Subdivision of metastatic colorectal cancer for identifying patients who benefit more from primary tumor resection

Dakui Luo

Fudan University Shanghai Cancer Center

Zezhi Shan

Fudan University Shanghai Cancer Center

Qi Liu

Fudan University Shanghai Cancer Center

Sanjun Cai

Fudan University Shanghai Cancer Center

Qingguo Li

Fudan University Shanghai Cancer Center

Xinxiang Li (✉ 1149lxx@sina.com)

Fudan University Shanghai Cancer Center <https://orcid.org/0000-0002-5902-3659>

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Abstract

Background

Stage IV colorectal cancer (CRC) patients are heterogeneous with distinctive clinicopathologic features and prognosis. Radical resection of primary tumor and distant metastases is associated with improved survival outcomes in metastatic CRC. The value of palliative primary tumor resection is controversial. The present study explored which subgroups benefited more from primary tumor resection in metastatic CRC.

Methods

Between 2004 and 2015, patients with metastatic CRC were identified using the surveillance, epidemiology, and end results (SEER) database. Uni- and multivariable Cox regression analysis were performed to identify factors associated with decreased cancer-specific mortality. The subgroups were divided based on the independent prognostic factors.

Results

Age, marital status, race, serum CEA, histologic type, differentiation, tumor location, surgery of primary or metastatic lesion, site of metastases, number of metastatic sites, chemotherapy and radiotherapy were identified as independent prognostic factors. Patients with non-white race, normal serum CEA, non-signet ring cell carcinoma, well or moderate differentiation, surgery of metastases, isolated liver metastasis, single metastasis, receiving chemotherapy or radiotherapy presented more survival benefit from primary tumor resection.

Conclusion

Subgroup of metastatic CRC optimizes decision-making and selected patients will benefit more from primary tumor resection.

Introduction

Colorectal cancer (CRC) is one of the most common malignant diseases globally[1, 2]. Approximately half of CRC patients developed distant metastases and over 80% of these patients have unresectable metastases[3–5]. The most common site of involvement is liver that accounted for more than one third of the total population[6].

Patients with a resectable primary and distant metastases could be managed with a staged or simultaneous resection and systemic chemotherapy. Cure is possible for these patients. However, for patients with unresectable metastases, palliative primary tumor resection is only required to manage

bleeding, obstruction or perforation. The value of palliative primary tumor resection in patients with asymptomatic primary tumors and unresectable metastatic disease is still under debate. A previous study demonstrated that patients with asymptomatic unresectable stage IV colorectal cancer did not benefit from resection of the primary tumor using propensity score matching[7]. Similarly, JCOG1007 study found that primary tumor resection followed by chemotherapy had no benefit over chemotherapy alone for CRC patients with asymptomatic primary tumor and synchronous unresectable metastases [8]. On the contrary, Shida et al revealed that palliative resection of the primary tumor may be associated with improved overall survival. Two large real-world studies also found that palliative primary tumor resection resulted in improved overall and cancer-specific survival[9, 10]. Besides that, the benefits of palliative resection of the primary tumor appeared to be consistent whether patients received systemic chemotherapy or not [11]. In short, the results seem to be not conclusive enough resulted from inconsistency, and it remains unclear which subgroup of these patients would benefit more from primary tumor resection. In the present study, we performed a large population-based study and subdivided patients with stage IV CRC into different subgroups to identify patients who responded well to primary tumor resection.

Materials And Methods

Patients selection

Patients with metastatic CRC and definite record of primary tumor surgery were identified in the surveillance, epidemiology, and end results (SEER) database (2004–2015). The inclusion criteria were as follows: (1) The site code is 018 (colon) or 130 (rectum); (2) CRC was the only type of primary cancer; (3) information about radiotherapy and survival were available. The following data were documented: age at diagnosis, gender, marital status, race, serum CEA, histologic type, differentiation tumor location, surgery of primary lesion, surgery of metastases, site of metastases, chemotherapy, radiotherapy and survival data.

Statistical analysis

Uni- and multivariable Cox regression analysis were performed to recognize the prognostic factors. Groups with survival difference were divided into different subgroups. The Cox proportional hazards model was built to estimate the hazard ratios (HR) for cancer-specific mortality after receiving primary tumor resection. All statistical analyses were performed with SPSS 25.0.

Results

Baseline Characteristics

A total of 60358 stage IV CRC patients were identified. 34177 patients received primary tumor resection while 26181 patients did not receive primary tumor resection. If the patients with surgery of metastases were excluded, 25126 patients received palliative primary tumor resection while 24750 patients did not

receive palliative primary tumor resection. The data about site of metastases were only available between 2010-2015. There were 302, 107, 16501, and 1918 patients with isolated bone, brain, liver and lung metastases, respectively. There were 18828, 5720, 707, and 41 patients with single, double, triple, and quadruple metastatic sites, respectively.

Prognostic factors of cancer-specific survival

Based on univariate analysis, age at diagnosis, gender, marital status, race, serum CEA, histologic type, differentiation tumor location, surgery of primary lesion, surgery of metastases, site of metastases, chemotherapy and radiotherapy affected significantly cancer-specific survival. When these factors were entered a multivariate analysis, it showed that age at diagnosis, marital status, race, serum CEA, histologic type, differentiation tumor location, surgery of primary lesion, surgery of metastases, site of metastases, chemotherapy and radiotherapy were significantly associated with cancer-specific survival (Table 1).

Subgroup of metastatic CRC

We next divided the patients into different subgroups to evaluate the value of primary tumor resection according to the independent prognostic factors. Univariable Cox regression analysis revealed that patients under 60 years old benefited more from primary tumor resection as compared to those over 60 years old (≤ 60 years old: HR, 0.454; 95% CI, 0.440-0.468; $P < 0.001$, > 60 years old: HR, 0.500; 95% CI, 0.488-0.512, $P < 0.001$). Besides that, patients with non-white people (white: HR, 0.489; 95% CI, 0.478-0.500; $P < 0.001$, black: HR, 0.447; 95% CI, 0.426-0.469, $P < 0.001$), normal serum CEA (normal serum CEA: HR, 0.445; 95% CI, 0.418-0.473; $P < 0.001$, elevated serum CEA: HR, 0.498; 95% CI, 0.485-0.510, $P < 0.001$), well or moderate differentiation (well differentiation: HR, 0.483; 95% CI, 0.437-0.534; $P < 0.001$, moderate differentiation: HR, 0.482; 95% CI, 0.469-0.496, $P < 0.001$, poor differentiation: HR, 0.558; 95% CI, 0.535-0.582; $P < 0.001$, undifferentiated differentiation: HR, 0.569; 95% CI, 0.492-0.658, $P < 0.001$), surgery of metastases (no surgery: HR, 0.514; 95% CI, 0.504-0.525; $P < 0.001$, surgery: HR, 0.456; 95% CI, 0.427-0.487, $P < 0.001$), isolated liver metastases (lung only: HR, 0.484; 95% CI, 0.427-0.549; $P < 0.001$, liver only: HR, 0.453; 95% CI, 0.435-0.471, $P < 0.001$, brain only: HR, 0.717; 95% CI, 0.459-1.120; $P = 0.144$, bone only: HR, 0.665; 95% CI, 0.491-0.899, $P = 0.008$), single metastatic site (single site: HR, 0.463; 95% CI, 0.446-0.481; $P < 0.001$, double sites: HR, 0.643; 95% CI, 0.601-0.688, $P < 0.001$, triple sites: HR, 0.631; 95% CI, 0.512-0.777; $P < 0.001$, quadruple sites: HR, 0.913; 95% CI, 0.376-2.215, $P = 0.840$), chemotherapy (no chemotherapy or unknown: HR, 0.520; 95% CI, 0.505-0.535; $P < 0.001$, chemotherapy: HR, 0.457; 95% CI, 0.446-0.469, $P < 0.001$) and radiotherapy (no radiotherapy: HR, 0.472; 95% CI, 0.463-0.482; $P < 0.001$, radiotherapy: HR, 0.414; 95% CI, 0.391-0.438, $P < 0.001$) gained more survival benefits. Of note, patients with signet ring cell carcinoma benefited less from primary tumor resection (adenocarcinoma: HR, 0.472; 95% CI, 0.462-0.482; $P < 0.001$, mucinous adenocarcinoma: HR, 0.484; 95% CI, 0.451-0.519, $P < 0.001$, signet ring cell carcinoma: HR, 0.623; 95% CI, 0.550-0.707; $P < 0.001$). No significant difference in survival benefit was observed between patients with different marital status (unmarried: HR, 0.493; 95% CI, 0.479-0.507; $P < 0.001$, married: HR, 0.476; 95% CI, 0.464-0.490, $P < 0.001$) or different tumor location (colon: HR, 0.436; 95% CI,

0.426-0.446; $P < 0.001$, rectum: HR, 0.452; 95% CI, 0.435-0.470, $P < 0.001$). Similar results were observed in multivariable Cox regression analysis except for age (Table 2). To evaluate the value of palliative resection of primary tumor, patients who underwent surgery of metastases were excluded from the analysis. Intriguingly, subgroups that benefited more from palliative resection of primary tumor were consistent with those in entire cohort (Table 3).

Discussion

To date, the value of palliative resection of primary tumor in stage IV CRC patients with unresectable metastases is controversial. It is unreasonable to perform resection of primary tumor for all stage IV CRC patients. Previous studies did explore the subgroups who would gain more survival benefit from palliative resection of primary tumor. Our study focused on which subgroups benefited more from primary tumor resection in metastatic CRC to identify patients who required aggressive therapy. The independent prognostic factors were identified using multivariable Cox regression analysis. Based on these factors, we divided stage IV CRC patients into different subgroups. Our findings indicated that selected patients would gain more survival benefit from primary tumor resection.

Although young CRC patients are apt to have more aggressive characteristics, they have better survival outcomes as compared to elderly patients[12, 13]. Our study also found that young stage IV CRC patients had superior prognosis as compared to elderly patients. In the univariable Cox regression analysis, primary tumor resection resulted in 54.6% and 50% decreased mortality risk in patients under 60 years old and those over 60 years old. However, the advantage of primary tumor resection in young patients decreased obviously using multivariable Cox regression analysis. It is reasonable to assume that young patients tend to have better performance status and they can tolerate and benefit from more intensive therapy. After adjusting for chemotherapy and radiotherapy, the predictive value of age for primary tumor resection is no longer significant.

Although black patients had poor prognosis as compared to white patients, black patients had 55.8% decreased mortality risk while white patients had 52% decreased mortality risk after receiving primary tumor resection. Serum carcinoembryonic antigen (CEA) testing is performed routinely for diagnosis, surveillance and treatment monitoring among CRC patients. Besides that, preoperative serum CEA was an independent prognostic factor in CRC [14] and CEA levels as an indicator could predict pathological complete response after neoadjuvant therapy for rectal cancer[15]. Our study found that serum elevated CEA levels were associated with worse prognosis in metastatic CRC. Primary tumor resection resulted in approximately 55.9% and 51.9% reduction in mortality risk for patients with normal and elevated CEA levels. Primary tumor resection is preferred in patients with normal CEA levels. Our previous study also evaluated guiding role of CEA levels in clinical decision-making in stage IIA colon cancer. We found that adjuvant chemotherapy did not acquire substantial survival benefit in patients with elevated pretreatment serum CEA levels[16].

Primary colorectal signet-ring cell carcinoma has distinct molecular features[17], aggressive behavior and worse prognosis[18] as compared to other histological subtypes. Our study found that primary tumor resection only decreased 37.7% mortality risk for patients with signet ring cell carcinoma. Shi et al found that metastatic CRC patients with signet ring cell carcinoma receiving chemotherapy had better survival than patients treated with surgery[19]. The value of primary tumor resection for stage IV CRC patients with signet ring cell type is limited and chemotherapy seems to be more useful for these patients. Similarly, for patients with poor or undifferentiated differentiation, survival benefits conferred by primary tumor resection were less than those with well or moderate differentiation.

Our previous study found that distant metastasis site and the number of metastatic sites were associated with survival of stage IV CRC. Patients with isolated lung metastases presented better prognosis as compared to those with metastases at any other sites[20]. Different metastasis site had distinctive clinicopathological and molecular characteristics. Robinson et al suggested that patients with rectal cancer are more likely than patients with colon cancer to present with synchronous lung metastases[21]. Tie et al. reported that prevalence of KRAS mutations is higher in lung metastases than in liver metastases. It is in question whether different metastasis site affects the therapeutic effect of primary tumor resection[22]. As expected, we found that patients with isolated liver metastases benefited more from primary tumor resection. Although patients with isolated lung metastases had better prognosis than those with isolated liver metastases, patients with isolated lung metastases gained less survival benefit from primary tumor resection than those with isolated liver metastases. In addition, patients with isolated brain metastases did not benefit from primary tumor resection, which may attribute to limited sample size. The number of metastatic sites also had an effect on therapeutic effect of primary tumor resection. Patients with single metastatic site benefited more from primary tumor resection while patients with quadruple metastatic sites did not get benefit from primary tumor resection.

For patients receiving primary tumor resection combined with other therapy, such as surgery of metastases, chemotherapy and radiotherapy, the survival benefits conferred by primary tumor resection were enlarged. Surgery of metastases, chemotherapy and radiotherapy had a synergistic effect on primary tumor resection. For patients who can tolerate the intensive therapy, combination therapy will benefit selected patients. Similarly, for patients with unresectable metastases, palliative primary tumor resection was associated with more survival benefit in patients who received chemotherapy or radiotherapy.

Inevitably, our study has several limitations. Firstly, some prognostic variables were missing in SEER database, such as perineural invasion, vascular invasion, chemotherapy regimens, response to chemotherapy and other metastatic sites, making it impossible to adjust for other potential confounders. Secondly, the sample size in some subgroups is insufficient. Thirdly, it is hard to acquire progression-free survival, which is critical for evaluation of therapeutic effect in stage IV disease.

In conclusion, the subdivision of metastatic CRC contributes to maximization of the value of primary tumor resection and facilitates individualized treatment options.

Declarations

Ethics approval and consent to participate

This study was carried out based on SEER database which is publicly accessible. We have acquired permit from official mission for the research purpose. No personal identifying information was reflected. The informed consent was not required for our study.

Consent for publication

Yes.

Competing interests

We declare no conflicts of interest.

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Consent to participate

Yes.

Authors' contributions

XL and QL conceived this study. DL and QL improved the study design and contributed to the interpretation of results. ZS collected the data. SC performed data processing and statistical analysis. DL and ZS wrote the manuscript. QL revised the manuscript. All authors approved the final version.

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Data Availability Statement

The datasets are available in the SEER repository and can be obtained from <https://seer.cancer.gov>.

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Tables

Table 1 Univariate and multivariate analysis for cancer-specific survival in metastatic colorectal cancer.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI) value	<i>P</i>	HR (95% CI)	<i>P</i> value
Age				
≤60	Reference		Reference	
>60	1.558 (1.528- 1.587)	<0.001 1.320)	1.294 (1.269-	<0.001
Sex				
Male	Reference		Reference	
Female	1.044 (1.025- 1.063)	<0.001 1.007)	0.988 (0.970-	0.214
Marital status				
Unmarried	Reference		Reference	
Married	0.776 (0.761- 0.790)	<0.001 0.905)	0.888 (0.870-	<0.001
Unknown	/		/	
Race				
White	Reference		Reference	
Black	1.100 (1.072- 1.129)	<0.001 1.080)	1.052 (1.025-	<0.001
Others	0.888 (0.859- 0.918)	<0.001 0.931)	0.900 (0.870-	<0.001
Serum CEA				
Normal	Reference		Reference	
Elevated	1.505 (1.459- 1.553)	<0.001 1.515)	1.469 (1.424-	<0.001
Unknown	/		/	

Histologic type				
Adenocarcinoma	Reference		Reference	
Mucinous adenocarcinoma	1.070 (1.035-1.106)	<0.001 1.138)	1.101 (1.064-	<0.001
Signet ring cell carcinoma	1.578 (1.482-1.679)	<0.001 1.438)	1.349 (1.266-	<0.001
Others	1.709 (1.635-1.785)	<0.001 1.376)	1.316 (1.257-	<0.001
Differentiation				
Well	Reference		Reference	
Moderate	0.956 (0.909-1.005)	0.080 1.139)	1.083 (1.030-	<0.001
Poor	1.433 (1.361-1.510)	<0.001 1.722)	1.634 (1.550-	<0.001
Undifferentiated	1.453 (1.349-1.564)	<0.001 1.954)	1.814 (1.683-	<0.001
Unknown	/		/	
Tumor location				
Colon	Reference		Reference	
Rectum	0.819 (0.802-0.836)	<0.001 0.816)	0.797 (0.779-	<0.001
Surgery of primary lesion				
No	Reference		Reference	
Yes	0.479 (0.470-0.488)	<0.001 0.486)	0.475 (0.464-	<0.001
Surgery of metastases				
No			Reference	

	Reference			
Yes	0.615 (0.599- 0.631)	<0.001 0.837)	0.815 (0.793-	<0.001
Unknown	/		/	
Site of metastases				
Lung only	Reference		Reference	
Liver only	1.240 (1.163- 1.322)	<0.001 1.464)	1.372 (1.286-	<0.001
Brain only	2.116 (1.683- 2.660)	<0.001 2.685)	2.130 (1.690-	<0.001
Bone only	1.909 (1.643- 2.218)	<0.001 1.937)	1.665 (1.431-	<0.001
Multiple	1.988 (1.858- 2.127)	<0.001	/	
Number of metastatic sites				
Single	Reference		Reference	
Double	1.557 (1.502- 1.614)	<0.001 1.934)	1.805 (1.684-	<0.001
Triple	2.247 (2.066- 2.445)	<0.001 2.720)	2.452 (2.210-	<0.001
Quadruple	3.271 (2.358- 4.538)	<0.001 6.206)	4.443 (3.181-	<0.001
Chemotherapy				
No/Unknown	Reference		Reference	
Yes	0.393 (0.386- 0.401)	<0.001 0.430)	0.421 (0.413-	<0.001
Radiotherapy				

No	Reference	Reference	Reference	Reference
Yes	0.728 (0.708- 0.750)	<0.001 0.957)	0.927 (0.898-	<0.001
Unknown	/	/	/	/

Table 2 Univariate and multivariate analysis of cancer-specific mortality for patients with or without primary tumor resection.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI) value	<i>P</i>	HR (95% CI)	<i>P</i> value
Age				
≤60	Reference		Reference	
	0.454 (0.440- 0.468)	<0.001 0.481)	0.464 (0.448-	<0.001
>60	Reference			
	0.500 (0.488- 0.512)	<0.001 0.498)	0.483 (0.469-	<0.001
Marital status				
Unmarried	Reference		Reference	
	0.493 (0.479- 0.507)	<0.001 0.501)	0.484 (0.468-	<0.001
Married	Reference		Reference	
	0.476 (0.464- 0.490)	<0.001 0.483)	0.467 (0.453-	<0.001
Race				
White	Reference		Reference	
	0.489 (0.478- 0.500)	<0.001 0.493	0.480 (0.468-	
Black	Reference		Reference	
	0.447 (0.426- 0.469)	<0.001 0.468)	0.442 (0.417-	<0.001
Others	Reference		Reference	
	0.447 (0.418-	<0.001 0.519)	0.480 (0.444-	<0.001

	0.477)			
Serum CEA				
Normal	Reference		Reference	
	0.445 (0.418- 0.473)	<0.001 0.475)	0.441 (0.410-	<0.001
Elevated	Reference			
	0.498 (0.485- 0.510)	<0.001 0.496)	0.481 (0.467-	<0.001
Histologic type				
Adenocarcinoma	Reference		Reference	
	0.472 (0.462- 0.482)	<0.001 0.480)	0.468 (0.457-	<0.001
	Reference		Reference	
Mucinous adenocarcinoma	0.484 (0.451- 0.519)	<0.001 0.496)	0.453 (0.414-	<0.001
	Reference		Reference	
Signet ring cell carcinoma	0.623 (0.550- 0.707)	<0.001 0.762)	0.657 (0.567-	<0.001
	Reference		Reference	
Others	0.575 (0.525- 0.629)	<0.001 0.590)	0.530 (0.476-	<0.001
Differentiation				
Well	Reference		Reference	
	0.483 (0.437- 0.534)	<0.001 0.495)	0.442 (0.395-	<0.001
Moderate	Reference		Reference	

	0.482 (0.469- 0.496)	<0.001 0.464)	0.450 (0.436-	<0.001
Poor	Reference		Reference	
	0.558 (0.535- 0.582)	<0.001 0.554)	0.529 (0.505-	<0.001
Undifferentiated	Reference		Reference	
	0.569 (0.492- 0.658)	<0.001 0.668)	0.570 (0.486-	<0.001
Tumor location				
Colon	Reference		Reference	
	0.436 (0.426- 0.446)	<0.001 0.485)	0.472 (0.459-	<0.001
Rectum	Reference		Reference	
	0.452 (0.435- 0.470)	<0.001 0.511)	0.490 (0.471-	<0.001
Surgery of metastases				
No	Reference		Reference	
	0.514 (0.504- 0.525)	<0.001 0.492)	0.480 (0.469-	<0.001
Yes			Reference	
	0.456 (0.427- 0.487)	<0.001 0.485)	0.448 (0.415-	<0.001
Site of metastases				
Lung only	Reference		Reference	
	0.484 (0.427-	<0.001 0.542)	0.466 (0.401-	<0.001

	0.549)			
Liver only	Reference			
	0.453 (0.435- 0.471)	<0.001 0.495)	0.471 (0.449-	<0.001
Brain only	Reference			
	0.717 (0.459- 1.120)	0.144 1.096)	0.649 (0.385-	<0.001
Bone only	Reference			
	0.665 (0.491- 0.899)	0.008 0.704)	0.499 (0.353-	<0.001
Multiple	Reference			
	0.634 (0.595- 0.676)	<0.001 0.642)	0.596 (0.554-	<0.001
Number of metastatic sites				
Single	Reference		Reference	
	0.463 (0.446- 0.481)	<0.001 0.493)	0.471 (0.450-	<0.001
Double	Reference		Reference	
	0.643 (0.601- 0.688)	<0.001 0.646)	0.598 (0.553-	<0.001
Triple	Reference		Reference	
	0.631 (0.512- 0.777)	<0.001 0.708)	0.563 (0.448-	<0.001
Quadruple	Reference		Reference	
	0.913 (0.376-	0.840 2.327)	0.707 (0.215-	0.569

	2.215)			
Chemotherapy				
No/Unknown	Reference		Reference	
	0.520 (0.505- 0.535)	<0.001 0.541)	0.522 (0.503-	<0.001
Yes	Reference		Reference	
	0.457 (0.446- 0.469)	<0.001 0.477)	0.464 (0.450-	<0.001
Radiotherapy				
No	Reference		Reference	
	0.472 (0.463- 0.482)	<0.001 0.492)	0.480 (0.469-	
Yes	Reference		Reference	
	0.414 (0.391- 0.438)	<0.001 0.472)	0.443 (0.416-	<0.001

Table 3 Univariate and multivariate analysis of cancer-specific mortality for patients with or without palliative primary tumor resection.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI) value	<i>P</i>	HR (95% CI)	<i>P</i> value
Age				
≤60	Reference		Reference	
	0.454 (0.440- 0.468)	<0.001 0.481)	0.464 (0.448-	<0.001
>60	Reference			
	0.500 (0.488- 0.512)	<0.001 0.498)	0.483 (0.469-	<0.001
Marital status				
Unmarried	Reference		Reference	
	0.493 (0.479- 0.507)	<0.001 0.501)	0.484 (0.468-	<0.001
Married	Reference		Reference	
	0.476 (0.464- 0.490)	<0.001 0.483)	0.467 (0.453-	<0.001
Race				
White	Reference		Reference	
	0.489 (0.478- 0.500)	<0.001 0.493	0.480 (0.468-	
Black	Reference		Reference	
	0.447 (0.426- 0.469)	<0.001 0.468)	0.442 (0.417-	<0.001
Others	Reference		Reference	
	0.447 (0.418-	<0.001 0.519)	0.480 (0.444-	<0.001

	0.477)			
Serum CEA				
Normal	Reference		Reference	
	0.445 (0.418- 0.473)	<0.001 0.475)	0.441 (0.410-	<0.001
Elevated	Reference			
	0.498 (0.485- 0.510)	<0.001 0.496)	0.481 (0.467-	<0.001
Histologic type				
Adenocarcinoma	Reference		Reference	
	0.472 (0.462- 0.482)	<0.001 0.480)	0.468 (0.457-	<0.001
	Reference		Reference	
Mucinous adenocarcinoma	0.484 (0.451- 0.519)	<0.001 0.496)	0.453 (0.414-	<0.001
	Reference		Reference	
Signet ring cell carcinoma	0.623 (0.550- 0.707)	<0.001 0.762)	0.657 (0.567-	<0.001
	Reference		Reference	
Others	0.575 (0.525- 0.629)	<0.001 0.590)	0.530 (0.476-	<0.001
Differentiation				
Well	Reference		Reference	
	0.483 (0.437- 0.534)	<0.001 0.495)	0.442 (0.395-	<0.001
Moderate	Reference		Reference	

	0.482 (0.469- 0.496)	<0.001 0.464)	0.450 (0.436-	<0.001
Poor	Reference		Reference	
	0.558 (0.535- 0.582)	<0.001 0.554)	0.529 (0.505-	<0.001
Undifferentiated	Reference		Reference	
	0.569 (0.492- 0.658)	<0.001 0.668)	0.570 (0.486-	<0.001
Tumor location				
Colon	Reference		Reference	
	0.467 (0.456- 0.479)	<0.001 0.485)	0.472 (0.459-	<0.001
Rectum	Reference		Reference	
	0.492 (0.472- 0.513)	<0.001 0.511)	0.490 (0.471-	<0.001
Site of metastases				
Lung only	Reference		Reference	
	0.484 (0.427- 0.549)	<0.001 0.542)	0.466 (0.401-	<0.001
Liver only	Reference			
	0.453 (0.435- 0.471)	<0.001 0.495)	0.471 (0.449-	<0.001
Brain only	Reference			
	0.717 (0.459- 1.120)	0.144 1.096)	0.649 (0.385-	<0.001

Bone only	Reference			
	0.665 (0.491- 0.899)	0.008 0.704)	0.499 (0.353-	<0.001
Multiple	Reference			
	0.634 (0.595- 0.676)	<0.001 0.642)	0.596 (0.554-	<0.001
Number of metastatic sites				
Single	Reference		Reference	
	0.463 (0.446- 0.481)	<0.001 0.493)	0.471 (0.450-	<0.001
Double	Reference		Reference	
	0.643 (0.601- 0.688)	<0.001 0.646)	0.598 (0.553-	<0.001
Triple	Reference		Reference	
	0.631 (0.512- 0.777)	<0.001 0.708)	0.563 (0.448-	<0.001
Quadruple	Reference		Reference	
	0.913 (0.376- 2.215)	0.840 2.327)	0.707 (0.215-	0.569
Chemotherapy				
No/Unknown	Reference		Reference	
	0.520 (0.505- 0.535)	<0.001 0.541)	0.522 (0.503-	<0.001
Yes	Reference		Reference	
	0.457 (0.446-	<0.001 0.477)	0.464 (0.450-	<0.001

0.469)				
Radiotherapy				
No	Reference		Reference	
	0.472 (0.463- 0.482)	<0.001 0.492)	0.480 (0.469-	
Yes	Reference		Reference	
	0.414 (0.391- 0.438)	<0.001 0.472)	0.443 (0.416-	<0.001