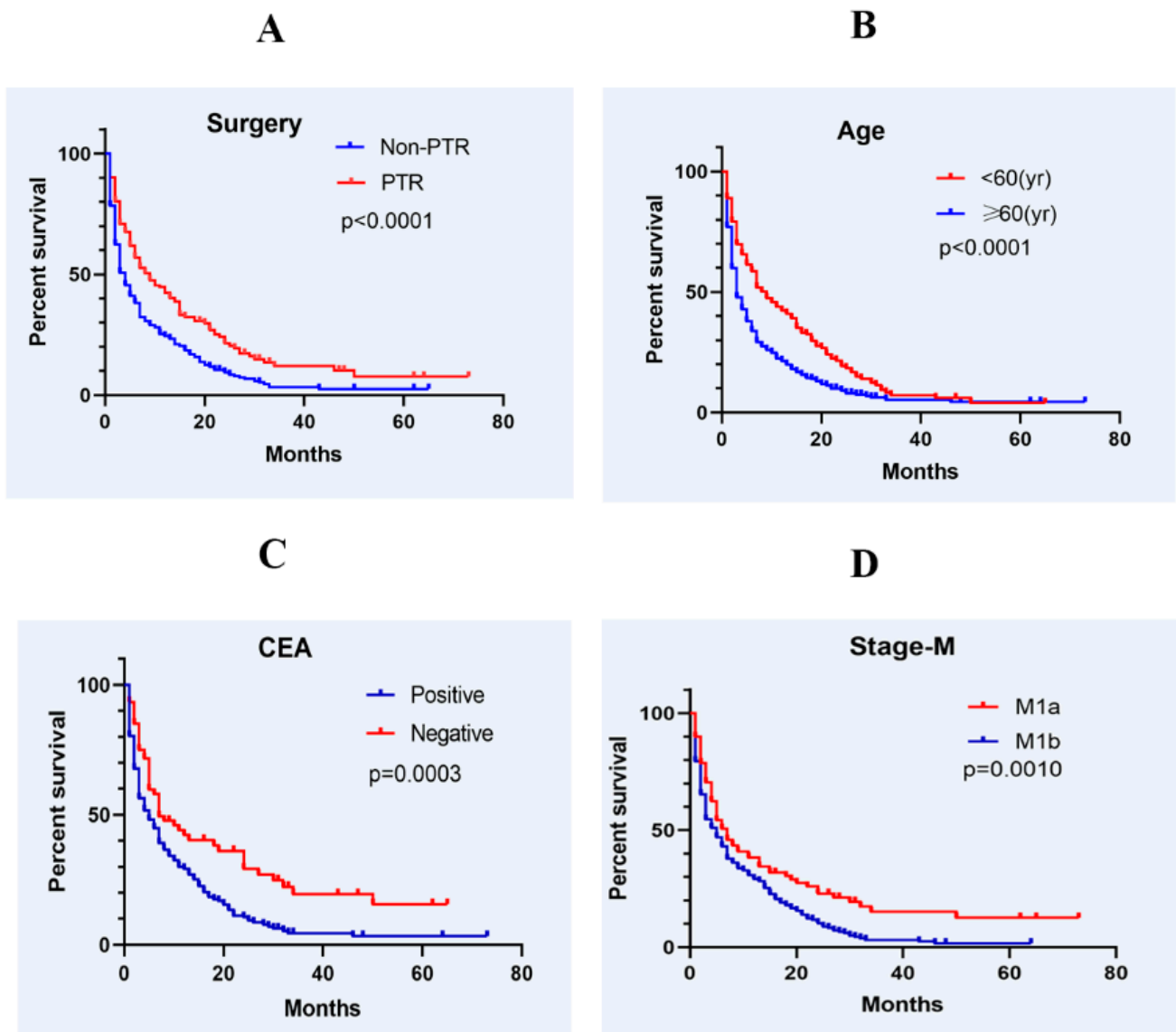


Figure 2. Kaplan-Meier survival curve analysis for overall survival in CRC patients with synchronous BMs. Surgery (A), Age (B), CEA level (C), and extracranial metastases (D) were included in the analysis.

In univariate analysis, age, CEA level, primary surgical site, and extracranial metastasis impacted OS in CRC patients with synchronous BMs (Table 2). However, race, sex, primary tumor location, tumor grade, histological types, T stage, and N stage were insignificant.

A multivariate analysis incorporating the significant variables showed that age, CEA level, and PTR were independent prognostic factors (Table 3). Patients ≥ 60 years (hazard ratio [HR] 1.718, 95% confidence interval [CI] 1.423–2.075, $p < 0.0001$) had a shorter OS than patients < 60 years of age. OS was better in CEA-negative than in CEA-positive patients (HR 0.652, 95% CI 0.472–0.899, $p = 0.009$). Similarly, patients in whom the primary tumor was removed had a considerably improved prognosis (HR 0.654, 95% CI 0.531–0.805, $p < 0.0001$).

Table 2. Univariate Cox regression for overall survival among patients with brain metastases.

Clinicopathologic Variable	HR	95%CI	p Value
Age (yr)			
<60	Reference		
≥60	1.708	1.418–2.057	<0.0001
Race			
Black	Reference		
White	0.903	0.693–1.176	0.447
Other	0.972	0.648–1.458	0.893
Gender			
Female	Reference		
Male	1.087	0.911–1.297	0.356
Primary tumor site			
RCC	Reference		
LCC	0.840	0.655–1.078	0.171
RC	0.838	0.671–1.046	0.118
Unknown	1.236	0.949–1.611	0.116
Histology			
Adenocarcinoma	Reference		
Other	1.090	0.840–1.414	0.518
Tumor grade			
Well/moderately	Reference		
Poorly/undifferentiated	1.118	0.884–1.413	0.352
Unknown	1.432	1.170–1.751	<0.0001
T stage			
T0/T1	Reference		
T2	1.219	0.721–2.063	0.460
T3	0.886	0.634–1.237	0.476
T4	1.171	0.831–1.651	0.366
Tx	1.336	0.988–1.806	0.060
N stage			
N0	Reference		
N1	1.006	0.801–1.264	0.958
N2	0.863	0.655–1.137	0.295
Nx	1.242	0.980–1.573	0.073
M stage			
M1a	Reference		
M1b	1.393	1.094–1.772	0.007
M1x	1.349	0.959–1.898	0.086
CEA			
Positive	Reference		
Negative	0.556	0.406–0.759	<0.0001
Unknown	1.167	0.965–1.410	0.110
Surgery			
Non-PTR	Reference		
PTR	0.629	0.515–0.768	<0.0001

Abbreviations: PTR, primary tumor resection; RCC, right colon cancer; LCC, left colon cancer; RC, rectal cancer; CI, confidence interval; HR, hazard ratio.

To balance the selection bias between the PTR and non-PTR groups, we further analyzed the corresponding subgroups. Figure 3 shows the adjusted HRs for OS based on the location of the primary tumor, extracranial metastases, and serum CEA level from the subgroup analysis. Except for CEA negative patients, other subgroups of patients with primary tumor resection achieved a survival advantage.

Table 3. Multivariable Cox regression for overall survival among patients with brain metastases.

Clinicopathologic Variable	HR	95%CI	p Value
Age (yr)			
<60	Reference		
≥60	1.718	1.423–2.075	<0.0001
M stage			
M1a	Reference		
M1b	1.167	0.905–1.506	0.234
M1x	1.020	0.716–1.454	0.912
CEA			
Positive	Reference		
Negative	0.652	0.472–0.899	0.009
Unknown	1.140	0.935–1.389	0.196
Surgery			
Non-PTR	Reference		
PTR	0.654	0.531–0.805	<0.0001

Abbreviations: PTR, primary tumor resection; CI, confidence interval; HR, hazard ratio.

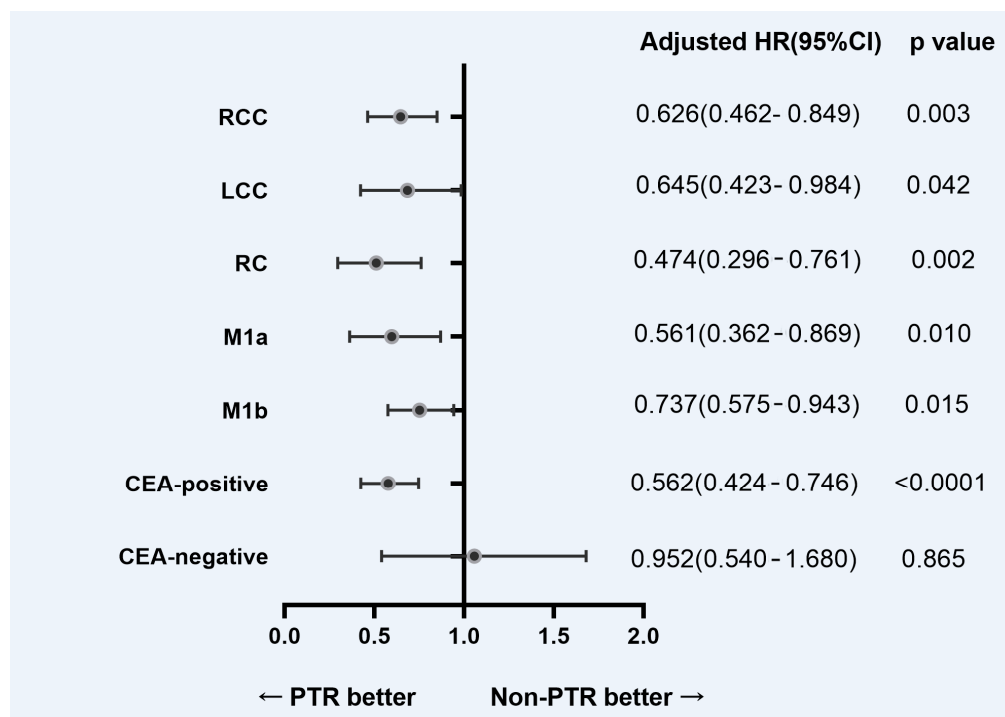


Figure 3. Adjusted hazard ratios for overall survival from the subgroup analysis. Abbreviation: PTR = primary tumor resection; RCC = right colon cancer; LCC = left colon cancer; RC = rectal cancer.

4. Discussion

Brain metastases (BMs) in CRC are uncommon, with an incidence of only 0.3–9% [3,8,20]. The somewhat lower incidence in our cohort (0.26%) can be explained by the fact that our study was limited to synchronous brain metastases, which account for 3.4–43% of brain metastases in CRC [6,20]. The prognosis of CRC patients with brain metastases is very poor, as the median survival is only 3 months (range: 2–9.6 months) [3,8,13,21–25]. Understanding the prognostic variables for BMs is critical for determining survival and treatment options. However, there have been very few studies, and a consensus on treatment for BMs in CRC is lacking. From 2010 to 2016, the SEER database included 581 CRC patients with synchronous BMs. According to a multivariate Cox regression analysis performed in this

study, age, CEA level, and Primary tumor resection were independent risk factors for synchronous BMs in CRC.

A growing amount of research suggests that patients who have their primary tumor removed have a better chance of surviving. In epithelial ovarian and renal cancers, improved survival results linked with surgical debulking have a well established data foundation [26,27]. However, in advanced CRC, the survival benefit of the PTR is debatable, and current NCCN guidelines support PTR only when symptoms are present [28]. According to some clinicians, the improvement in OS is unclear, such that the morbidity and mortality resulting from tumor resection should be avoided as it will delay the start of chemotherapy, which may reduce survival [19,29]. However, some studies have shown that primary tumor resection considerably improves OS [30,31], as demonstrated in our cohort of CRC patients with synchronous brain metastases. In the primary tumor resection group of this study, the 1-year survival rate was 38.8% compared to 20.9% in patients with unresected primary tumors ($p < 0.0001$). To balance the selection bias between the PTR and non-PTR groups, we further analyzed the corresponding subgroups. Our results showed that PTR had a survival benefit regardless of the site of the primary tumor and with or without extracranial metastases. The higher survival rate following PTR can be related to the decrease of cancer stem cells resistant to chemotherapy and the reduction of primary tumor load [32]. PTR significantly lowered the risk of CRC-related complications such as acute bleeding, perforation, and obstruction, which might result in increased surgical mortality and morbidity [33]. Our forest plot of subgroup analysis revealed that PTR improved survival in CEA-positive CRC BMs patients, but it did not affect CEA-negative patients. This suggests that we should be more cautious about whether to perform surgery for the primary tumor in patients with CRC BMs complicated with CEA negative.

Our results also identified age as a significant prognostic factor for brain metastases in CRC. Patients in our study were divided into two age groups: <60 and ≥ 60 years. Patients < 60 years of age had a better prognosis. Yang et al. [34] found a considerably poorer prognosis in patients > 70 years than in those 40 years of age. Quan et al. [13] also defined three age groups among CRC patients: <60 , 60–74, and ≥ 75 years. Similar to our findings, patients ≥ 75 years of age had the poorest prognosis, and those < 60 years had the best prognosis. In another study, older age was also identified as an unfavorable prognostic factor for BMs in CRC [35]. Because the prognosis of patients with CRC and synchronous BMs worsens with age, younger individuals should be treated more aggressively than older patients.

The tumor marker CEA is frequently used to monitor CRC patients during treatment. Among patients with metastatic disease, CEA levels are increased (>5 ng/mL) by $\sim 70\%$ [36,37]. Several studies have reported higher CEA levels at the time of brain metastasis diagnosis in CRC patients [38–41], but only three reported a putative predictive effect [6,13,42]. Consistent with those reports, our study identified CEA as an independent prognostic predictor, with a 1-year survival rate of 26.8% for CEA-positive patients and 40.3% for CEA-negative patients. Thus, CEA positivity is a poor prognostic indicator in CRC patients with brain metastases.

According to our findings, the location of the primary tumor had no prognostic impact in CRC patients with brain metastases. In a univariate analysis, Huerta et al. [43] found that patients with RCC had a poorer survival rate than those with LCC (4.6 vs. 10.7 months; HR 3.5, $p = 0.025$), but in a multivariate Cox regression analysis, the difference was not significant. Another study found that CRC BMs patients with a left-sided primary tumor had a 1.5-fold better prognosis than those with a right-sided primary [14]. Right-sided CRC has a poorer prognosis than left-sided CRC, as evidenced by a greater prevalence of mucinous, undifferentiated, and signet-ring cell tumors, as well as a later stage of cancer at diagnosis [44–46]. The lack of a significant link in our study is most likely because it only focused on synchronous BMs. But a recent meta-analysis revealed that the primary CRC site had little impact on the OS [12]. The effect of primary tumor location on the prognosis of patients with BMs of CRC needs further study. In the univariate Cox

regression performed in our study, extracranial metastases were significantly related to a poor prognosis, but this result was not confirmed in the multivariate Cox regression. Patients with extracranial metastases and numerous BMs have had poor survival results in prior studies [3,47–49]. The survival rate was reduced by up to two-thirds as brain lesions increased [10,11]. CRC patients with synchronous BMs may have a different prognosis risk than those with metachronous BMs. Patients with CRC BMs with a KPS score > 70 had a 4–7 months survival benefit over those with a KPS score < 70 [50–52]. Radiation, surgery, chemotherapy, or a combination of the three were the most prevalent treatments for BMs. Patients who had brain metastasectomy had a longer overall survival time than those who had radiotherapy [12]. Metastasectomy or multiagent chemotherapy has been linked to a higher overall survival rate [53]. Survival was reduced by approximately 80% in BMs that were not amenable to targeted treatment [11]. The presence of PD-L1 in the primary tumor was linked to a reduced chance of survival, whereas RAS and BRAF status were not [49].

Our study had several limitations. First, only patients with synchronous BMs with CRC were included because the SEER database only records the status of BMs at the time of initial diagnosis. Second, the SEER database does not contain information on KPS, the number of BMs, comprehensive treatment of BMs, or molecular markers; hence, these parameters were not included in our analysis.

In conclusion, primary tumor resection (PTR) offers survival benefits to patients with synchronous BMs from CRC. Age, CEA level, and PTR were identified as independent risk factors affecting the survival of CRC patients with synchronous BMs.

Author Contributions: X.C. and Y.L. were responsible for study conception, design of the study, data acquisition, and analysis and interpretation of results. Y.L. and D.C. were responsible for data acquisition. F.Z. and X.X. took part in the discussion of the paper. X.C. wrote the manuscript that was reviewed and revised by F.L. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the Zhejiang Province Natural Science Foundation of China (LY19H160040).

Institutional Review Board Statement: The study was based on a secondary analysis of the previously collected, publicly available, and de-identified data. The SEER database holds no identifying patient information. All data are anonymous.

Informed Consent Statement: Written informed consent was not needed for this study. This investigation was conducted in accordance with ethical standards according to the Declaration of Helsinki and national and international guidelines, and the institutional review board of our hospital approved this study.

Data Availability Statement: The data that support the findings of this study are openly available in the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute at <https://seer.cancer.gov/> (accessed on 15 November 2021).

Conflicts of Interest: The authors declare that they have no competing interest, and all authors confirm accuracy.

Abbreviations

CRC	colorectal cancer
BMs	brain metastases
SEER	Surveillance, Epidemiology, and End Results
CEA	carcinoembryonic antigen
RCC	right colon cancer
LCC	left colon cancer
RC	rectal cancer
CI	confidence interval

References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2018**, *68*, 394–424. [[CrossRef](#)]
2. Van Cutsem, E.; Nordlinger, B.; Cervantes, A.; Group, E.G.W. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. *Ann. Oncol.* **2010**, *21* (Suppl. 5), v93–v97. [[CrossRef](#)]
3. Muller, S.; Kohler, F.; Hendricks, A.; Kastner, C.; Borner, K.; Diers, J.; Lock, J.F.; Petritsch, B.; Germer, C.T.; Wiegner, A. Brain Metastases from Colorectal Cancer: A Systematic Review of the Literature and Meta-Analysis to Establish a Guideline for Daily Treatment. *Cancers* **2021**, *13*, 900. [[CrossRef](#)] [[PubMed](#)]
4. Ferlay, J.; Soerjomataram, I.; Dikshit, R.; Eser, S.; Mathers, C.; Rebelo, M.; Parkin, D.M.; Forman, D.; Bray, F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* **2015**, *136*, E359–E386. [[CrossRef](#)] [[PubMed](#)]
5. Berghoff, A.S.; Schur, S.; Fureder, L.M.; Gatterbauer, B.; Dieckmann, K.; Widhalm, G.; Hainfellner, J.; Zielinski, C.C.; Birner, P.; Bartsch, R.; et al. Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers. *ESMO Open* **2016**, *1*, e000024. [[CrossRef](#)]
6. Noura, S.; Ohue, M.; Shingai, T.; Fujiwara, A.; Imada, S.; Sueda, T.; Yamada, T.; Fujiwara, Y.; Ohigashi, H.; Yano, M.; et al. Brain metastasis from colorectal cancer: Prognostic factors and survival. *J. Surg. Oncol.* **2012**, *106*, 144–148. [[CrossRef](#)] [[PubMed](#)]
7. Tapia Rico, G.; Price, T.J.; Karapetis, C.; Piantadosi, C.; Padbury, R.; Roy, A.; Maddern, G.; Moore, J.; Carruthers, S.; Roder, D.; et al. Brain metastasis in advanced colorectal cancer: Results from the South Australian metastatic colorectal cancer (SAMCRC) registry. *Cancer Biol. Med.* **2017**, *14*, 371–376. [[CrossRef](#)] [[PubMed](#)]
8. Gu, X.D.; Cai, Y.T.; Zhou, Y.M.; Li, Z.Y.; Xiang, J.B.; Chen, Z.Y. Prognostic factors and multidisciplinary treatment modalities for brain metastases from colorectal cancer: Analysis of 93 patients. *BMC Cancer* **2015**, *15*, 902. [[CrossRef](#)] [[PubMed](#)]
9. Bartelt, S.; Momm, F.; Weissenberger, C.; Lutterbach, J. Patients with brain metastases from gastrointestinal tract cancer treated with whole brain radiation therapy: Prognostic factors and survival. *World J. Gastroenterol.* **2004**, *10*, 3345–3348. [[CrossRef](#)] [[PubMed](#)]
10. Cagney, D.N.; Martin, A.M.; Catalano, P.J.; Redig, A.J.; Lin, N.U.; Lee, E.Q.; Wen, P.Y.; Dunn, I.F.; Bi, W.L.; Weiss, S.E.; et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: A population-based study. *Neuro. Oncol.* **2017**, *19*, 1511–1521. [[CrossRef](#)] [[PubMed](#)]
11. Tokoro, T.; Okuno, K.; Hida, J.C.; Ueda, K.; Yoshifuji, T.; Daito, K.; Sugiura, F. Prognostic factors for patients with advanced colorectal cancer and symptomatic brain metastases. *Clin. Colorectal Cancer* **2014**, *13*, 226–231. [[CrossRef](#)]
12. Chang, Y.; Wong, C.E.; Lee, P.H.; Huang, C.C.; Lee, J.S. Survival Outcome of Surgical Resection vs. Radiotherapy in Brain Metastasis From Colorectal Cancer: A Meta-Analysis. *Front. Med.* **2022**, *9*, 768896. [[CrossRef](#)]
13. Quan, J.C.; Guan, X.; Ma, C.X.; Liu, Z.; Yang, M.; Zhao, Z.X.; Sun, P.; Zhuang, M.; Wang, S.; Jiang, Z.; et al. Prognostic scoring system for synchronous brain metastasis at diagnosis of colorectal cancer: A population-based study. *World J. Gastrointest. Oncol.* **2020**, *12*, 195–204. [[CrossRef](#)] [[PubMed](#)]
14. Bergen, E.S.; Scherleitner, P.; Ferreira, P.; Kiesel, B.; Muller, C.; Widhalm, G.; Dieckmann, K.; Prager, G.; Preusser, M.; Berghoff, A.S. Primary tumor side is associated with prognosis of colorectal cancer patients with brain metastases. *ESMO Open* **2021**, *6*, 100168. [[CrossRef](#)] [[PubMed](#)]
15. Vogelbaum, M.A.; Suh, J.H. Resectable brain metastases. *J. Clin. Oncol.* **2006**, *24*, 1289–1294. [[CrossRef](#)] [[PubMed](#)]
16. Palmer, J.D.; Trifiletti, D.M.; Gondi, V.; Chan, M.; Minniti, G.; Rusthoven, C.G.; Schild, S.E.; Mishra, M.V.; Bovi, J.; Williams, N.; et al. Multidisciplinary patient-centered management of brain metastases and future directions. *Neurooncol. Adv.* **2020**, *2*, vdaa034. [[CrossRef](#)]
17. Wilkinson, K.J.; Chua, W.; Ng, W.; Roohullah, A. Management of asymptomatic primary tumours in stage IV colorectal cancer: Review of outcomes. *World J. Gastrointest. Oncol.* **2015**, *7*, 513–523. [[CrossRef](#)]
18. Ruo, L.; Gougoutas, C.; Paty, P.B.; Guillem, J.G.; Cohen, A.M.; Wong, W.D. Elective bowel resection for incurable stage IV colorectal cancer: Prognostic variables for asymptomatic patients. *J. Am. Coll. Surg.* **2003**, *196*, 722–728. [[CrossRef](#)]
19. Poultsides, G.A.; Servais, E.L.; Saltz, L.B.; Patil, S.; Kemeny, N.E.; Guillem, J.G.; Weiser, M.; Temple, L.K.; Wong, W.D.; Paty, P.B. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J. Clin. Oncol.* **2009**, *27*, 3379–3384. [[CrossRef](#)]
20. Mege, D.; Ouaiissi, M.; Fuks, D.; Metellus, P.; Peltier, J.; Dufour, H.; Regimbeau, J.M.; Dahan, L.; Sieleznoff, I.; Sastre, B. Patients with brain metastases from colorectal cancer are not condemned. *Anticancer. Res.* **2013**, *33*, 5645–5648.
21. Prasanna, T.; Karapetis, C.S.; Roder, D.; Tie, J.; Padbury, R.; Price, T.; Wong, R.; Shapiro, J.; Nott, L.; Lee, M.; et al. The survival outcome of patients with metastatic colorectal cancer based on the site of metastases and the impact of molecular markers and site of primary cancer on metastatic pattern. *Acta Oncol.* **2018**, *57*, 1438–1444. [[CrossRef](#)] [[PubMed](#)]
22. Boysen, A.K.; Ording, A.G.; Astradsson, A.; Hoyer, M.; Spindler, K.L. Metastasis directed treatment of brain metastases from colorectal cancer—A Danish population-based cohort study. *Acta Oncol.* **2020**, *59*, 1118–1122. [[CrossRef](#)]
23. Kruser, T.J.; Chao, S.T.; Elson, P.; Barnett, G.H.; Vogelbaum, M.A.; Angelov, L.; Weil, R.J.; Pelley, R.; Suh, J.H. Multidisciplinary management of colorectal brain metastases: A retrospective study. *Cancer* **2008**, *113*, 158–165. [[CrossRef](#)] [[PubMed](#)]
24. Damiens, K.; Ayoub, J.P.; Lemieux, B.; Aubin, F.; Saliba, W.; Campeau, M.P.; Tehfe, M. Clinical features and course of brain metastases in colorectal cancer: An experience from a single institution. *Curr. Oncol.* **2012**, *19*, 254–258. [[CrossRef](#)] [[PubMed](#)]

25. Fountzilias, C.; Chang, K.; Hernandez, B.; Michalek, J.; Crownover, R.; Floyd, J.; Mahalingam, D. Clinical characteristics and treatment outcomes of patients with colorectal cancer who develop brain metastasis: A single institution experience. *J. Gastrointest. Oncol.* **2017**, *8*, 55–63. [[CrossRef](#)]
26. van der Burg, M.E.; van Lent, M.; Buyse, M.; Kobierska, A.; Colombo, N.; Favalli, G.; Lacave, A.J.; Nardi, M.; Renard, J.; Pecorelli, S. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N. Engl. J. Med.* **1995**, *332*, 629–634. [[CrossRef](#)]
27. Flanigan, R.C.; Salmon, S.E.; Blumenstein, B.A.; Bearman, S.I.; Roy, V.; McGrath, P.C.; Caton, J.R., Jr.; Munshi, N.; Crawford, E.D. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N. Engl. J. Med.* **2001**, *345*, 1655–1659. [[CrossRef](#)]
28. Benson, A.B.; Venook, A.P.; Al-Hawary, M.M.; Arain, M.A.; Chen, Y.J.; Ciombor, K.K.; Cohen, S.; Cooper, H.S.; Deming, D.; Farkas, L.; et al. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Canc. Netw.* **2021**, *19*, 329–359. [[CrossRef](#)]
29. Sarella, A.I.; Guthrie, J.A.; Seymour, M.T.; Ride, E.; Guillou, P.J.; O’Riordain, D.S. Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer. *Br. J. Surg.* **2001**, *88*, 1352–1356. [[CrossRef](#)]
30. Ahmed, S.; Leis, A.; Fields, A.; Chandra-Kanthan, S.; Haider, K.; Alvi, R.; Reeder, B.; Pahwa, P. Survival impact of surgical resection of primary tumor in patients with stage IV colorectal cancer: Results from a large population-based cohort study. *Cancer* **2014**, *120*, 683–691. [[CrossRef](#)]
31. Stillwell, A.P.; Buettner, P.G.; Ho, Y.H. Meta-analysis of survival of patients with stage IV colorectal cancer managed with surgical resection versus chemotherapy alone. *World J. Surg.* **2010**, *34*, 797–807. [[CrossRef](#)] [[PubMed](#)]
32. Xu, H.; Xia, Z.; Jia, X.; Chen, K.; Li, D.; Dai, Y.; Tao, M.; Mao, Y. Primary Tumor Resection Is Associated with Improved Survival in Stage IV Colorectal Cancer: An Instrumental Variable Analysis. *Sci. Rep.* **2015**, *5*, 16516. [[CrossRef](#)] [[PubMed](#)]
33. Sterpetti, A.V.; Costi, U.; D’Ermo, G. National statistics about resection of the primary tumor in asymptomatic patients with Stage IV colorectal cancer and unresectable metastases. Need for improvement in data collection. A systematic review with meta-analysis. *Surg. Oncol.* **2020**, *33*, 11–18. [[CrossRef](#)] [[PubMed](#)]
34. Yang, L.; He, W.; Xie, Q.; Liu, S.; Kong, P.; Jiang, C.; Zhang, B.; Xia, L. Brain metastases in newly diagnosed colorectal cancer: A population-based study. *Cancer Manag. Res.* **2018**, *10*, 5649–5658. [[CrossRef](#)]
35. Farnell, G.F.; Buckner, J.C.; Cascino, T.L.; O’Connell, M.J.; Schomberg, P.J.; Suman, V. Brain metastases from colorectal carcinoma. The long term survivors. *Cancer* **1996**, *78*, 711–716. [[CrossRef](#)]
36. Duffy, M.J.; Lamerz, R.; Haglund, C.; Nicolini, A.; Kalousova, M.; Holubec, L.; Sturgeon, C. Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update. *Int. J. Cancer* **2014**, *134*, 2513–2522. [[CrossRef](#)]
37. Tampellini, M.; Ottone, A.; Alabiso, I.; Baratelli, C.; Forti, L.; Berruti, A.; Aroasio, E.; Scagliotti, G.V. The prognostic role of baseline CEA and CA 19-9 values and their time-dependent variations in advanced colorectal cancer patients submitted to first-line therapy. *Tumor Biol.* **2015**, *36*, 1519–1527. [[CrossRef](#)]
38. Cascino, T.L.; Leavengood, J.M.; Kemeny, N.; Posner, J.B. Brain metastases from colon cancer. *J. Neurooncol.* **1983**, *1*, 203–209. [[CrossRef](#)]
39. Tanriverdi, O.; Kaytan-Saglam, E.; Ulger, S.; Bayoglu, I.V.; Turker, I.; Ozturk-Topcu, T.; Cokmert, S.; Turhal, S.; Oktay, E.; Karabulut, B.; et al. The clinical and pathological features of 133 colorectal cancer patients with brain metastasis: A multicenter retrospective analysis of the Gastrointestinal Tumors Working Committee of the Turkish Oncology Group (TOG). *Med. Oncol.* **2014**, *31*, 152. [[CrossRef](#)]
40. Kye, B.H.; Kim, H.J.; Kang, W.K.; Cho, H.M.; Hong, Y.K.; Oh, S.T. Brain metastases from colorectal cancer: The role of surgical resection in selected patients. *Colorectal Dis.* **2012**, *14*, e378–e385. [[CrossRef](#)]
41. Christensen, T.D.; Spindler, K.L.; Palshof, J.A.; Nielsen, D.L. Systematic review: Brain metastases from colorectal cancer—Incidence and patient characteristics. *BMC Cancer* **2016**, *16*, 260. [[CrossRef](#)] [[PubMed](#)]
42. Mo, S.; Cai, X.; Zhou, Z.; Li, Y.; Hu, X.; Ma, X.; Zhang, L.; Cai, S.; Peng, J. Nomograms for predicting specific distant metastatic sites and overall survival of colorectal cancer patients: A large population-based real-world study. *Clin. Transl. Med.* **2020**, *10*, 169–181. [[CrossRef](#)] [[PubMed](#)]
43. Del Carpio Huerta, L.; Virgili Manrique, A.C.; Szafranska, J.; Martin-Richard, M.; Paez Lopez-Bravo, D.; Sebio Garcia, A.; Espinosa Mariscal, I.; Gomila Pons, P.; Andres Granyo, M.; Barba Joaquin, A.; et al. Brain metastases in colorectal cancer: Prognostic factors and survival analysis. *Int. J. Colorectal Dis.* **2018**, *33*, 1517–1523. [[CrossRef](#)] [[PubMed](#)]
44. Missiaglia, E.; Jacobs, B.; D’Ario, G.; Di Narzo, A.F.; Sonesson, C.; Budinska, E.; Popovici, V.; Vecchione, L.; Gerster, S.; Yan, P.; et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. *Ann. Oncol.* **2014**, *25*, 1995–2001. [[CrossRef](#)] [[PubMed](#)]
45. Zheng, C.; Jiang, F.; Lin, H.; Li, S. Clinical characteristics and prognosis of different primary tumor location in colorectal cancer: A population-based cohort study. *Clin. Transl. Oncol.* **2019**, *21*, 1524–1531. [[CrossRef](#)]
46. Renzi, G.D.; Gaballo, G.; Gazzaniga, P.; Nicolazzo, C.J.O. Molecular Biomarkers according to Primary Tumor Location in Colorectal Cancer: Current Standard and New Insights. *Oncology* **2021**, *99*, 135–143. [[CrossRef](#)]

47. Roussille, P.; Auvray, M.; Vansteene, D.; Lecomte, T.; Rigault, E.; Maillet, M.; Locher, C.; Dior, M.; Hautefeuille, V.; Artru, P.; et al. Prognostic factors of colorectal cancer patients with brain metastases. *Radiother. Oncol.* **2021**, *158*, 67–73. [[CrossRef](#)]
48. Imaizumi, J.; Shida, D.; Narita, Y.; Miyakita, Y.; Tanabe, T.; Takashima, A.; Boku, N.; Igaki, H.; Itami, J.; Kanemitsu, Y. Prognostic factors of brain metastases from colorectal cancer. *BMC Cancer* **2019**, *19*, 755. [[CrossRef](#)]
49. Roussille, P.; Tachon, G.; Villalva, C.; Milin, S.; Frouin, E.; Godet, J.; Berger, A.; Emambux, S.; Petropoulos, C.; Wager, M.; et al. Pathological and Molecular Characteristics of Colorectal Cancer with Brain Metastases. *Cancers* **2018**, *10*, 504. [[CrossRef](#)]
50. Lu, X.; Cai, Y.; Xia, L.; Ju, H.; Zhao, X. Treatment modalities and relative survival in patients with brain metastasis from colorectal cancer. *Biosci. Trends* **2019**, *13*, 182–188. [[CrossRef](#)]
51. Quan, J.; Ma, C.; Sun, P.; Wang, S.; Zhuang, M.; Liu, Z.; Jiang, Z.; Chen, H.; Yang, M.; Zhao, Z.; et al. Brain metastasis from colorectal cancer: Clinical characteristics, timing, survival and prognostic factors. *Scand. J. Gastroenterol.* **2019**, *54*, 1370–1375. [[CrossRef](#)] [[PubMed](#)]
52. Mjahed, R.B.; Astaras, C.; Roth, A.; Koessler, T. Where Are We Now and Where Might We Be Headed in Understanding and Managing Brain Metastases in Colorectal Cancer Patients? *Curr. Treat. Options Oncol.* **2022**, *23*, 980–1000. [[CrossRef](#)] [[PubMed](#)]
53. Goksu, S.Y.; Beg, M.S.; Sanjeevaiah, A.; Gumusgoz, E.; Hsieh, D.; Ozer, M.; Jones, A.L.; Kainthla, R.; Verma, U.; Al Mutar, S.; et al. The pattern of brain metastasis in colorectal cancer: Efficacy of metastasectomy, chemotherapy. *J. Clin. Oncol.* **2021**, *39*, 40. [[CrossRef](#)]