Primary Tumor Size as a Predictor of Prognosis in Patients with Stage IV Colorectal Cancer: Population analysis based on two centers

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Abstract

Background

The prognostic significance of primary tumor size in patients with stage IV colorectal cancer (CRC) has not been established. This study aimed to evaluate the prognostic value of tumor size in stage IV CRC.

Methods

We retrospectively analyzed the data of patients with stage IV CRC in the Surveillance, Epidemiology and End Results (SEER) database and patients with stage IV CRC treated at the Sixth Affiliated Hospital of Sun Yat-sen University (SYSU). The optimal cutoff value for tumor size was determined using the X-Tile program. Multivariable Cox regression analysis were used to examine whether tumor size was an independent predictor of prognosis.

Results

There were 16,283 patients in the SEER cohort and 462 in the SYSU cohort. With the help of the X-Tile program, we selected 60mm as the optimal tumor size cutoff. Multivariate analysis confirmed that tumor size (HR = 1.17, 95%CI: 1.13–1.22) was an independent prognostic factor in stage IV CRC. Across all subgroups in the SEER cohort, survival probability was significantly lower in patients with tumor size ≥ 60 mm than in patients with tumor size < 60 mm.

Conclusions

Tumor size appears to be an independent predictor of survival in patients with stage IV CRC. Patients with tumor size ≥ 60 mm have poor prognosis.

Background

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second most common cause of cancer death worldwide, with approximately 1.9 million new cases and 0.9 million deaths reported in 2020 alone (1, 2). Due to inadequate screening, approximately 20% of patients have metastatic disease (stage IV CRC) and poor prognosis at the time of diagnosis (3). Traditionally, treatment selection and prognosis prediction are based on the tumor–node–metastasis (TNM) stage of the American Joint Committee on Cancer (AJCC)/the Union for International Cancer Control (UICC) (4, 5). But, because of the heterogeneous nature of the tumor, patients with the same TNM stage may have different prognosis.

Previous studies exploring the predictors of prognosis in stage IV CRC have reported inconsistent results (6, 7). Among these, tumor size and T stage were representatives of two developing dimensions of CRC, horizontally and vertically. The T stage on depth of tumor invasion through the different layers of the bowel rather than tumor size. Tumor size is a key component in the response evaluation criteria in solid tumors (RECIST) (8, 9). Theoretically, tumor size ought to serve as a key predictor of treatment response and prognosis. While tumor size has been shown to have prognostic value in stage II and III CRC (10–12), its value in stage IV CRC is not yet established.

This study aimed to evaluate the prognostic value of tumor size in stage IV CRC.

Patients And Methods

We retrospectively analyzed the data of two large cohorts of patients with stage IV CRC: the Surveillance, Epidemiology, and End Results (SEER) cohort and the Sixth Affiliated Hospital of Sun Yat-sen University (SYSU) cohort.

The Surveillance, Epidemiology, and End Results cohort

The SEER program collects and registers information for a subset of the population (approximately 28%) from 20 geographic areas of the US (13) .The SEER*Stat software (version 8.3.5; National Cancer Institute, USA) (14) was used to extract all data related to CRC survivors. The inclusion criteria were 1) age ≥ 18 years at time of diagnosis and 2) diagnosis of AJCC stage IV CRC. The exclusion criteria were 1) concurrent other cancer; 2) familial adenomatous polyposis, Lynch syndrome, ulcerative colitis, or other diseases predisposing to CRC; 3) missing survival status data; 4) missing clinical data; or 5) ambiguous information on chemotherapy and radiotherapy.

The Sixth Affiliated Hospital of Sun Yat-sen University cohort

The SYSU cohort comprised patients with stage IV CRC treated in the Sixth Affiliated Hospital of Sun Yat-sen University from 2013 to 2016. The inclusion and exclusion criteria were the same as for the SEER cohort.

For both cohorts, information was collected on patients' age, sex, and race; tumor location and size, TNM stage, and histological differentiation grade; number of metastatic lymph nodes retrieved; organ metastasis; and receipt of radiotherapy and/or chemotherapy. Tumor size—defined as the widest horizontal diameter of the tumor—was measured on MR images.

X-Tile software (Yale University, New Haven, CT, USA) was used to determine the optimal cutoff value for tumor size (Fig. 1). The software identified 59 mm as the optimal cutoff value; we rounded it off to 60 mm and classified tumors as < 60 mm or ≥ 60 mm. According to location, tumors were classified as right-sided colon (in cecum, ascending colon, hepatic flexure and/or transverse colon) or as left-sided (in the

splenic flexure, descending, or sigmoid colon). Staging was performed according to the AJCC TNM Staging Classification for Carcinoma of the Colon and Rectum (Seventh Edition). The number of positive lymph nodes retrieved was classified according to the National Comprehensive Cancer Network (NCCN) guidelines of colon cancer (version 2.2021) (15). Overall survival (OS) was defined as the time from surgery to death or final follow-up. For the SEER cohort, the date of last follow-up was December 31, 2017, because the database contains death information only until 2017. For the SYSU cohort, the date of last follow-up was April 7, 2021.

Ethics statement

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki (as revised in Edinburgh 2000) and the Ethical Guidelines for Clinical Research. This study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-Sen University, with waiver of the need for informed consent.

Statistical analysis

Normally distributed measurement data were summarized as means ± standard deviation and non-normally distributed data as medians (Q25, Q75). Dichotomous data were summarized as numbers and percentages. Univariate and multivariate Cox regression models were used to identify the factors associated with OS. Only those variables significantly associated with OS in univariate analysis were retained in the multivariate Cox model. Statistical significance was at $p < 0.05$. SPSS 24.0 (IBM Corp., Armonk NY, USA) and R 4.1.1 (https://www.r-project.org/) were used for statistical analysis.

Results

The SEER cohort

The SEER cohort comprised 16 277 patients with stage IV CRC (Fig. 2). Table 1 summarizes the demographic characteristics and pathologic features. In this cohort, 82.5% patients were ≥ 50 years old, 45.1% patients had right colon tumors, 64.4% tumors were moderately differentiated, 78.9% patients had organ metastases, and 70.5% patients had received chemotherapy.

Table 1
Characteristics of patients from SEER database

Variable	All (N = 16277)
Age	
< 50 Y	2848 (17.5%)
≥ 50 Y	13429 (82.5%)
Race	
White	12366 (76.0%)
African American	2387 (14.7%)
Other	1524 (9.3%)
Sex	
Female	7553 (46.4%)
Male	8724 (53.6%)
Tumor site	
Right colon	7341 (45.1%)
Left colon	6405 (39.4%)
Rectum	2531 (15.5%)
Differentiated degree	
Well	772 (4.8%)
Moderately	10488 (64.4%)
Poorly	5017 (30.8%)
T stage	
T1-2	1417 (8.7%)
T3	8343 (51.3%)
T4	6517 (40.0%)
N stage	
N0	3295 (20.2%)
N1	6358 (39.1%)

Note: Data are shown as number (%).

Variable	All (N = 16277)
N2	6624 (40.7%)
Radiotherapy	
Yes	1359 (8.4%)
No	14918 (91.6%)
Chemotherapy	
Yes	11472 (70.5%)
No	4805 (29.5%)
Number of organ metastasis	
0	3430 (21.1%)
1	10568 (64.9%)
≥ 2	2279 (14.0%)
Number of lymph node metastasis	
0	4814 (29.6%)
≥ 1	11463 (70.4%)
Tumor size	
< 60 mm	9815 (60.3%)
≥ 60 mm	6462 (37.9%)
Note: Data are shown as number (%).	

A total of 9,815 (60.3%) patients had tumor size < 60 mm, and 6,462 (39.7%) had tumor size ≥ 60 mm. In univariate analysis, the factors significantly associated with OS were age, race, tumor location, tumor size, T stage, N stage, histological differentiation grade, number of positive lymph nodes retrieved, number of organ metastases, radiotherapy, and chemotherapy. In multivariate analysis (Table 2), the factors independently associated with OS were age (≥ 50, HR = 1.29, 95%CI: 1.22–1.36), race (White, HR = 0.91, 95%CI: 0.87–0.96; Other, HR = 0.85, 95%CI: 0.78–0.91), tumor location (left colon, HR = 0.75, 95%CI: 0.72–0.91; rectum, HR = 0.81, 95%CI: 0.76–0.86), tumor size (≥ 60 mm, HR = 1.17, 95%CI: 1.13–1.22), T stage (T3, HR = 0.87, 95%CI: 0.81–0.93; T4, HR = 1.18, 95%CI: 1.09–1.27), N stage (N1, HR = 1.13, 95%CI: 1.07–1.19; N2, HR = 1.52, 95%CI: 1.44–1.61), histological differentiation grade (moderately differentiated, HR = 1.31, 95%CI: 1.2–1.44; poorly differentiated, HR = 2.08, 95%CI: 1.89–2.29), number of positive lymph nodes retrieved (≥ 1, HR = 0.6, 95%CI: 0.58–0.63), number of organ metastases (1, HR =

1.30, 95%CI: 1.24–1.37; ≥2, HR = 2.16, 95%CI: 2.03–2.30), radiotherapy (yes, HR = 0.79, 95%CI: 0.73–0.86), and chemotherapy(yes, HR = 0.35, 95%CI: 0.34–0.36).

Table 2
Univariate and multivariate Cox model analyses of prognostic factors of SEER database

Variable	Univariate analysis		Multivariate analysis	
	HR(95%CI)	*P* value	HR(95%CI)	*P* value
Age				
< 50	1		1	
≥ 50	1.53 (1.45–1.61)	< 0.001	1.29 (1.22–1.36)	< 0.001
Race				
African American	1		1	
White	0.94 (0.89–0.99)	0.013	0.91 (0.87–0.96)	0.005
Other	0.85 (0.79–0.92)	< 0.001	0.85 (0.78–0.91)	< 0.001
Sex				
Female	1			
Male	0.99 (0.96–1.03)	0.67		
Tumor site				
Right colon	1		1	
Left colon	0.66 (0.63–0.68)	< 0.001	0.75 (0.72–0.91)	< 0.001
Rectum	0.67 (0.63–0.71)	< 0.001	0.81 (0.76–0.86)	< 0.001
Differentiated degree				
Well	1		1	
Moderately	1.06 (0.97–1.16)	0.205	1.31 (1.2–1.44)	< 0.001
Poorly	1.81 (1.65–1.99)	< 0.001	2.08 (1.89–2.29)	< 0.001
T stage				
T1-2	1		1	
T3	0.81(0.76–0.86)	< 0.001	0.87 (0.81–0.93)	< 0.001
T4	1.20(1.12–1.29)	< 0.001	1.18 (1.09–1.27)	< 0.001
N stage				
N0	1		1	
N1	1.05 (0.99–1.10)	0.079	1.13 (1.07–1.19)	< 0.001
N2	1.38 (1.31–1.45)	< 0.001	1.52 (1.44–1.61)	< 0.001

Variable	Univariate analysis		Multivariate analysis	
	HR(95%CI)	*P* value	HR(95%CI)	*P* value
Radiotherapy				
No	1		1	
Yes	0.56 (0.52–0.61)	< 0.001	0.79 (0.73–0.86)	< 0.001
Chemotherapy				
No	1		1	
Yes	0.35 (0.34–0.37)	< 0.001	0.35 (0.34–0.36)	< 0.001
Tumor size				
< 60mm	1			
≥ 60mm	1.27 (1.22–1.32)	< 0.001	1.17 (1.13–1.22)	< 0.001
Number of organ metastasis				
0	1		1	
1	0.99 (0.95–1.04)	0.827	1.30 (1.24–1.37)	< 0.001
≥ 2	1.70 (1.60–1.81)	< 0.001	2.16 (2.03–2.30)	< 0.001
Number of lymph node metastasis				
0	1		1	
≥ 1	0.69 (0.67–0.72)	< 0.001	0.6 (0.58–0.63)	< 0.001

We investigated the prognostic role of tumor size in different subgroups of age, tumor site, T stage, N stage, histological differentiation grade, number of lymph node metastases, number of organ metastases, radiotherapy, and chemotherapy. Across all subgroups, survival probability was lower in patients with tumor size ≥ 60 mm (all HR > 1.0) than in patients with tumor size < 60 mm (Fig. 3). Thus, subgroup analyses supported the findings of multivariate analysis of the entire cohort.

The SYSU cohort

The SYSU cohort included 462 stage IV CRC patients. Figure 2 shows the patient selection process, and Table 3 summarizes the patients' demographics and pathological features. In univariate analysis. The factors significantly associated with OS were age, histological differentiation grade, tumor size, T stage, N stage, chemotherapy and number of organ metastases. In multivariate Cox analysis (Table 4), the factors independently associated with OS were age (≥ 50 years, HR = 1.42, 95%CI: 1.04–1.93), tumor size (≥ 60 mm, HR = 1.53, 95%CI: 1.16–2.02), N stage (N1, HR = 1.72, 95%CI: 1.29–2.29; N2, HR = 1.89, 95%CI: 1.34–2.64), histological differentiation grade (moderately differentiated, HR = 1.60, 95%CI: 1.11–2.31;

poorly differentiated, HR = 1.84, 95%CI: 1.16–2.93), number of organ metastases (1, HR = 1.33, 95%CI: 1.03–1.72; ≥2, HR = 1.96, 95%CI: 1.27–3.03), and chemotherapy (yes, HR = 0.55, 95%CI: 0.42–0.71). T stage was not significantly associated with OS. In subgroup analysis, tumor size ≥ 60 mm was significantly associated with worse survival in most subgroups. (Fig. 4).

Table 3
Characteristics of patients from SYSU database

Variable	All (N = 462)
Age	
< 50	111(24.0%)
≥ 50	351((76.0%)
Sex	
Female	174(37.7%)
Male	288(62.3%)
Tumor site	
Right colon	110(23.8%)
Left colon	168(36.4%)
Rectum	184(39.8%)
Differentiated degree	
Well	69(14.9%)
Moderately	331(71.7%)
Poorly	62(13.4%)
T stage	
T1-2	14(3.0%)
T3	345(74.7%)
T4	103(22.3%)
N stage	
N0	130(28.1%)
N1	223(48.3%)
N2	109(23.6%)
Radiotherapy	
Yes	10(8.2%)
No	452(97.8%)
Note: Data are shown as number (%).	

Variable	All (N = 462)
Chemotherapy	
Yes	344(74.5%)
No	118(25.5%)
Number of organ metastasis	
0	250(54.1%)
1	166(35.9%)
≥ 2	46(10.0%)
Number of lymph node metastasis	
0	239(51.7%)
≥ 1	223(48.3%)
Tumor size	
< 60 mm	373 (80.7%)
≥ 60 mm	89 (19.3%)
Note: Data are shown as number (%).	

Table 4
Univariate and multivariate Cox model analyses of prognostic factors of SYSU database

Variable	Univariate analysis		Multivariate analysis	
	HR(95%CI)	*P* value	HR(95%CI)	*P* value
Age				
< 50 Y	1		1	
≥ 50 Y	1.56 (1.19–2.05)	0.001	1.42 (1.04–1.93)	0.026
Sex				
Female	1			
Male	1.11 (0.87–1.40)	0.40		
Tumor site				
Right colon	1			
Left colon	0.81 (0.60–1.09)	0.17		
Rectum	0.85 (0.63–1.14)	0.27		
Differentiated degree				
Well	1		1	
Moderately	1.63 (1.14–2.33)	0.007	1.60 (1.11–2.31)	0.012
Poorly	2.61 (1.68–4.07)	< 0.001	1.84 (1.16–2.93)	0.01
T stage				
T1-2	1		1	
T3	1.52 (0.72–3.23)	0.28	1.06 (0.49–2.28)	0.879
T4	2.97 (1.37–6.47)	0.006	1.66 (0.74–3.72)	0.215
N stage				
N0	1		1	
N1	1.70 (1.28–2.27)	< 0.001	1.72 (1.29–2.29)	< 0.001
N2	1.86 (1.34–2.59)	0.007	1.89 (1.34–2.64)	< 0.001
Radiotherapy				
No	1			
Yes	0.61 (0.25–1.48)	0.28		
Chemotherapy				

Variable	Univariate analysis		Multivariate analysis	
	HR(95%CI)	*P* value	HR(95%CI)	*P* value
No	1		1	
Yes	0.48 (0.37–0.62)	< 0.001	0.55 (0.42–0.71)	< 0.001
Tumor size				
< 60 mm	1			
≥ 60 mm	1.56 (1.19–2.05)	0.001	1.53 (1.16–2.02)	0.003
Number of organ metastasis				
0	1		1	
1	1.43 (1.12–1.83)	0.003	1.33 (1.03–1.71)	0.026
≥ 2	2.37 (1.62–3.47)	< 0.001	1.96 (1.27–3.03)	0.003
Number of lymph node metastasis				
0	1			
≥ 1	0.96 (0.77–1.22)	0.78		

Discussion

Tumor size is an important predictor of clinical outcomes in some solid tumors, but is rarely mentioned in current staging systems for CRC. Its value as a prognostic factor in CRC is still controversial. The current study showed that tumor size ≥ 60 mm was an independent predictor of OS in patients with stage IV CRC in both the population-based SEER cohort and the smaller hospital-based SYSU cohort.

There could be several reasons for the association between tumor size and prognosis. Larger tumor size reflects a greater ability to proliferate. Rapid proliferation can lead to necrosis of the tumor. A recent study has shown that tumor necrosis is associated with increased risk for overall mortality (16). In addition, necrosis may lead to chronic bleeding and result in anemia. Ho et al. (17) have shown that tumor size is a risk factor for anemia in patients with colon carcinoma. Further, many studies have demonstrated that preoperative anemia is significantly associated with a poor prognosis in CRC (18–20). Large tumor size may also indicate a more biologically aggressive phenotype (11). While biomarkers could be used to identify such phenotypes, measurement of tumor size is a more convenient and widely applicable method in routine clinical practice.

Our study is supported by several previous studies (10–12, 21). Saha et al. (11) examined the role of tumor size in a large retrospective analysis of 300,386 patients and reported that tumor size was positively associated with important prognostic factors (such as T stage and N stage) and had negative

impact on survival. These findings are consistent with the current study. Meanwhile, there are some studies (22–28) that contradict our results; however, review of those studies showed that most were limited by small sample sizes (ranging from 47 to 579 patients).

In this study, subgroup analysis of the SEER cohort showed better 5-year survival probability among patients with tumor size < 60 mm than among patients with tumor size ≥ 60 mm tumors in all subgroups. In the SYSU cohort, similar survival advantage was not seen the subgroups of age < 50 years, right colon tumors, well-differentiated tumors, T1-2 and T3 stage, N0 stage, chemotherapy, no organ metastasis, and no lymph node metastasis. This may have been because, compared with the SEER cohort, the SYSU cohort was small; in some subgroups, there were too few patients (~ 10 patients). Further, while the SEER cohort included patients of various races, the SYSU cohort only included Chinese patients. Although the SYSU data were limited, 60 mm was the optimal cutoff value for tumor size in patients with stage IV CRC. So our findings are likely to be reliable.

Although the findings of this study are based on analysis of two large cohorts, some limitations must be acknowledged. First, in the SYSU cohort, there were only a small number of patients with T1 and T2 stage. This may explain why T stage was not significantly associated with survival in the SYSU cohort, but showed strong association in the SEER cohort. Second, this was a retrospective analysis of available data; some bias is inevitable.

Conclusions

In conclusion, tumor size appears to be a predictor of prognosis in stage IV CRC. Individualized treatment strategies in patients with poor prognosis (i.e., tumor size ≥ 60 mm) might help improve outcomes.

Abbreviations

American Joint Committee on Cancer
AJCC
CRC
colorectal cancer
Kaplan-Meier
KM
NCCN
National Comprehensive Cancer Network
OS
overall survival
SEER
the Surveillance, Epidemiology, and End Results
TNM
tumor-node-metastasis

UICC, the Union for International Cancer Control.

Declarations

Availability of data and materials

The data that support the findings of this study are available from the Sixth Affiliated Hospital of Sun Yat-Sen University (SYSU) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of SYSU .

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki (as revised in Edinburgh 2000) and the Ethical Guidelines for Clinical Research. This study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-Sen University, with waiver of the need for informed consent.

Consent for publication

We reached an agreement of all participants in this study to publish this document.

Competing interests

The authors declared no financial conflict of interests.

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Authors' contributions

JGC, XJC and MYL contributed equally to this study. MYL, XJC, JGC, JCH and XSH contributed to the study concept and design, the acquisition, analysis, and interpretation of data, and the drafting of the manuscript. BZ, YYL, TZH, DGH, and GML contributed to the data collections and manuscript reviews. All authors read and approved the final manuscript.

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Figures

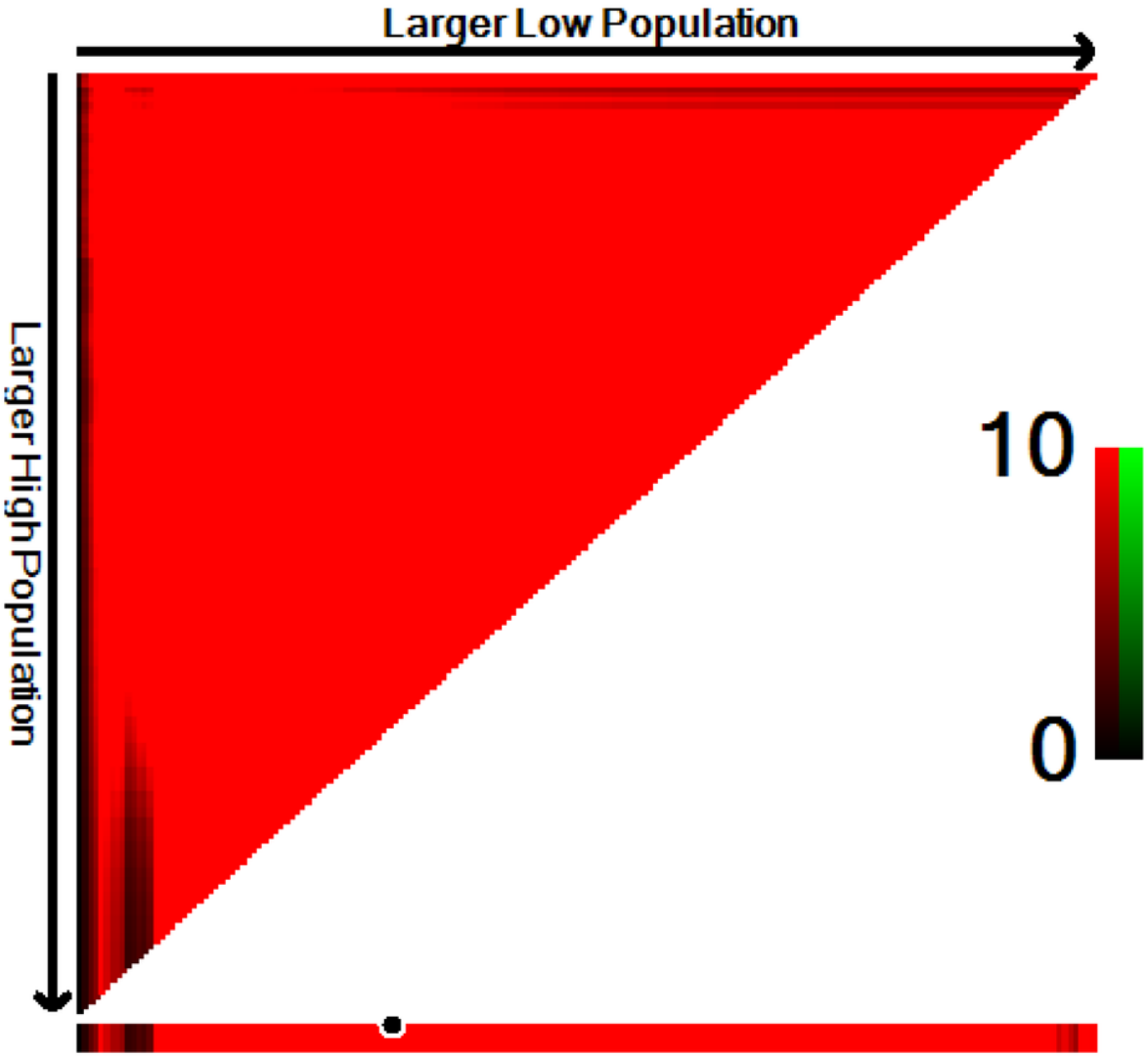

Figure 1

X-Tile plots of tumor size in the Surveillance, Epidemiology and End Results cohort of patients with stage IV CRC. The data is presented as a right triangle grid graph, where each point represents a set of data for a given partition.

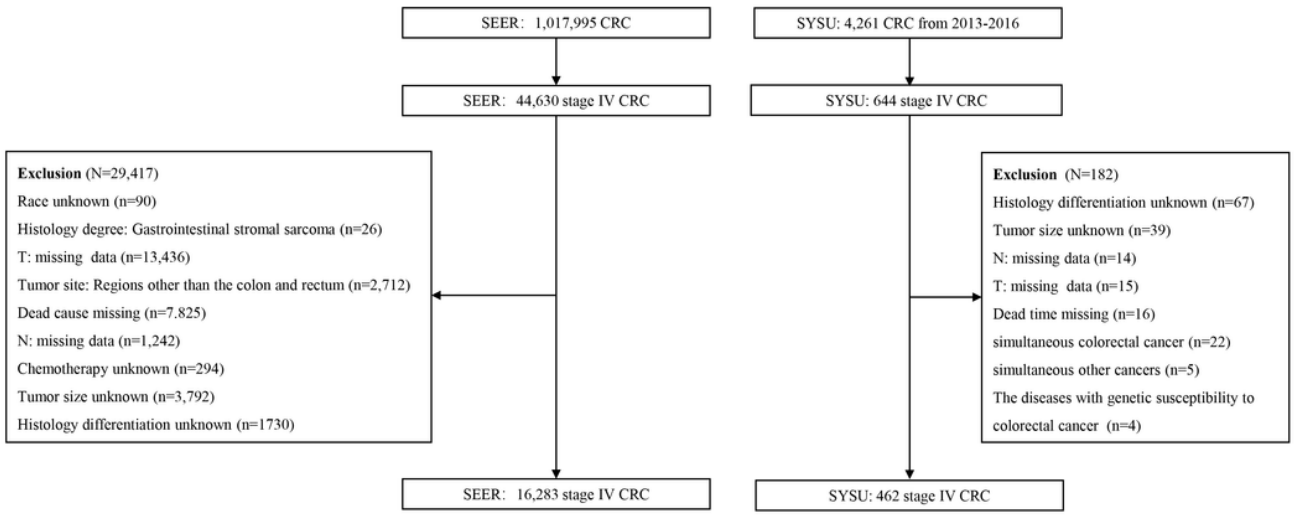

Figure 2

Flow chart showing SEER cohort and SYSU cohort selection process.

Subgroup	tumor size＜60mm n(%)	tumor size≥60mm n(%)	HR (95%CI)	P value
All patients	**9815(60.3)**	**6462 (39.7)**		
Age				
＜50	1762 (18.0)	1086 (16.8)	1.38 (1.25-1.51)	＜0.001
≥50	8053 (82.0)	5376 (83.2)	1.24 (1.19-1.29)	＜0.001
Tumor site				
Right colon	4160 (42.4)	3181 (49.2)	1.21 (1.15-1.28)	＜0.001
Left colon	4114 (41.9)	2291 (35.5)	1.18 (1.11-1.26)	＜0.001
Rectum	1541 (15.7)	990 (15.3)	1.45 (1.32-1.60)	＜0.001
Differentiated degree				
Well	485 (4.9)	287 (4.4)	1.33 (1.11-1.59)	0.002
Moderately	6604 (67.3)	3884 (60.1)	1.21 (1.16-1.27)	＜0.001
Poorly	2726 (27.8)	2291 (35.5)	1.25 (1.17-1.33)	＜0.001
T sagte				
T1-2	1021 (10.4)	396 (6.1)	1.44 (1.26-1.65)	＜0.001
T3	5383 (51.8)	2960 (45.8)	1.23 (1.16-1.30)	＜0.001
T4	3411 (34.8)	3106 (48.1)	1.17 (1.11-1.24)	＜0.001
N stage				
N0	2018 (20.6)	1277 (19.8)	1.12 (1.03-1.22)	0.01
N1	3907 (39.8)	2451 (37.9)	1.29 (1.21-1.37)	＜0.001
N2	3890 (39.6)	2734 (42.3)	1.31 (1.24-1.38)	＜0.001
Chemotherapy				
Yes	7062 (72.0)	4410 (68.2)	1.27 (1.21-1.33)	＜0.001
No	2753 (28.0)	2052 (37.8)	1.19 (1.12-1.27)	＜0.001
Number of organ metastasis				
0	1921 (19.6)	1509 (23.4)	1.20 (1.10-1.30)	＜0.001
1	6550 (66.7)	4018 (62.2)	1.28 (1.23-1.35)	＜0.001
≥2	1344 (13.7)	935 (14.4)	1.25 (1.14-1.37)	＜0.001
Number of lymph node metastasis				
0	2912 (29.7)	1902 (29.4)	1.30 (1.22-1.39)	＜0.001
≥1	6903 (70.3)	4560 (70.6)	1.26 (1.20-1.32)	＜0.001

Figure 3

Subgroup analysis in the SEER cohort.

Subgroup	tumor size＜60mm n(%)	tumor size≥60mm n(%)	HR (95%CI)	P value
All patients	**373 (80.7)**	**89 (19.3)**		
Age				
＜50	93(24.9)	18(20.2)		0.137
≥50	280(75.1)	71(78.8)	1.53 (1.13-2.06)	0.006
Tumor site				
Right colon	78(20.9)	32(36.0)		0.17
Left colon	133(35.7)	35(39.3)	1.67 (1.08-2.58)	0.022
Rectum	162(43.4)	22(24.7)	1.7 (1.01-2.85)	0.044
Differentiated degree				
Well	54(14.5)	15(16.8)		0.359
Moderately	278(74.5)	53(59.6)	1.46 (1.03-2.07)	0.04
Poorly	41(11.0)	21(23.6)	2.03 (1.11-3.71)	0.025
T sagte				
T1-2	14(3.8)	0(0)		
T3	282(75.6)	63(70.8)		0.056
T4	77(20.6)	26(29.2)	2.04 (1.23-3.39)	0.006
N stage				
N0	104(27.9)	26(29.2)		0.857
N1	184(49.3)	39(43.8)	1.95 (1.32-2.88)	0.001
N2	85(22.8)	24(27.0)	1.75 (1.06-2.91)	0.038
Chemotherapy				
Yes	293(78.6)	51(57.3)		0.137
No	80(21.4)	38(42.7)		0.067
Number of organ metastasis				
0	205(55.0)	45(50.6)		0.13
1	135(36.2)	31(34.8)	1.65 (1.05-2.59)	0.029
≥2	33(8.8)	13(14.6)	3.12 (1.48-6.59)	0.003
Number of lymph node metastasis				
0	192(51.5)	47(52.8)		0.065
≥1	181(48.5)	42(47.2)	1.71 (1.15-2.55)	0.008

Figure 4

Subgroup analysis in the SYSU cohort.