Prognostic Value of Tumor Deposits in Colorectal Cancer: A Population-based Retrospective Cohort Study

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Research Article

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Abstract

Background

The role of tumor deposits (TDs) in TNM staging of colorectal cancer is controversial, especially the relationship with distant metastasis.

Purpose

The aim of this study was to determine the effect of TDs on the survival of colorectal cancer and the occurrence of distant metastasis, and to determine whether TDs (+) patients behaved similarly to stage IV patients.

Methods

Retrospective analysis of CRC patients from two large independent cohorts from the Surveillance Epidemiology and End Results (SEER) database (n=58775) and the First Affiliated Hospital of Dalian Medical University (n=742).

Results

Univariate logistic analyses revealed that TDs as an independent predictor of liver metastasis [p<0.001; odds ratio (OR): 5.738; 95% confidence interval (CI): 3.560-9.248] in the The First Affiliated Hospital of Dalian Medical University's patients. Meanwhile, TDs was also an independent predictor of isolated organ metastasis [p<0.001; odds ratio (OR): 3.028; 95% confidence interval (CI): 2.414 - 3.79; multiple organ metastases [p<0.001; odds ratio (OR): 4.778; 95% confidence interval (CI): 4.109 - 5.556]; isolated liver metastasis [p<0.001; odds ratio (OR): 4.395; 95% confidence interval (CI): 4.099 - 4.713] and isolated lung metastasis [p<0.001; odds ratio (OR): 5.738; 95% confidence interval (CI): 3.560-9.248] in the SEER database. Multivariate analyses suggested TDs were an independent poor prognostic factor for distant metastasis (p<0.001).

Conclusions

Our results have shown that compared with patients with negative TDs, CRC patients with positive TDs are more likely to develop distant metastasis. Patients who categorized T4aN2bM0 TDs (+) and T4bN2M0 TDs (+) have similar prognosis as those with stage IV, and these patients should be classified as stage IV.

1. Introduction

It is estimated that by 2020, there will be 140,000 new cases of colorectal cancer and 50,000 deaths in the United States, ranking fourth and second in morbidity and mortality respectively(1). In China, the latest cancer statistics reported by the National Cancer Center in 2019 show that the incidence of colorectal cancer in our country is ranked third, the mortality rate is ranked fifth, and the mortality rate is generally on

the rise(2). In recently years, great progress has been made in the early diagnosis and treatment of colorectal cancer, but the 5-year survival rate of colorectal cancer is still unsatisfactory, mainly because most of patients were diagnosed as terminal or distant metastasis(3). The prognosis of colorectal cancer depends on different clinical and pathological factors, many of which have been incorporated into different staging systems(4). Tumor staging is the basis of cancer therapy, and the TNM staging system, based on histopathological and radiological classification methods, is currently considered as the gold standard for various tumor staging(5). After the diagnosis of colorectal cancer, detailed staging can enable patients to benefit from more precise treatment methods.

Tumor deposits (TDs) are tumor cells clustered around colorectal cancer and mesenteric adipose tissue. The microscopic features of TDs are discrete foci far away from the front of aggressive tumors, and there are no signs of residual lymph nodes(6). TDs are significantly correlated with poor prognosis after colorectal cancer surgery(7, 8).Whether to consider TDs as positive lymph nodes in determining the TNM staging of colorectal cancer has been widely debated for many years, which has led to modifications and changes in subsequent versions of the TNM staging system. Both AJCC 7th TNM and AJCC 8th TNM classified regional LNM-negative, TDs-positive pT lesions as N1c(9). The existence and quantity of TDs are strongly correlated with the prognosis of colorectal cancer patients(6, 10–12), and more and more people support that the TDs as a sign of distant metastasis.

Part of colorectal cancer patients enrolled in the Surveillance, Epidemiology, and End Results (SEER) database and The First Affiliated Hospital of Dalian Medical University were included in this study to explore the impact of TDs on the survival and prognosis of patients and the relationship between TDs and distant metastasis.

2. Patients And Methods

2.1 Inclusion and exclusion criteria

The treatment data of stage I-IV CRC patients in the two groups were analyzed retrospectively. The first set of data comes from the SEER database, with a total of 970,163 patients with colorectal cancer. Inclusion and exclusion criteria: (1) Tumor site was restricted to the colon and rectum according to the international Classification of Diseases Code version 3 (ICD-O-3/WHO2008); (2) Select the treatment method for primary tumor resection, the operation code is limited to 30, 32, 40, 41, 50, 51, 60, 61, 70, and 80 to screen patients after surgery. (3) Include diagnostic age, gender, race, AJCC staging, TNM staging, primary site, tumor grade, TDs, neurological invasion, liver metastasis, lung metastasis, bone metastasis, brain metastasis, survival time, survival status, etc. A total of 80428 patients were obtained; (4) Patients with incomplete information above were excluded. In the end, a total of 58,775 patients who met the screening criteria were included (Figure 1).

The second set of data comes from the Department of General Surgery, The First Affiliated Hospital of Dalian Medical University, and selected 742 CRC patients who underwent surgical treatment from January

2011 to December 2015. Inclusion and exclusion criteria: (1) Patients undergoing surgery for colorectal cancer for the first time; (2) Postoperative pathologically confirmed colorectal cancer; (3) No radiotherapy or chemotherapy was performed before surgery; (4) Postoperative tumor progression originated from Colorectal cancer; (5) Exclude a history of colorectal cancer surgery; (6) Exclude other malignant tumors; (7) Exclude patients undergoing radiotherapy and chemotherapy before surgery.

2.2 Statistical analysis

All statistical analyses were performed using SPSS 26.0. The Chi-square test was used to analyze the demographic and clinical characteristics of categorical variables. The logistical regression coefficients were used to estimate the odds ratios (OR) for the relationship between TDs and distant metastasis patterns. The Kaplan-Meier curve was used to calculate the survival rate, and the log-rank test was used to assess the difference. Calculated hazard ratio (HR) and 95.0% confidence interval (CI). Cox proportional hazards model was used for univariate and multivariate analysis. In multivariate analyses, the clinicopathological characteristics with $p<0.05$ in univariate analysis were included to determine independent prognostic factors. Significance was set at $p < 0.05$.

3. Results

3.1 Characteristics of patients

We extracted two sets of data, including 58,775 and 742 CRC patients, respectively. Overall, the TDs positive patients in SEER database and the First Affiliated Hospital of Dalian Medical University were 12.07% (n = 7096) and 27.90% (n = 207), respectively.

In the SEER database, the most common sites of metastasis are the liver (8.29%, n=4874), followed by the lung (1.74%, n=1024), bone (0.27%, n=159), and brain (0.09%, n=54). Only liver metastasis (11.46%, n=85) was shown in the data from the The First Affiliated Hospital of Dalian Medical University. Table 1 shows detailed clinicopathological data from the SEER Database and the The First Affiliated Hospital of Dalian Medical University.

3.2 TDs associated with OS in SEER cohort

Compared to the patients with negative TDs, the patients with positive TDs was significantly associated with worse OS in the entire cohort (54.37 vs 36.56 months, $p<0.001$) and stage IV cohort (29.36 vs 22.21 months, $p<0.001$). In order to better investigate the significance of TDs in stage IV patients, we divided the stage IV patients into isolated organ metastasis cohort and multiple organ metastases cohort, and the isolated organ metastasis group was further divided into isolated liver metastasis group and isolated lung metastasis group. The results showed that TDs positive patients still showed worse OS in the isolated organ metastasis cohort (30.59 vs 22.55 months, $p<0.001$) and multiple organ metastases cohort (18.92 vs 16.18 months, $p=0.027$). Similarly, the same results were obtained in the isolate liver metastasis cohort (30.59 vs 22.55 months, $p<0.001$) and isolate lung metastasis cohort (30.59 vs 22.55 months, $p<0.001$, Figure. 2).

3.3 TDs was an independent prognostic factor of OS in SEER cohort

Univariate analysis in the entire cohort demonstrated that age, gender, race, AJCC staging, TNM staging, primary site, tumor grade, TDs, neurological invasion, liver metastasis, lung metastasis, bone metastasis, brain metastasis affects the patient's OS. Moreover, multivariate analyses demonstrated that TDs was an independent prognostic factor. Using TDs negative as a reference, patients with positive TDs represented worse OS (HR=1.346, 95%CI: 1.296-1.398, p<0.001, Table 2).

3.4. TDs was an independent risk factor for distant metastasis in SEER and the The First Affiliated Hospital of Dalian Medical University cohort

In order to study the relationship between TDs and distant metastasis, we compared the positive rates of TDs in various metastasis patterns. The results showed that the positive rates of TDs in distant metastasis cohort, isolated organ metastasis cohort, multiple organ metastases cohort, isolated liver metastasis cohort and isolated lung metastasis cohort were 37.28%, 33.65%, 38.85%, 33.81%, 29.16%, respectively. This was significantly higher than the TDs positive rate in the SEER cohort. Moreover, the chi-square test showed that the distribution of TDs in the above cohorts was statistically significant (p<0.001, Figure. 3).

We further performed univariate and multivariate logistic regression analyses on variables in the two large cohorts to investigate the risk factors affecting patients with distant metastasis. Univariate logistic analyses revealed that TDs was an independent predictor of liver metastasis [p<0.001; odds ratio (OR): 5.738; 95% confidence interval (CI): 3.560-9.248] in the The First Affiliated Hospital of Dalian Medical University’s patients. Meanwhile, TDs was also an independent predictor of isolated organ metastasis [p<0.001; odds ratio (OR): 3.028; 95% confidence interval (CI): 2.414 - 3.797]; multiple organ metastases [p<0.001; odds ratio (OR): 4.778; 95% confidence interval (CI): 4.109-5.556]; isolated liver metastasis [p<0.001; odds ratio (OR): 4.395; 95% confidence interval (CI): 4.099-4.713] and isolated lung metastasis [p<0.001; odds ratio (OR): 5.738; 95% confidence interval (CI): 3.560-9.248] and in the SEER database. Multivariate analyses suggested TDs were an independent adverse prognostic factor for distant metastasis (p<0.001, Table 3).

3.5. Some TDs positive patients have similar OS to stage IV patients.

We wondered whether some stage III TDs positive patients were already showing similar outcomes to stage IV patients? We performed a survival analysis for each subcategory of stage III and stage IV patients, survival information are shown in Table 4 and Figure 4, where T3aN2bM0 TDs (+) and T4N2M0 TDs (+) patients showed the average survival period similar to patients in stage IV (28.8, 24.8 and 29.3 months, respectively) and different to those in stage IIIc (41.5 months), stage IIIb (52.7 months), and stage IIIa (60.3 months) (p < 0.001).

4. Discussion

Gabriel et al. first reported TDs in rectal cancer patients in 1935, believing that it was a blood derived metastasis confined to the surrounding tumor rather than a lymph node metastasis(13). Goldstein et al. conducted postoperative pathology biopsies of 418 patients with T3N+M0 colorectal cancer. They found that TDs were usually distributed in large blood vessels, perinerves or blood vessels near the primary tumor and formed when the tumor extended beyond the proper muscle. They are different from lymph node metastasis and should be described separately from lymph node metastasis(10) .This may help explain the correlation between TDs and patients' short survival time and their susceptibility to intraperitoneal metastasis. Yamano et al. divided TDs into infiltrating TDs (iTDs: cancer cell aggregates with lymphatic or perineural infiltration or cancer cell clusters) and nodular TDs (nTDs: smooth or irregularly shaped cancer cells without iTDs), found that iTDs and nTDs are independent poor prognostic factors for recurrence-free survival in patients with lymph node metastasis, and colorectal cancer patients with positive iTDs often have liver metastasis, and the probability of transition to distant lymph nodes is higher than that of patients with positive nTDs. This finding suggests that in patients with colorectal cancer, tumor cells in iTDs may transfer to the liver through the portal vein system and then to lymph nodes far away from the liver (14).

This study aims to clarify the effect of TDs on the prognosis of colorectal cancer patients, including the occurrence of distant metastasis and death. We found that for overall patients, TDs-positive patients had poor OS, which was similar to the results reported in the previous study (6, 7, 11, 15). We also found that the TDs are still affect patients with distant metastasis independent prognostic factors for survival. However, the latest version of TNM staging only considers TDs without lymph node metastasis, which may lose useful information. For patients with both lymph node metastasis and TDs positive, it is not clear whether TDs has an adverse effect on prognosis and whether it should be included in TNM staging. In addition, there is growing support for the inclusion of TDs in category M rather than N or T in TNM staging (16–18). The current version of the TNM staging does not mention the sites of TDs, but Yagi et al. emphasized the clinical significance of TDs in the tubercle area of pelvis. According to the metastatic status of the LPLN area, they divided 172 patients with stage Ⅱ and Ⅲ rectal cancer into three groups: patients without lymph node metastasis (no-LP-M group), patients with lymph node metastasis (LP-LNM group), and patients with TDs but without lymph node metastasis (LP-EX group). Multivariate Cox regression analysis showed that LP-EX is an important prognostic factor affecting OS and RFS, and the initial distant recurrence rate of LP-EX group (9/14, 64.3%) was significantly higher than other groups (42/158, 26.6 %) (P=0.006), indicating that TDs in extrapelvic lymph node area may be a systemic disease rather than a local disease (19). Tong et al. found that the prognosis of TDs-positive and negative colorectal cancer patients with T3N1cM0 stage was significantly different (P=0.038), and it was assumed that TDs in more than 7 lymph node metastases at the same time might be similar to cases with distant metastasis. The prognosis of these cases should be attributed to stage IV(18). Leonardo et al. conducted a cross-sectional study on 392 patients with colon adenocarcinoma, and grouped patients with stage I-III with TDs as “stage IV-TD”. According to statistical analysis, the average survival time of this patients was similar to that of patients in stage IV (69.3 months vs 64.6 months), but was different from that of

patients in other stages (P<0.001). It can be seen that the current staging method does not fully consider the difference in the prognostic impact of TDs(20).

Although this study did not prove that TDs are directly related to stage IV patients, it is concluded that TDs are a risk factor for distant metastasis in CRC patients. Based on the above research, we should reconsider the meaning of TDs. In the long term, TDs have a good guiding significance for follow-up treatment. XiaoLi et al. found that TDs positive stage III CRC patients had a poor prognosis, and did not show that DFS benefited from chemotherapy. Therefore, for TDs positive patients, more detailed surgery and more rigorous follow-up are needed, as well as further research on optimal treatment strategies(21). At present, TDs are identified by pathological slices after surgery. Due to the lack of strict pathological examinations, and the recovery rate of lymph nodes varies with the quality of the operation, the detection of TDs has great heterogeneity. Although the latest advances in imaging have allowed MRI to detect TDs, it still takes a long time before it can be used in clinical practice(22). The circulating tumor cells (CTC), called "liquid biopsy", have always attracted much attention from scholars. CTC refers to the heterogeneous tumor cells that are released into the peripheral blood circulation from the primary tumor or metastasis due to spontaneous or diagnosis and treatment operations, and can be detected in the patient's peripheral blood(23). As mentioned above, TDs are closely related to distant metastases, but after surgical resection, they lose meaning in subsequent treatment and monitoring. As a more sensitive predictor, CTC has great practical significance for monitoring tumor recurrence and metastasis and treatment response(24). Therefore, we can focus on patients with positive TDs after surgery, and guide the follow-up treatment of patients by detecting the count and change trend of CTC in the blood, and monitor whether the patient has recurrence and metastasis. This kind of dynamic monitoring based on molecular characteristics can promptly select CRC patients who are at risk of metastasis, reduce unnecessary costs for patients and avoid the toxic side effects of related drugs, and guide patients to precise treatment is an inevitable trend in future development.

This study included the SEER database and the information of colorectal cancer patients in the The First Affiliated Hospital of Dalian Medical University, but there are still limitations. The data of the The First Affiliated Hospital of Dalian Medical University only contains information on liver metastasis. Information such as surgical procedures for tumors, some tumor markers, specific chemotherapy conditions, and the treatment of metastases may lead to deviations in research results.

Conclusions

In conclusion, colorectal cancer patients with negative TDs have better survival benefits than patients with positive TDs. And colorectal cancer patients with positive TDs are more likely to develop distant metastasis than patients with negative TDs. Therefore, large-scale, multi-center clinical studies should be carried out to prove the relationship between TDs and metastatic colorectal cancer, and the significance of TDs in colorectal cancer should be reconsidered.

Abbreviations

CRC: Colorectal cancer

TDs: Tumor deposits

SEER: Surveillance, Epidemiology, and End Results

AJCC: American Joint Committee on Cancer

OS: Overall survival

LNM: Lymph node metastasis

iTDs: Cancer cell aggregates with lymphatic or perineural infiltration or cancer cell clusters

nTDs: Smooth or irregularly shaped cancer cells without iTDs

CTC: Circulating tumor cells

Declarations

Availability of data and materials

Access to the database may be obtained from the corresponding author on reasonable request.

Data Statement

Our data are available and publicly accessible. The original data comes from the Surveillance, Epidemiology, and End Results (SEER) database and the Department of General Surgery, The First Affiliated Hospital of Dalian Medical University.

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Contributions

Peng Gong, Peng Liu designed the study; Tong Qiu and Shun Zeng collected the data; Wenhao Wu and Shulin Li analyzed the data and presented the results; Wenhao Wu and Xianbin Zhang wrote the manuscript. All of the authors listed have revised and approved the manuscript.

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Ethics declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University. The study outcomes will not affect the future management of the patients.

Consent for publication

The requirement for informed consent was waived.

Competing interests

The authors declare no conflicts of interest.

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Tables

Table1. Baseline of the demographic and related clinical characteristics for patients diagnosed with colorectal cancer

Table2. Univariate and multivariate analyses of overall survival for the SEER cohort.

Characteristics	No. of colorectal cancer patients SEER (2010–2012)			No. of colorectal cancer patients Dalian (2011–2015)		
	With TDs N=7096, 12.07%	Without TDs N=51679, 87.92%	*p* value	With TDs N=207,27.90%	Without TDs N=535,72.10%	*p* value
Age, in years			<0.001			0.826
<65	3263 13.80	20379 86.20		115 27.58	302 72.42	
≥65	3833 10.91	31300 89.09		92 28.31	233 71.69	
Sex			0.217			0.011
Male	3450 11.58	25530 88.42		137 31.42	299 68.58	
Female	3046 10.51	26149 89.49		70 22.89	236 77.11	
Race			0.230			
White	5687 12.05	41510 87.95		—	—	
Black	810 12.29	5780 87.71		—	—	
Other	559 12.00	4389 88.00		—	—	
AJCC			<0.001			<0.001
I	66 0.47	13816 99.53		3 3.33	87 96.67	
II	582 3.02	18705 96.98		58 16.76	288 83.24	
III	3855 20.63	14830 79.37		109 44.49	136 55.51	
IV	2573 37.28	4328 62.72		37 60.66	24 39.34	
T stage			<0.001			<0.001
T1	104 1.40	7318 99.60		0 0	19 100	
T2	258 2.73	9198 97.27		8 9.30	78 91.70	

T3	4087 (12.55)	28487 (87.45)		6 (10.71)	50 (89.29)	
T4	2647 (28.39)	6676 (71.61)		193 (30.22)	388 (69.78)	
N stage			<0.001			<0.001
N0	823 (2.39)	33611 (97.61)		70 (15.35)	386 (84.65)	
N1	3095 (20.92)	11695 (79.08)		94 (42.53)	127 (57.47)	
N2	3178 (33.27)	6373 (66.73)		43 (66.15)	22 (33.85)	
M stage			<0.001			<0.001
M0	4523 (8.72)	47351 (91.28)		151 (22.27)	527 (77.73)	
M1	2573 (37.28)	4328 (62.72)		56 (87.50)	8 (13.50)	
Primary site			<0.001			0.199
Colon	5509 (11.84)	40929 (88.16)		99 (25.85)	284 (74.15)	
Rectum	1587 (12.97)	10750 (87.03)		108 (30.08)	251 (69.92)	
Grade			<0.001			
I	274 (5.99)	4300 (94.01)		—	—	
II	4396 (10.33)	38149 (89.67)		—	—	
III	1909 (19.90)	7683 (80.10)		—	—	
IV	517 (25.05)	1547 (84.95)		—	—	
Perineural invasion			<0.001			
None	4761 (9.11)	47473 (90.89)		—	—	
Yes	2335 (35.70)	4206 (64.30)		—	—	
Vascular tumor						<0.001

thrombus						
None	—	—		139（22.53）	478（77.47）	
Yes	—	—		68（54.40）	57（45.60）	
Liver Met			<0.001			<0.001
None	5409 （10.04）	48492 （89.96）		153（23.29）	504（76.71）	
Yes	1687 （34.61）	3187 （65.39）		54（63.53）	31（36.47）	
Lung Met			<0.001			
None	6736 （11.66）	51015 （88.34）		—	—	
Yes	360 （35.16）	664 （64.84）		—	—	
Bone Met			<0.001			
None	7032 （12.00）	51584 （88.00）		—	—	
Yes	64 （40.25）	95（59.75）		—	—	
Brain Met			0.002			
None	7082 （12.06）	51639 （87.94）		—	—	
Yes	14 （25.93）	40（74.07）		—	—	

	Univariate Cox analysis		Multivariate Cox analysis	
Variable	HR（95% CI）	*p* value	HR（95% CI）	*p* value
Age				
<65	1 [Reference]		1 [Reference]	
≥65	1.936 (1.879-1.995)	<0.001	2.362 (2.291-2.436)	<0.001
Sex				
Male	1 [Reference]		1 [Reference]	
Female	1.052 (1.024-1.081)	<0.001	1.104 (1.075-1.135)	<0.001
Race				
Other	1 [Reference]		1 [Reference]	
White	1.260 (1.194-1.329)	<0.001	1.245 (1.180-1.314)	<0.001
Black	1.440 (1.350-1.535)	<0.001	1.497 (1.404-1.596)	<0.001
AJCC				
I	1 [Reference]		1 [Reference]	
II	1.642 (1.568-1.720)	<0.001	0.962 (0.881-1.051)	0.393
III	2.333 (2.231-2.439)	<0.001	1.277 (1.147-1.423)	<0.001
IV	7.674 (7.325-8.041)	<0.001	2.836 (2.532-3.176)	<0.001
T stage				
T1	1 [Reference]		1 [Reference]	
T2	1.369 (1.278-1.467)	<0.001	1.220 (1.138-1.309)	<0.001
T3	2.416 (2.281-2.559)	<0.001	1.696 (1.548-1.859)	<0.001
T4	5.258 (4.948-5.586)	<0.001	2.647 (2.408-2.909)	<0.001
N stage				<0.001
N0	1 [Reference]		1 [Reference]	
N1	1.663 (1.609-1.718)	<0.001	0.956 (0.885-1.032)	0.248
N2	3.221 (3.117-3.328)	<0.001	1.365 (1.266-1.472)	<0.001
Primary site				
Rectum	1 [Reference]		1 [Reference]	
Colon	1.326 (1.280-1.373)	<0.001	1.064 (1.026-1.103)	0.001

Grade				0.001
I	1 [Reference]		1 [Reference]	
II	1.289 (1.215-1.366)	0.001	1.023 (0.965-1.086)	0.445
III	2.225 (2.089-2.369)	0.001	1.284 (1.204-1.370)	0.001
IV	2.554 (2.353-2.773)	0.001	1.402 (1.289-1.524)	0.001
TDs				
Negative	1 [Reference]		1 [Reference]	
Positive	2.611 (2.526-2.699)	0.001	1.346 (1.296-1.398)	0.001
Perineural invasion				
Negative	1 [Reference]		1 [Reference]	
Positive	2.143 (2.068-2.220)	0.001	1.171 (1.127-1.216)	0.001
Liver metastasis				
Negative	1 [Reference]		1 [Reference]	
Positive	4.273 (4.126-4.425)	0.001	1.318 (1.242-1.399)	0.001
Lung metastasis				
Negative	1 [Reference]		1 [Reference]	
Positive	4.232 (3.955-4.529)	0.001	1.226 (1.139-1.319)	0.001
Bone metastasis				
Negative	1 [Reference]		1 [Reference]	
Positive	5.223 (4.422-6.168)	0.001	1.368 (1.154-1.622)	0.001
Brain metastasis				
Negative	1 [Reference]		1 [Reference]	
Positive	6.603 (4.974-8.767)	0.001	1.935 (1.452-2.579)	0.001

Table 3. Univariate and multivariate logistic analyses of different metastatic patterns for the SEER and Dalian cohort.

Distant metastasis patterns	Isolated organ metastasis OR (95% CI)	Multiple organ metastases OR (95% CI)	Isolated liver metastasis OR (95% CI)	Isolated lung metastasis OR (95% CI)	Liver metastasis OR (95% CI)
Univariate analysis TDs (+) vs TDs (-)	4.375 (4.091-4.680)	4.778 (4.109-5.556)	4.395 (4.099-4.713)	3.028 (2.414-3.797)	5.738 (3.560-9.248)
Multivariate analysis TDs (+) vs TDs (-)	1.633 (1.514-1.761)	1.667 (1.414-1.966)	1.633 (1.510-1.766)	1.402 (1.093-1.799)	4.662 (2.743-7.923)

Table 4. Survival Analysis according to clinical stage.

Clinical stage	Mean survival (months)	95% Confidence interval
Stage IIIa	60.259	59.393 - 61.124
Stage IIIb	52.739	52.286 - 53.191
Stage IIIc	41.481	40.584 - 42.378
T4aN2bM0 TDs (+)	28.796	25.541 - 32.052
T4bN2M0 TDs (+)	24.789	26.132 - 27.261
Stage IV	29.355	28.616 - 30.094

Figures

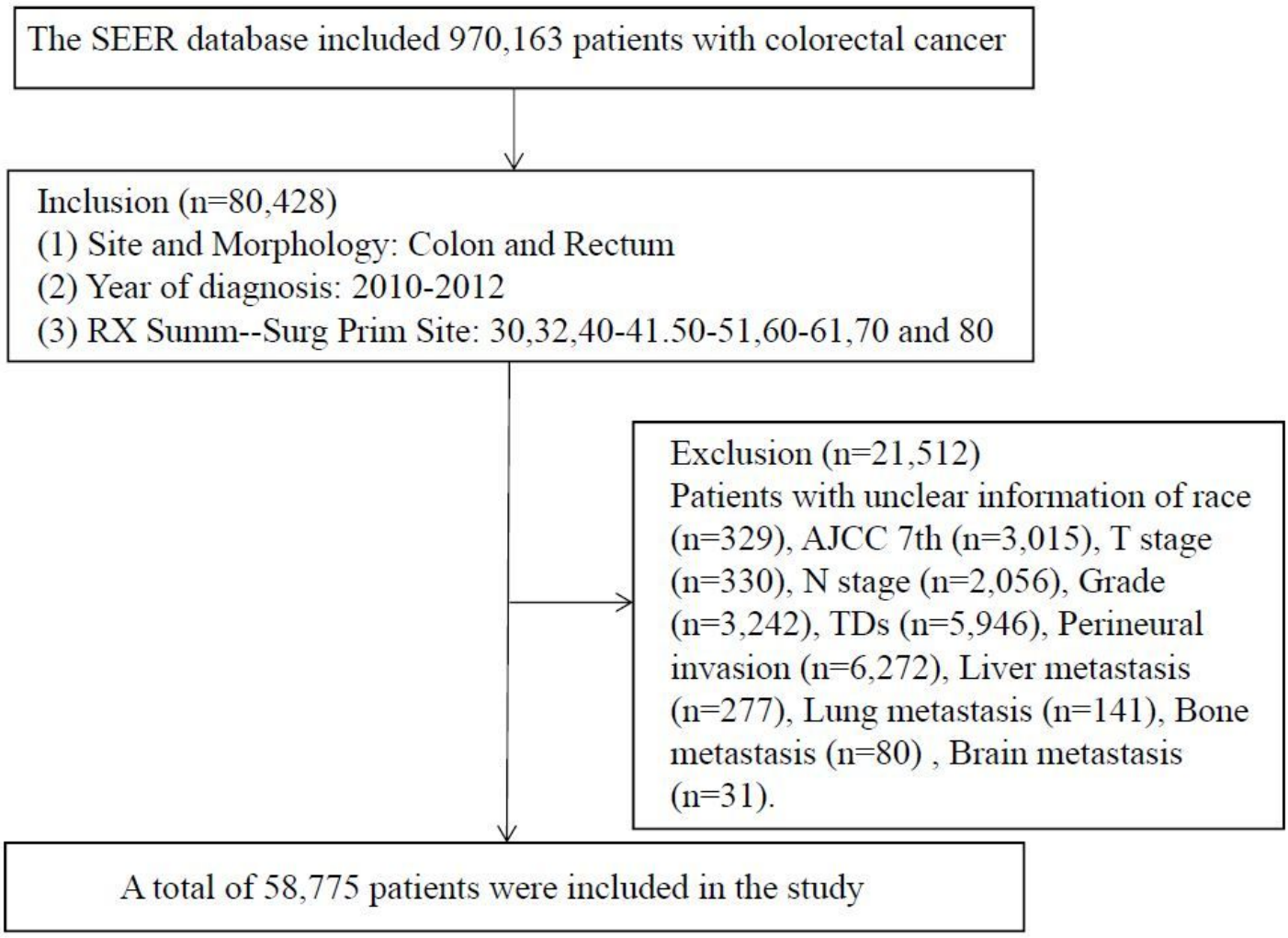


Figure 1

Flowchart of patient selection.

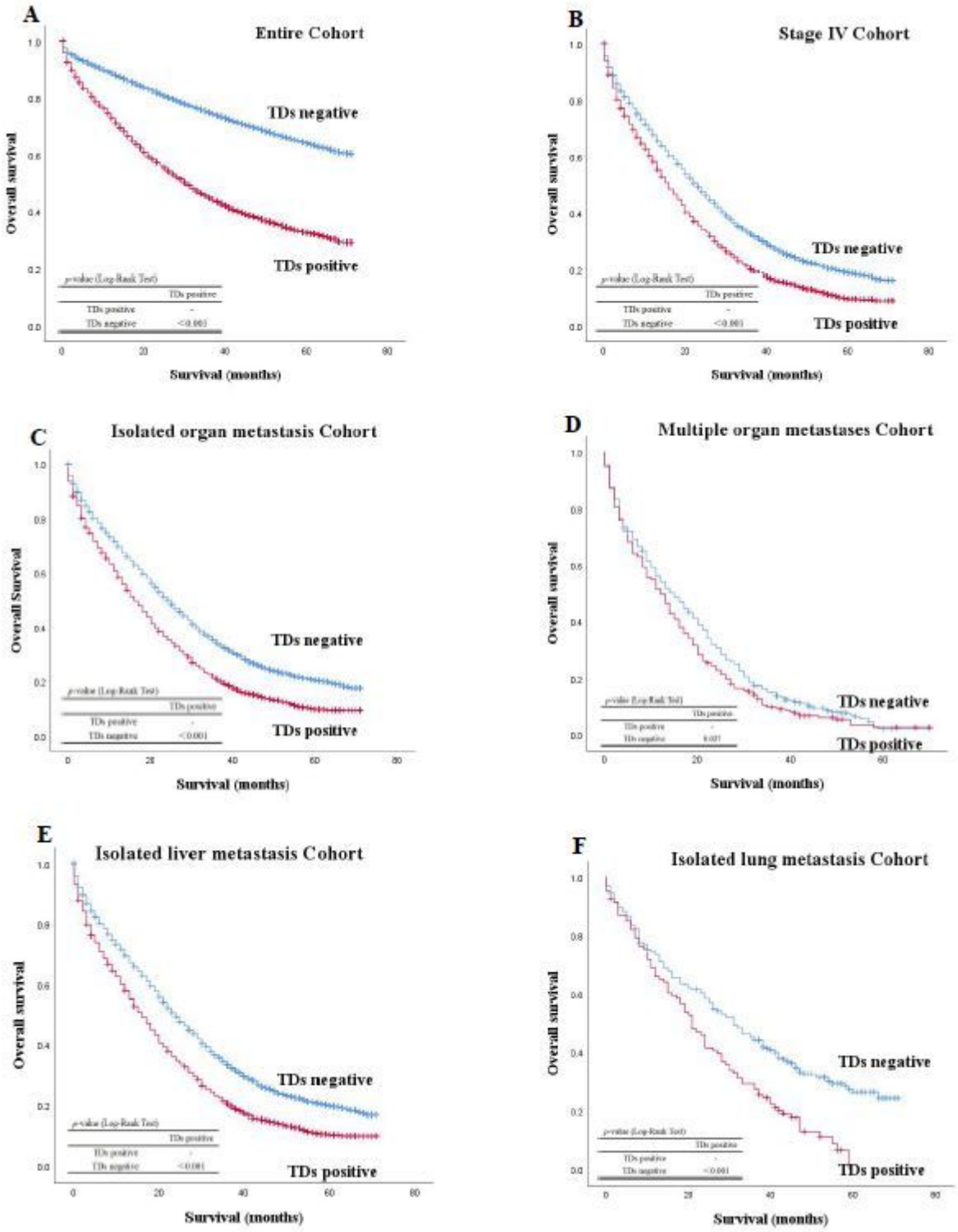
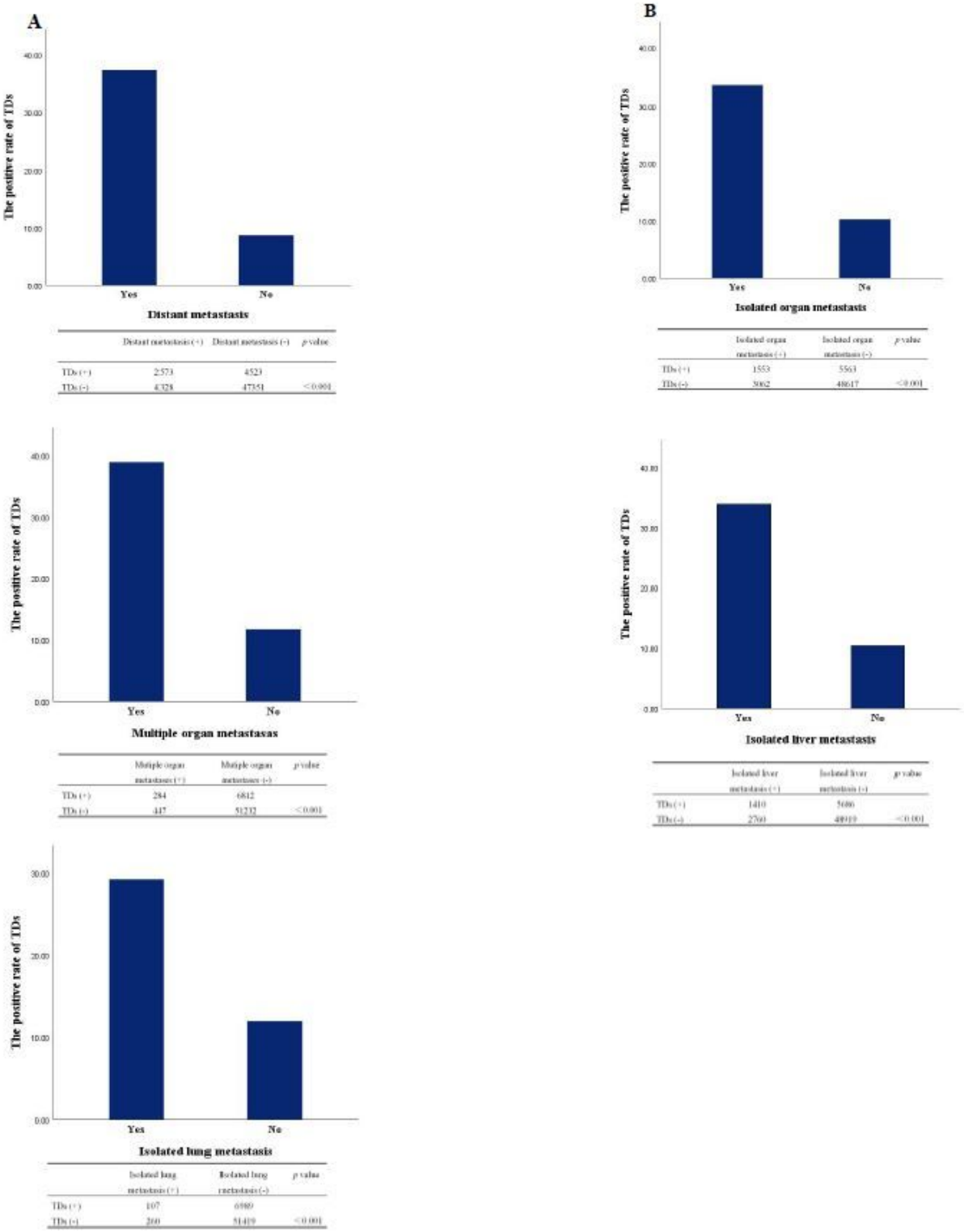


Figure 2

The Kaplan-Meier and log-rank test of overall survival (OS) based on the different cohort. The patients with TDs showed significantly shorter OS than patients without TDs. A Entire cohort. B Stage IV cohort. C Isolated organ metastasis cohort. D Multiple organ metastases cohort. E Isolated liver metastasis cohort. F Isolated lung metastasis cohort.



	Distant metastasis (+)	Distant metastasis (-)	p value
TDs (+)	2573	4523	
TDs (-)	4728	47351	<0.001

	Isolated organ metastasis (+)	Isolated organ metastasis (-)	p value
TDs (+)	1553	5563	
TDs (-)	3062	48617	<0.001

	Multiple organ metastases (+)	Multiple organ metastases (-)	p value
TDs (+)	284	6812	
TDs (-)	447	51232	<0.001

	Isolated liver metastasis (+)	Isolated liver metastasis (-)	p value
TDs (+)	1410	5686	
TDs (-)	2760	49919	<0.001

	Isolated lung metastasis (+)	Isolated lung metastasis (-)	p value
TDs (+)	107	6989	
TDs (-)	260	51419	<0.001

Figure 3

The positive rate of TDs based on whether or not metastasis in different patterns and Chi-square test verifies the distribution of TDs.

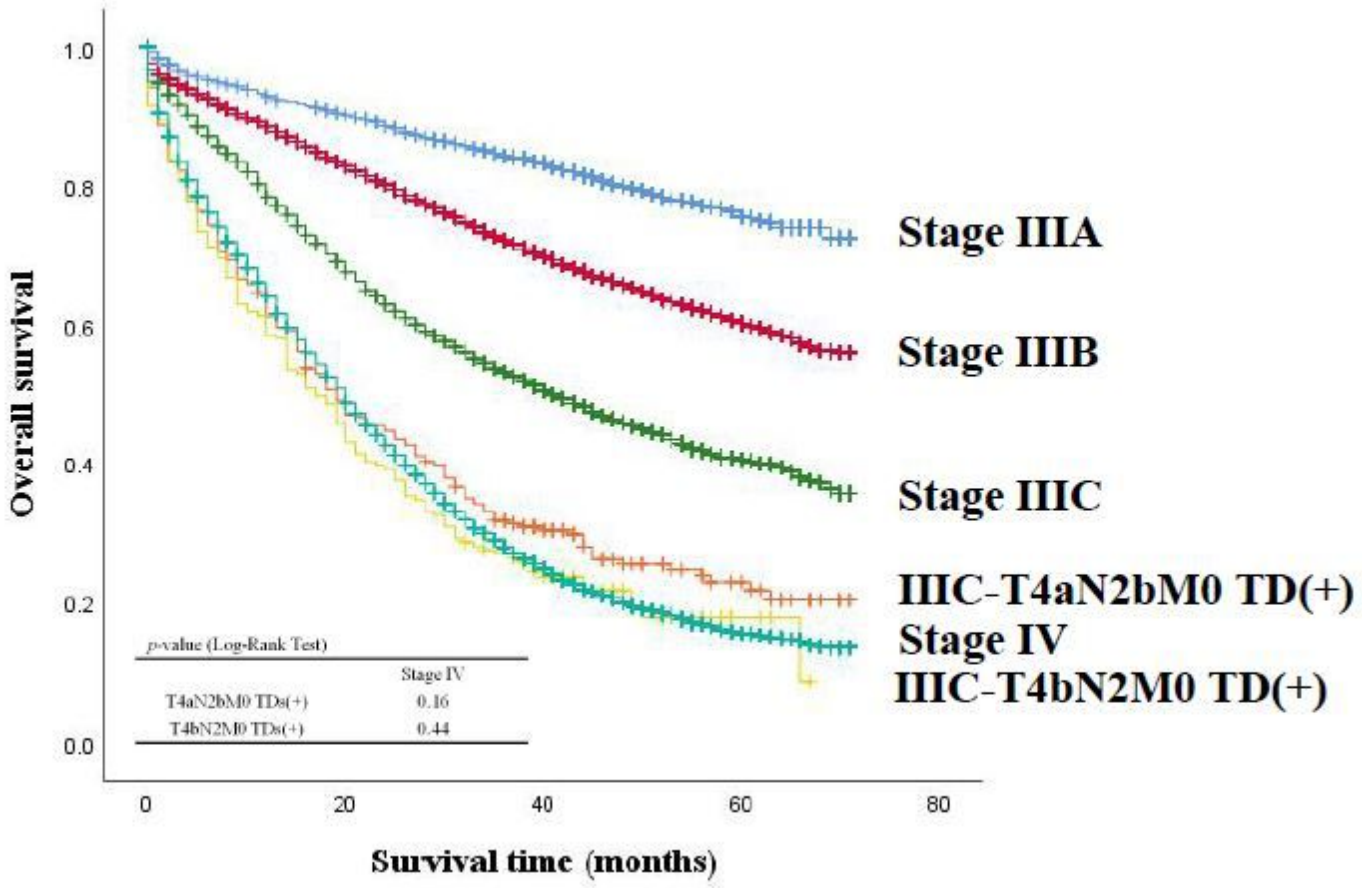


Figure 4

The Kaplan-Meier and log-rank test of overall survival (OS) based on the clinical stage. Note the survival curve of the“T4aN2bM0 TDs (+)” and “T4bN2M0 TDs (+)” group, which shows decreased survival compared with clinical stage III, and it is similar to the stage IV group.