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Efficacy of Primary Tumor Resection in Metastatic Colorectal Cancer

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Statistical Analysis C
Data Interpretation D
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Background: The aim of this study was to evaluate the survival benefit of palliative primary tumor resection in colorectal cancer (CRC) patients with unresectable metastases.


Material/Methods: Clinicopathological characteristics of eligible patients who underwent surgery to remove the primary tumor and those who did not between 2004 and 2013 were compared. We also evaluated the association between survival and different clinicopathologic characteristics in metastatic CRC.

Results: The percentage of patients undergoing surgical resection of the primary tumor was higher during the earlier years and trended toward less use of surgery in later years. Palliative primary tumor resection was strongly associated with better cause-specific survival (hazard ratio=0.403, 95% confidence interval=0.389 to 0.417, $P<0.001$).

Conclusions: We added new strong evidence supporting the survival benefit of palliative resection, which should be confirmed in future randomized controlled trials.

MeSH Keywords: **Colorectal Neoplasms • Neoplasm Metastasis • Neoplasms, Unknown Primary • Palliative Care**

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Background

Colorectal cancer (CRC) is one of the commonest malignant tumors worldwide. Approximately 25% of patients are diagnosed with metastatic disease and another 25% develop metachronous metastases [1].

It is estimated that 75–90% of metastatic CRC patients have incurable synchronous metastases and require palliative management [2]. Although surgical resection has a vital role in earlier stages of colorectal disease, surgical resection of the primary tumor is not considered curative unless done with resection of the metastatic sites [2].

With regard to CRC patients with unresectable metastases, palliative resection or other treatment is necessary in people presenting with symptoms correlated with the primary colorectal tumor such as bleeding, perforation, obstruction, etc. However, a large percentage of CRC patients with unresectable metastases are asymptomatic [3].

To varying degrees, many previous studies [1,3–12] supported the survival benefit of palliative primary tumor resection; however, both the overall and cancer-specific survival benefit of operative treatment of the primary colorectal tumor are uncertain [13,14]. Moreover, operative treatment of the primary tumor is associated with some postoperative complications and delays life-prolonging systemic chemotherapy [15]. Therefore, whether those patients should receive palliative primary tumor resection is still controversial.

Unfortunately, retrospective analyses with large sample sizes on oncologic outcomes of unresectable metastatic CRC patients who did and did not undergo palliative resection of the primary tumor are scarce. Therefore, this large population-based study using the newly released Surveillance, Epidemiology, and End Results (SEER) database is necessary and of clinical significance.

Material and Methods

Patient selection and data source

In this study, data were collected from the SEER program of the U.S. National Cancer Institute (NCI). As an authoritative and the largest population-based publicly available cancer data set, the SEER program collects patient demographic information, cancer diagnostic information, and outcomes from 18 cancer registries in the United States, thus covering approximately 26% of the U.S. population.

Data extraction was performed using SEER*Stat software version 8.3.5 and the flow chart for patient selection is shown in

Figure 1. We obtained data including age at diagnosis (years), tumor location (colon and rectum), American Joint Committee on Cancer (AJCC) tumor (T) stage (T1, T2, T3, T4, and unknown), AJCC lymph node (N) stage (N0, N1, N2, and unknown), race (white, black, and other), gender (male and female), year of diagnosis (2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, and 2013), and chemotherapy. For tumor stage, all patients selected from the SEER database were divided into two groups on the basis of the 7th edition AJCC TN-metastases (M) staging system for colorectal carcinoma.

At first, 69 850 patients diagnosed with stage IV CRC between January 1, 2004 and December 31, 2013 were identified from the SEER database. We chose to include these years for the two reasons: (1) because AJCC got the updated edition at 2004, our analyses included patients diagnosed with CRC starting from 2004; (2) we wanted to allow for adequate follow-up time, and therefore, we excluded patients diagnosed after 2013.

Those patients with a lack of positive histological confirmation, with nonadenocarcinoma histologies, no active follow-up, or unknown race were excluded from our analyses. Those with no surgery on distant metastatic sites were identified. A total of 48 126 CRC patients who presented with unresectable metastases was included in the present study.

Statistical analyses

The clinicopathologic characteristics of CRC patients with unresectable metastases who underwent surgery to remove the primary tumor and those who did not were compared using Pearson's chi-square test. Cox proportional hazards models were applied to estimate the independent effects of the prognostic variables. In our analyses, the clinicopathologic characteristics that showed prognostic significance (log rank, $P < 0.20$) in univariate Cox analysis were entered in the multivariate Cox analysis, including age at diagnosis, tumor location, T stage, N stage, race, gender, year at diagnosis, and chemotherapy. All the hazard ratios (HR) were shown with confidence intervals (CI), which were set as 95%.

We also evaluated the association between survival and different clinicopathologic characteristics using the methods of Kaplan-Meier. The log-rank tests were used to assess statistical significance. All tests were two sided, and $P < 0.05$ indicated statistical significance. The primary outcome of interest used in our study was cause-specific survival (CSS), which was calculated from the date of diagnosis to the date of colon cancer death; patients who died of other causes were removed from the study at the date of death. Overall survival (OS) was also used to validate our findings, which was calculated from the time of diagnosis to the end of the follow-up time. Statistical analyses were performed using SPSS version 22.0 (Statistic Package for Social Science, Chicago, IL).

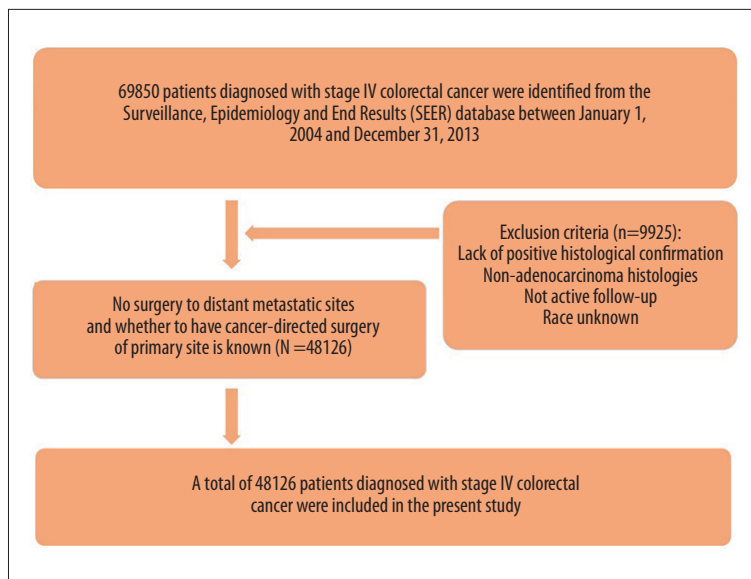


Figure 1. Flow chart for selecting colorectal cancer patients with unresectable metastases from the Surveillance, Epidemiology, and End Results database.

Results

Clinical characteristics of the overall cohort

In all, 48 126 CRC patients with unresectable metastases were included in the present study. Among them, there were 26 501 males (55.1%) and 21 625 females (44.9%). The median age was 66 years, as expected (51–70 years) [4,10,12]. Of the patients, 26 606 (55.3%) received primary tumor resection and 21 520 patients (44.7%) did not. The median OS time of the whole cohort was 12 months, and 34 099 patients (70.9%) died of CRC at the end of the follow-up time.

Table 1 shows the comparison of the baseline clinicopathologic characteristics of the whole cohort. Overall, approximately 55.3% of CRC patients who presented with unresectable metastases received palliative primary tumor resection. Patients who underwent palliative primary tumor resection tended to be younger than those who did not ($P<0.001$). For patients who underwent resection, the mean age was 66 years, compared with 67 years for those who did not. The likelihood of palliative primary tumor resection correlated with the anatomical location of the colorectal tumor. Patients with colon cancer were more likely to undergo primary tumor resection than patients with rectal cancer. CRC patients with higher T or N stage were associated with higher possibility of undergoing palliative primary tumor resection ($P<0.001$).

Race was associated with the rate of undergoing a surgical resection of the primary colorectal tumor. White people are more likely to receive this surgery, whereas black people are less likely to receive it, which might be mainly due to the higher poverty rate among blacks relative to whites. There were more males (26 501) than females (21 625) diagnosed with

CRC with unresectable metastases. With regard to the whole cohort in our study, the percentage of patients undergoing surgical resection of the primary tumor was higher during the earlier years and trended toward less use of surgery in later years (65.0% for 2004, 62.9% for 2005, 62.2% for 2006, 58.2% for 2007, 56.9% for 2008, 52.5% for 2009, 53.1% for 2010, 49.8% for 2011, 47.7% for 2012, 45.9% for 2013; Figure 2).

Resection of the primary tumor was strongly associated with better survival in CRC with unresectable metastases

In our analyses, Kaplan-Meier CSS and OS curves were used to analyze the prognosis of CRC with unresectable primary tumor. As shown as Figure 3, patients with palliative primary tumor resection presented with obviously better CSS compared with those who did not. The median CSS time of patients with resection of the primary tumor was 24 months, with a 3-year CSS rate of 34.6% and a 5-year CSS rate of 20.8%; for patients who did not receive palliative primary tumor resection, however, the median CSS time was only 11 months, with a 3-year CSS rate of 13.4% and a 5-year CSS rate of 5.82%. It was also found that patients with resection of the primary tumor presented with obviously better OS compared with those who did not (Figure 4). With regard to the whole cohort, the median OS time was 12 months. The median OS time of patients with palliative primary tumor resection was 18 months, with a 3-year OS rate of 25.24% and a 5-year OS rate of 13.28%; for patients who did not receive resection of the primary tumor, however, the median OS time was only 7 months, with a 3-year OS rate of 7.64% and a 5-year OS rate of 2.72%.

Cox proportional hazards models were conducted to identify the variables independently associated with CSS and OS in the overall cohort. The results of multivariate Cox regression

Table 1. The comparison of clinicopathologic characteristics of the whole cohort from the SEER database.

Characteristics	No. of patients (%)		P
	No surgery of primary site (N=21520)	Surgery of primary site (N=26606)	
Age at diagnosis (years)			<0.001
<65	10150 (47.2)	13068 (49.1)	
≥65	11370 (52.8)	13548 (50.9)	
Tumor location			<0.001
Colon	13458 (62.5)	21362 (80.3)	
Rectum	8062 (37.5)	5244 (19.7)	
T stage			<0.001
T1	3645 (16.9)	685 (2.6)	
T2	235 (1.1)	829 (3.1)	
T3	2494 (11.6)	15351 (57.7)	
T4	3217 (14.9)	9195 (34.6)	
Unknown	11929 (55.4)	546 (2.1)	
N stage			<0.001
N0	8798 (40.9)	5460 (20.5)	
N1	4528 (21.0)	8699 (32.7)	
N2	633 (2.9)	11941 (44.9)	
Unknown	7561 (35.1)	506 (1.9)	
Race			<0.001
White	16338 (75.9)	20646 (77.6)	
Black	3430 (15.9)	3724 (14.0)	
Other	1752 (8.1)	2236 (8.4)	
Gender			<0.001
Male	12228 (56.8)	14273 (53.6)	
Female	9292 (43.2)	12333 (46.4)	
Year of diagnosis			<0.001
2004	1671 (7.8)	3101 (11.7)	
2005	1697 (7.9)	2872 (10.8)	
2006	1780 (8.3)	2934 (11.0)	
2007	1979 (9.2)	2758 (10.4)	
2008	2077 (9.7)	2740 (10.3)	
2009	2281 (10.6)	2520 (9.5)	
2010	2277 (10.6)	2581 (9.7)	
2011	2495 (11.6)	2472 (9.3)	
2012	2586 (12.0)	2361 (8.9)	
2013	2677 (12.4)	2267 (8.5)	
Chemotherapy			<0.001
No	9333 (43.4)	10464 (39.3)	
Yes	12187 (56.6)	16142 (60.7)	

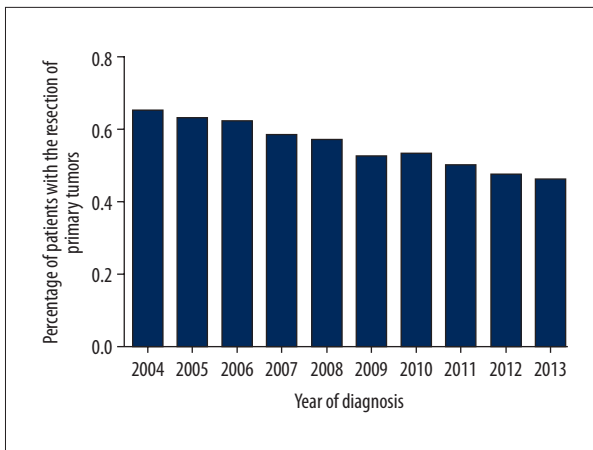


Figure 2. Percentage of patients with resection of primary colorectal tumors from 2004 to 2013.

analyses of CSS in the whole cohort are detailed in Table 2. After adjusting for known prognostic factors, younger age, rectal cancer, T2–3 stages, lower N stage, being white, later years of diagnosis, and chemotherapy were thought to be independently associated with better CSS ($P<0.05$). More important, palliative primary tumor resection was found to be strongly associated with better CSS (HR=0.403, 95% CI=0.389–0.417,

$P<0.001$). The results of multivariate Cox regression analyses of OS in the whole cohort are detailed in Table 3, which also validated the aforementioned results. After adjusting for known prognostic factors, younger age, rectal cancer, T2–3 stages, lower N stage, being white, later years of diagnosis, and chemotherapy were thought to be independently associated with better OS ($P<0.05$). Similarly, palliative primary tumor resection was found to be strongly associated with better OS (HR=0.430, 95% CI=0.417–0.443, $P<0.001$).

Discussion

Some patients with stage IV CRC could undergo surgical treatment of both primary and metastatic sites, yet the majority of these patients has unresectable metastatic disease. Operative treatment of the primary colorectal tumor is frequently performed in people presenting with symptoms correlated with the primary tumor such as bleeding, perforation, obstruction, etc. As far as we know, only one prospective study focused on the survival benefit of palliative primary tumor resection. It was published as an abstract and showed that primary tumor resection followed by chemotherapy had no survival benefit over chemotherapy alone; however, the clinical value of

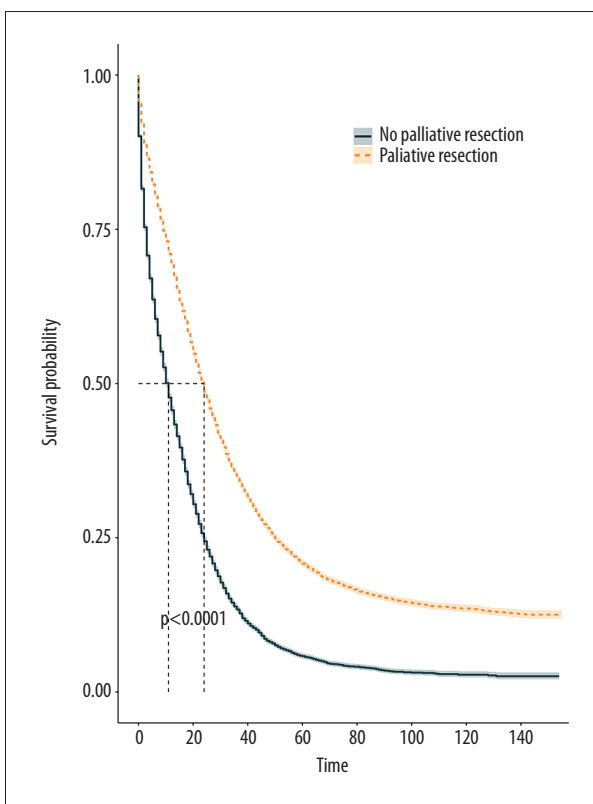


Figure 3. Cancer-specific survival curves of colorectal cancer patients with and without palliative resection of the primary tumors using Kaplan-Meier methods.

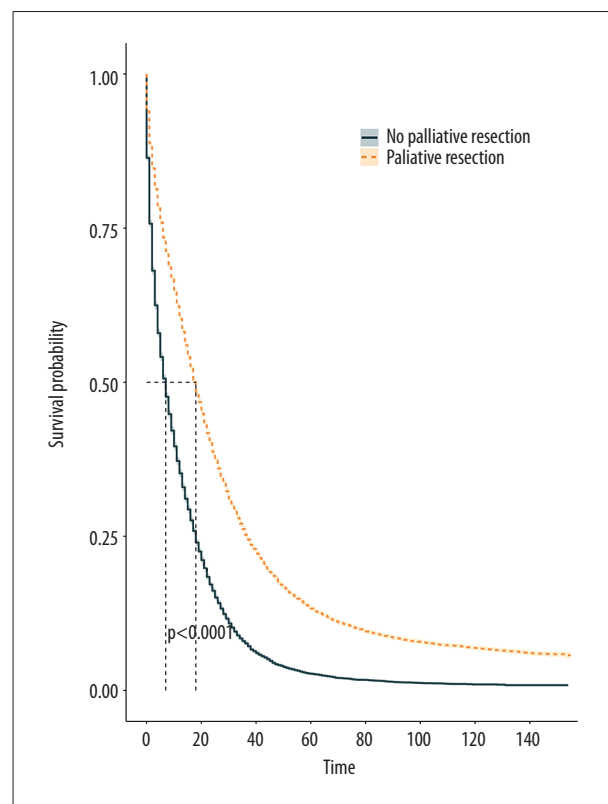


Figure 4. Overall survival curves of colorectal cancer patients with and without palliative resection of the primary tumors using Kaplan-Meier methods.

Table 2. The results of multivariate Cox regression analyses of CSS in the whole cohort.

Variable	Reference	Characteristic	Cancer-specific survival		
			HR (95% CI)	SE	P value
Age at diagnosis	<65	≥65	1.160 (1.134–1.186)	0.011	<0.001
Tumor location	Colon	Rectum	0.808 (0.788–1.829)	0.013	<0.001
Surgery of the primary tumor	No	Yes	0.403 (0.389–0.417)	0.017	<0.001
T stage	T1	T2	0.686 (0.627–0.750)	0.046	<0.001
		T3	0.908 (0.868–0.951)	0.023	<0.001
		T4	1.163 (1.112–1.217)	0.023	<0.001
		Unknown	1.105 (1.059–1.153)	0.022	<0.001
N stage	N0	N1	1.245 (1.208–1.283)	0.015	<0.001
		N2	1.741 (1.684–1.800)	0.017	<0.001
		Unknown	1.152 (1.112–1.194)	0.018	<0.001
Race	White	Black	1.138 (1.104–1.172)	0.015	<0.001
		Other	0.954 (0.917–0.991)	0.020	0.016
Gender	Male	Female	1.015 (0.993–1.037)	0.011	0.184
Year of diagnosis	2004	2005	1.021 (0.974–1.070)	0.024	0.385
		2006	0.980 (0.935–1.027)	0.024	0.391
		2007	0.982 (0.937–1.030)	0.024	0.461
		2008	0.946 (0.903–0.992)	0.024	0.022
		2009	0.887 (0.846–0.930)	0.024	<0.001
		2010	0.893 (0.851–0.936)	0.024	<0.001
		2011	0.954 (0.910–1.000)	0.024	0.050
		2012	0.867 (0.827–0.910)	0.024	<0.001
		2013	0.869 (0.828–0.913)	0.025	<0.001
Chemotherapy	No	Yes	0.488 (0.477–0.500)	0.012	<0.001

surgical resection in asymptomatic patients has long been controversial [16,17].

On the one hand, palliative primary tumor resection has been reported to be associated with 20 to 30% risk of postoperative morbidity and 1 to 6% risk of perioperative mortality [5,18]. The operative treatment could also delay the implementation of other life-prolonging therapy [19,20].

On the other hand, it was reported that surgery could not only prevent local symptoms but also reduce overall tumor burden [5,20,21]. Although certain studies [22] hold the view that resection of the primary tumor would not improve the prognosis of CRC patients, many previous studies support the survival benefit of palliative primary tumor resection [1,3–5,7–11,14]. In 2016, a large population-based study [23] in the Netherlands showed an overall survival benefit for patients with incurable

stage IV CRC who underwent primary tumor resection as the initial treatment after diagnosis. The median overall survival was 17.2 months (95% CI 16.3–18.1) for patients with primary tumor resection and 11.5 months (95% CI 11.0–12.0) for patients without primary tumor resection. The results of Cox regression analysis in this study showed that primary tumor resection was associated with 56% reduced risk of overall mortality (HR=0.44 [95% CI 0.35–0.55], $P<0.001$). Recently, van Rooijen et al. [20] conducted an analysis with individual patient data of 3423 patients enrolled into 8 randomized controlled trials that also demonstrated an improved survival of CRC patients with incurable synchronous metastases who underwent primary tumor resection.

To our knowledge, the present study is the largest retrospective and population-based study (48 126 CRC patients included) focused on the survival benefit of palliative primary tumor

Table 3. The results of multivariate Cox regression analyses of OS in the whole cohort.

Variable	Reference	Characteristic	Cancer-specific survival		
			HR (95% CI)	SE	P value
Age at diagnosis	<65	≥65	1.397 (1.370–1.425)	0.010	<0.001
Tumor location	Colon	Rectum	0.811 (0.793–0.829)	0.011	<0.001
Surgery of the primary tumor	No	Yes	0.430 (0.417–0.443)	0.015	<0.001
T stage	T1	T2	0.733 (0.681–0.790)	0.038	<0.001
		T3	0.889 (0.854–0.925)	0.020	<0.001
		T4	1.122 (1.079–1.168)	0.020	<0.001
		Unknown	1.078 (1.039–1.119)	0.019	<0.001
		N stage	N0	N1	1.188 (1.158–1.220)
N stage	N0	N2	1.594 (1.548–1.641)	0.015	<0.001
		Unknown	1.142 (1.107–1.178)	0.016	<0.001
		Race	White	Black	1.108 (1.079–1.138)
Race	White	Other	0.914 (0.883–0.946)	0.018	<0.001
		Gender	Male	Female	0.985 (0.967–1.004)
Year of diagnosis	2004	2005	1.024 (0.982–1.067)	0.021	0.262
		2006	0.989 (0.949–1.030)	0.021	0.595
		2007	1.000 (0.959–1.042)	0.021	0.995
		2008	0.987 (0.947–1.029)	0.021	0.535
		2009	0.924 (0.887–0.963)	0.021	<0.001
		2010	0.932 (0.894–0.971)	0.021	0.001
		2011	0.977 (0.938–1.019)	0.021	0.282
		2012	0.911 (0.873–0.950)	0.021	<0.001
		2013	0.904 (0.866–0.943)	0.022	<0.001
Chemotherapy	No	Yes	0.459 (0.450–0.468)	0.010	<0.001

resection in CRC patients with unresectable metastases using the newly released SEER database. In the present study, the less use of primary tumor resection in later years might result from the major advances that have been made in systemic treatment of metastatic CRC [1]. Moreover, the larger use of endoscopic stents might also account for the phenomenon, but the SEER database provides no data on this, which is a limitation of our study. Kaplan-Meier CSS curves showed that patients with resection of the primary tumor was associated with longer median CSS time and higher 5-year CSS rate. The results of multivariate Cox regression analyses also showed that patients with primary tumor resection had 59.7% reduced risk of cause-specific mortality. In addition, using Cox proportional hazard and Kaplan-Meier methods, we provide data regarding OS to validate our analyses. The median OS time of patients with palliative primary tumor resection was 18 months, with a 3-year OS rate of 25.24% and a 5-year OS

rate of 13.28%; for patients that did not receive resection of the primary tumor, however, the median OS time was only 7 months, with a 3-year OS rate of 7.64% and a 5-year OS rate of 2.72%. Palliative primary tumor resection was also found to be associated with 57% reduced risk of overall mortality, which is consistent with the aforementioned large population-based study from the Netherlands.

The clinical value of primary tumor resection should be confirmed by large and well-designed randomized controlled trials. As far as we know, several currently ongoing randomized controlled trials aim to compare prognosis of metastatic CRC plus resection with nonresection of the primary tumor. These studies include the CAIRO4 study, the SYNCHRONOUS trial, and the GRECCAR8 [24]. We hope these provide better evidence on the survival benefit of palliative resection of primary tumor in CRC patients with unresectable metastases.

The main strength of the present study was that, as the largest retrospective and population-based study regarding the clinical value of palliative primary tumor resection in CRC patients with unresectable metastases, using the authoritative and largest population-based publicly available cancer data set in the United States, we found that primary tumor resection was associated with significantly reduced risk of cause-specific mortality and added new strong evidence supporting the survival benefit of palliative resection.

However, our study also has some limitations. First, some prognostic factors are not available in the SEER database, such as tumor recurrence, mismatch repair status, BRAF V600E mutation, American Society of Anesthesiologists grade, Charlson comorbidity index, and so on, which could introduce biases to some extent [25]. Second, it is also unclear whether the primary tumor truly caused no symptoms, which might have influenced the selection of patients receiving the resection of the primary tumor. Third, because of the limitation of the SEER database,

we cannot provide analyses of the chemotherapy schemes and durations. Finally, the present study was merely based on retrospective data; higher-grade evidence of survival benefit of the palliative primary colorectal tumor resection are needed, such as prospective research with well-matched patient cohorts.

Conclusions

As the largest retrospective and population-based study of the clinical value of palliative primary tumor resection in CRC patients with unresectable metastases, we used the newly released SEER database to provide new strong evidence supporting the survival benefit of palliative resection, which should be confirmed in future randomized controlled trials.

Conflict of interest

None.

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