Female colon cancer: pattern and prognosis of distant metastases

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Abstract

Background: The purpose of this study was to compare the metastatic pattern and prognosis of female colon cancer (FCC) to that of male colon cancer (MCC) to ascertain the independent factors impacting the prognosis of patients with FCC.

Patients and Methods: The data of 135503 patients with colon cancer diagnosed between 2010 and 2017 with at least five years of follow-up were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database. The Pearson chi-square test and Fisher exact probability method were used to compare clinicopathological features. Kaplan-Meier analysis was used to compare survival differences. The Cox proportional risk model was utilized to evaluate the prognostic factors impacting overall survival.

Results: A total of 22977 patients with metastatic colon cancer were identified;12172(53.0%) in males and 10805(47.0%) in females. Compared to non-metastatic FCC patients, a greater proportion of metastatic FCC patients, were less than 60 years of age, black race, and grade III-IV. The primary sites were mainly located on the left side. Compared to metastatic MCC patients, a higher proportion of metastatic FCC patients ranged over 60 years of age, black race, and chemotherapy, while the primary site was located on the right side. Among CC patients who had distant metastasis of a single organ, Liver and lung were the two most common sites, and patients with lung metastases had a better prognosis than those with other types of metastasizes. FCC patients with liver metastasis had a worse prognosis than their MCC counterparts and were more likely to develop lung metastases. Cox multivariate regression analysis showed that the risk ratio was higher in metastatic FCC patients compared to those without metastases.

Conclusions: We report the survival comparison of metastatic FCC with non-metastatic FCC through the SEER database. Our results suggest that it has unique clinicopathologic features and differs from metastatic MCC. Furthermore, patients with liver metastatic FCC have a worse prognosis than those with MCC. Emphasis on screening for colon cancer in women and additional clinical care should be paid for, especially for patients with FCC with metastatic liver cancer.

1 Introduction

Colon cancer (CC) is the third most prevalent cancer in the United States, occurring in both men and women, and is also the third leading cause of mortality from cancer (1). The cumulative risk of developing colon cancer before 75 years is 1.51% and 1.12% for men and women, respectively, giving a rate of 1 in 66 men and 1 in 89 women to develop CC (2). Despite recent advances in chemotherapy and radiotherapy for CC, surgical resection remains the primary treatment, but there are gender differences in CC treatment choices (3, 4).

In general, body mass index and gender may be the first patient characteristic to be considered when discussing tumor differences between patient subgroups. Recent studies suggest that BMI does not significantly affect long-term outcomes in colorectal cancer patients (5). Gender differences in tumor behavior exist in patients with colon cancer (6), but the exact mechanisms are unknown. The high mortality rate of colon cancer is mainly due to distant metastases, and the degree of CC differentiation and histopathological type are all factors that affect the prognosis of CC patients (7, 8). While the clinical characteristics, metastatic patterns, and factors related to the prognosis in FCC with distant metastases have not been thoroughly described, which means these variables in the patient populations remain in uncharted territory for this type of disease to be explored. Thus, we identified the FCC data recorded in this study from 2010 to 2017 in the SEER database. We conducted cross-sectional and longitudinal studies of patients with metastatic FCC to determine their clinicopathological characteristics and differences from patients with metastatic MCC and identify independent factors that affect the prognosis of patients with FCC.

2 Materials And Methods

2.1 The SEER database

The SEER collects population-based data on cancer cases within the areas served by SEER cancer registries and contains data on demographics, tumor characteristics, first course of treatment, follow-up, vital status, and other information. SEER cancer registries follow the CoC requirements on follow-up and vital status (9). In this study, we used data from the SEER-18 registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, the Alaska Native, Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey), which represents 28% of the U.S. general population (10).

2.2 Study population

Patients included in the study were those ≥ 18 years old histologically diagnosed with colon cancer between 2010 and 2017. The inclusion criteria were as follows: (a) ICD-O-3 site codes: cecum, ascending colon, hepatic flexure of colon, transverse colon, splenic flexure of colon, descending colon, and sigmoid colon; overlapping lesion of colon, colon NOS; (b)colon cancer was the only primary malignancy; (c)patients who were under active follow-up; Furthermore, patients who met the following criteria were excluded: (a)patients with additional primary cancers; (b) patients with no information on the status of distant organ metastases; (c)unknown autopsy or death certificate diagnoses, diagnoses not confirmed by pathology ; (d) unknown survival months. After completing the necessary screening, we were able to identify 135503 individuals who were qualified for survival analysis and other investigations (Fig. 1). The patients were separated into two groups: FCC and MCC.

2.3 Study variables

The variables included in the present study were age at diagnosis, race(black,white,other), primary site, histological type, histological grade, AJCC TN status, tumor size, serum CEA levels, metastasis sites (liver, lung, brain, and bone), information of therapy (surgery, radiotherapy, and chemotherapy) and marital status. Patients in the SEER database who were classified as American Indians / Alaska Aboriginal or Asian / Pacific Islanders were categorized into the“others” race category to conduct the analysis. The AJCC 7th edition was used to determine clinicopathological staging (11). Metastasis of distant organs is defined in SEER as the state of metastasis of distant organs at the time of the first diagnosis of cancer. In our research, the primary outcome was overall survival(OS), which was defined as the time interval between the day of diagnosis and death for all causes. All information from the SEER program is available and free for the public, so the agreement of the medical ethics committee board was not necessary.

2.4 Statistical analysis

To summarize demographic and clinical factors, we performed descriptive statistics. The Pearson chi-square test and Fisher exact probability method were utilized to evaluate clinicopathological variables between cohorts. The OS of patients with MCC and FCC with distinct metastatic organs was analyzed by Kaplan-Meier and log-rank test. In addition, we looked for other factors that could impact prognosis using univariate and multivariate Cox proportional risk models. All the tests were two-sided, and statistical significance was defined as $p < 0.05$. The SEER*Stat program version 8.3.9 was used to collect all of the data. All statistical analyses were conducted using R software version 4.0.4.

3 Results

3.1 Patient clinicopathological data

A total number of 67855 FCC patients were enrolled in the study. 10805 cases (15.9%) of these FCC patients had distant metastases. A higher proportion of FCC patients with distant metastases were younger than 60 years, black, grade III-IV receiving chemotherapy and radiotherapy, and married than FCC patients without metastases. The proportion of patients with the primary site in the right colon, and surgery was lower. In addition, we compared the clinicopathological features of patients with metastatic colon cancer between different genders. Metastatic FCC patients had more diagnoses than metastatic MCC patients age > 60 years, black race, right colon, and unmarried; the former were less likely to receive chemotherapy than the latter. Nevertheless, Both groups had identical pathology, pathological grading, TN stage, CEA level, surgery, and radiation. Table 1 shows the detailed patient clinical characteristics.

Table 1
Clinical characteristics of male and female patients with colon cancer.

	MCC without metastasis		MCC with metastasis		FCC without metastasis		FCC with metastasis		P value†	P value‡	P value for female
	N 55476		N 12172		N 57050		N 10805				
Age at diagnosis(year)									< 0.0001	.001	< 0.0001
≤ 60	20225	36.5%	5081	41.7%	17163	30.1%	4278	39.6%			
>60	35251	63.5%	7091	58.3%	39887	69.9%	6527	60.4%			
Race									< 0.0001	< 0.0001	< 0.0001
Black	6658	12.0%	2039	16.8%	7697	13.5%	2028	18.8%			
White	42716	77.0%	9022	74.1%	43340	76.0%	7739	71.6%			
Others	5362	9.7%	1077	8.8%	5429	9.5%	1008	9.3%			
Unknown	740	1.3%	34	0.3%	584	1.0%	30	0.3%			
Primary site									< 0.0001	< 0.0001	< 0.0001
Right colon	29512	53.2%	5687	46.7%	34899	61.2%	5698	52.7%			
Left colon	24427	44.0%	5321	43.7%	20637	36.2%	3961	36.7%			
Overlapping lesion	721	1.3%	190	1.6%	761	1.3%	194	1.8%			
Unknown	816	1.5%	974	8.0%	753	1.3%	952	8.8%			
Histopathology type									< 0.0001	0.458	< 0.0001
Adenocarcinoma	53540	96.5%	11469	94.2%	54846	96.1%	10156	94.0%			
Others	1936	3.5%	703	5.8%	2204	3.9%	649	6.0%			
Pathology grade									< 0.0001	0.004	< 0.0001
I well-differentiated	5306	9.6%	475	3.9%	5148	9.0%	411	3.8%			
II moderately	35634	64.2%	6121	50.3%	35740	62.6%	5201	48.1%			
III poorly differentiated	6962	12.5%	2112	17.4%	8821	15.5%	1935	17.9%			
IV undifferentiated	1535	2.8%	393	3.2%	2066	3.6%	418	3.9%			
Unknown	6039	10.9%	3071	25.2%	5275	9.2%	2840	26.3%			
T									< 0.0001	0.119	< 0.0001

FCC = femalecolon cancer, MCC = male colon cancer

† Comparison between male colon cancer without metastasis and male colon cancer with metastasis.

‡ Comparison between male colon cancer with metastasis and female colon cancer with metastasis.

	MCC without metastasis		MCC with metastasis		FCC without metastasis		FCC with metastasis		P value†	P value‡	P value for female
	N 55476		N 12172		N 57050		N 10805				
T0-T1	13750	24.8%	1050	8.6%	12307	21.6%	917	8.5%			
T2	6877	12.4%	207	1.7%	7471	13.1%	166	1.5%			
T3	24564	44.3%	3786	31.1%	25894	45.4%	3214	29.7%			
T4	7987	14.4%	3133	25.7%	8965	15.7%	2879	26.6%			
Unknown	2298	4.1%	3996	32.8%	2413	4.2%	3629	33.6%			
N									< 0.0001	0.308	< 0.0001
N0	35759	64.5%	3774	31.0%	35853	62.8%	3430	31.7%			
N1	11935	21.5%	3760	30.9%	12730	22.3%	3218	29.8%			
N2	6397	11.5%	3051	25.1%	7012	12.3%	2747	25.4%			
Unknown	1385	2.5%	1587	13.0%	1455	2.6%	1410	13.0%			
Stage									< 0.0001	*	< 0.0001
0	4111	7.4%	0	0%	3465	6.1%	0	0%			
I	14094	25.4%	0	0%	13863	24.3%	0	0%			
II	16510	29.8%	0	0%	17426	30.5%	0	0%			
III	18332	33.0%	0	0%	19742	34.6%	0	0%			
IV	0	0%	12172	100%	0	0%	10805	0%			
Unknown	2429	4.4%	0	0%	2554	4.5%	0	0%			
Tumor size									< 0.0001	< 0.0001	< 0.0001
≤ 2cm	9007	16.2%	371	3.0%	8637	15.1%	350	3.2%			
2—5cm	22247	40.1%	3803	31.2%	24293	42.6%	3652	33.8%			
≥ 5cm	16244	29.3%	4024	33.1%	16927	29.7%	3238	30.0%			
Unknown	7978	14.4%	3974	32.6%	7193	12.6%	3565	33.0%			
CEA level									< 0.0001	0.309	< 0.0001
Positive	10414	18.8%	7292	59.9%	12169	21.3%	6574	60.8%			
Negative	19276	34.7%	1275	10.5%	18536	32.5%	1067	9.9%			
Boardline	159	0.3%	28	0.1%	183	0.3%	19	0.2%			
Unknown	25627	46.2%	3588	29.5%	26162	45.9%	3145	29.1%			

FCC = femalecolon cancer, MCC = male colon cancer

† Comparison between male colon cancer without metastasis and male colon cancer with metastasis.

‡ Comparison between male colon cancer with metastasis and female colon cancer with metastasis.

	MCC without metastasis		MCC with metastasis		FCC without metastasis		FCC with metastasis		P value†	P value‡	P value for female
	N 55476		N 12172		N 57050		N 10805				
Surgery									< 0.0001	< 0.0001	< 0.0001
No	2985	5.4%	5586	45.9%	3078	5.4%	4985	46.1%			
primary site resection	52249	94.2%	6518	53.5%	53575	93.9%	5725	53.0%			
primary site resection and metastasectomy	174	0.3%	44	0.4%	336	0.6%	85	0.8%			
Unknown	68	0.1%	24	0.2%	61	0.1%	10	0.1%			
Radiotherapy									< 0.0001	0.606	< 0.0001
No	54678	98.6%	11646	95.7%	56455	99.0%	10323	95.5%			
Yes	798	1.4%	526	4.3%	595	1.0%	482	4.5%			
Chemotherapy									< 0.0001	0.001	< 0.0001
No	39747	71.6%	4178	34.3%	41585	72.9%	3934	36.4%			
Yes	15729	28.4%	7994	65.7%	15465	27.1%	6871	63.6%			
Marital status									< 0.0001	< 0.0001	< 0.0001
Married	33522	60.4%	6922	56.9%	23952	42.0%	4596	42.5%			
Unmarried	18388	33.1%	4657	38.3%	29307	51.4%	5648	52.3%			
Unknown	3566	6.4%	593	0.9%	3791	6.6%	561	5.2%			
FCC = femalecolon cancer, MCC = male colon cancer											
† Comparison between male colon cancer without metastasis and male colon cancer with metastasis.											
‡ Comparison between male colon cancer with metastasis and female colon cancer with metastasis.											

3.2 Metastasis pattern

The majority (76.7%) of the cohort of FCC patients had distant metastasis of a single organ. The most common location of metastases was the liver, which represented 68.6% of the patients. The number of lung metastasis accounted for 716 (6.6%). Very few patients had bone or brain metastasis. Concerning the differences in metastasis patterns between FCC and MCC, MCC patients had a lower proportion of brain metastases only than their FCC counterparts (0.3 vs 0.5), as well as lung metastases only (5.2 vs 6.6%), whereas the percentage of bone and liver metastases was higher in MCC patients. (Table 2).

Table 2
Comparison of organ metastasis patterns between male and female patients with colon cancer.

Variable	Male		Female		P value
	N = 12172		N = 10805		
	n	%	n	%	
Bone metastasis only	123	1.0	101	0.9	0.560*
Brain metastasis only	38	0.3	54	0.5	0.025*
Liver metastasis only	8422	69.2	7413	68.6	0.339*
Lung metastasis only	639	5.2	716	6.6	< 0.0001*
Bone and brain	4	0.0	5	0.0	0.608*
Bone and liver	327	2.7	243	2.2	0.033*
Bone and lung	67	0.6	47	0.4	0.214
Brain and liver	32	0.3	31	0.3	0.728*
Brain and lung	24	0.2	20	0.2	0.834*
Liver and lung	2144	17.6	1907	17.6	0.945*
Bone, brain, and liver	14	0.1	10	0.1	0.599*
Bone, brain, and lung	9	0.1	5	0.0	0.396*
Bone, liver, and lung	255	2.1	200	1.9	0.185*
Brain, liver, and lung	44	0.4	37	0.3	0.808*
Bone, brain, liver, and lung	30	0.2	16	0.1	0.096*
One site metastasis	9222	75.8	8284	76.7	0.108*
Two sites metastasis	2598	21.3	2253	20.9	0.361*
Three sites metastasis	322	2.6	252	2.3	0.129*
Four sites metastasis	30	0.2	16	0.1	0.096*

*Pearson chi-squared test.

3.3 Survival analysis

We analyzed whether the effects of gender on survival was related to other independent prognostic factors. Our study showed that the less favorable survival rate of FCC patients was associated with the age at diagnosis, race, CEA level, and surgery. In each of the following subgroups, including > 60 years of age, blacks, positive CEA, and non-operation, The prognosis of female patients was worse than that of male patients (Fig. 2). Next, among patients with metastatic colon cancer by gender, liver metastases only, lung metastases only, and combined liver metastases with lung metastases accounted for more than 90% of the total metastatic population. We included these three groups in our survival and prognosis analyses to investigate the influence of distant metastases on prognosis. Kaplan-Meier analysis showed that for patients with liver metastases only, the survival rate of MCC patients was better than that of FCC patients and was statistically significant (p = 0.012), while for the other

two groups, our analysis showed no statistical difference in OS by gender (Fig. 3). However, it appears that patients between those three groups and non-metastatic FCC were significantly different (Fig. 4). Survival rates decreased as the number of metastatic sites increased in patients with metastatic FCC (Fig. 5). The Cox univariate analysis revealed that age, race, tumor primary site, histopathology type, pathology grade, TN stage, tumor size, CEA level, surgery, chemotherapy, marital status, and the metastatic sites were independent factors affecting OS ($p < 0.001$), and these variables were included in the multivariate model (Table 3).In detail, black, age > 60 years, primary tumor site in the right colon or the overlapping lesion, non-adenocarcinoma, pathological grade II, grade III and grade IV, tumor size > 2cm, positive CEA, distant metastasis, treatment without surgery, and chemotherapy, single, and distant metastasis correlated with poor prognosis. Radiation therapy did not affect the outcome of this study.

Table 3
Univariate and multivariate survival analysis of female colon cancer patients with liver alone, lung alone and, simultaneous liver and lung metastasis.

Characteristics	Univariate analysis	Multivariate analysis		
	p value	Hazard ratio	95%CI	P value
Age at diagnosis(year)	< .001			< .001
≤ 60		Reference		
>60		1.74	1.68–1.8	< .001
Race:	< .001			< .001
Black		Reference		
White		0.99	0.95–1.03	0.519
Others		0.84	0.79–0.89	< .001
Unknown		0.14	0.1–0.21	< .001
Primary site	< .001			< .001
Right colon		Reference		
Left colon		0.86	0.84–0.89	< .001
Overlapping lesion		1.13	1.02–1.24	0.015
Unknown		1.36	1.27–1.46	< .001
Histopathology type	< .001			< .001
Adenocarcinoma		Reference		
Others		1.14	1.08–1.21	< .001
Pathology grade	< .001			< .001
I well-differentiated		Reference		
II moderately		1.21	1.14–1.29	< .001
III poorly differentiated		1.64	1.54–1.76	< .001
IV undifferentiated		1.92	1.76–2.08	< .001
Unknown		1.18	1.1 – 1.26	< .001
T stage	< .001			< .001
T0-T1		Reference		
T2		0.92	0.87–1.01	0.109
T3		1.39	1.31–1.47	< .001
T4		2.60	2.45–2.75	< .001
Unknown		1.56	1.47–1.66	< .001
N stage	< .001			< .001
N0		Reference		

Characteristics	Univariate analysis	Multivariate analysis		
	p value	Hazard ratio	95%CI	P value
N1		1.65	1.59–1.71	< .001
N2		2.89	2.78–3.02	< .001
Unknown		1.15	1.08–1.22	< .001
Tumor size				
≤ 2cm	< .001	Reference		
2—5cm		1.38	1.29–1.47	< .001
≥ 5cm		1.50	1.4–1.6	< .001
Unknown		1.37	1.28–1.46	< .001
CEA level	< .001			
Positive		Reference		
Negative		0.64	0.62–0.67	< .001
Boardline		0.86	0.68–1.09	0.2128
Unknown		0.87	0.84–0.9	< .001
Surgery	< .001			< .001
No		Reference		
primary site resection		0.18	0.17–0.19	< .001
primary site resection and metastasectomy		0.21	0.17–0.24	< .001
Unknown		0.52	0.37–0.74	< .001
Radiotherapy	< .001			0.2236
No		Reference		
Yes		1.05	0.95–1.17	0.3189
Chemotherapy	< .001			< .001
No		Reference		
Yes		0.43	0.41–0.44	< .001
Marital status	< .001			< .001
Married		Reference		
Unmarried		1.37	1.33–1.41	< .001
Unknown		1.10	1.04–1.17	< .001
Metastasis	< .001			< .001
None		Reference		
Liver only		2.83	2.72–2.94	< .001
Lung only		2.17	1.98–2.38	< .001

Characteristics	Univariate analysis	Multivariate analysis		
	p value	Hazard ratio	95%CI	P value
Liver and lung		3.04	2.87–3.23	< .001

4 Discussion

In both men and women, colon cancer is one of the most prevalent causes of cancer development. Despite recent advances in CC screening, diagnosis, and treatment, the long-term prognosis of CC patients remains poor (1). The prognosis of patients with metastatic and non-metastatic FCC was compared with patients with MCC. To our knowledge, this study is the first gender-focused metastasis model-based analysis of colon cancer data.

In this study, the metastasis rate was 18.0% versus 15.9% in male versus female colon cancer patients, respectively. The incidence of colon cancer increased significantly with age. According to past research, younger cc patients are more likely to develop metastases than older patients and have limited surgical and chemotherapeutic treatment (12). Similarly, younger CC patients in this study developed metastases significantly more than older CC patients, and when women were diagnosed with colon cancer, they were significantly older than men and presented with more severe disease. The 2015 National Health Interview Survey showed that colorectal cancer screening was slightly lower in women than in men (60.2% vs 62.4%)(13). This may be explained by the lower rate of screening colonoscopy in women over 65 years of age than men of the same age (14). A higher rate of incomplete colonoscopy in women has also been reported (15), contributing to more colon cancers in women of advanced age. The population was more than 3/4 white in the data we included, but we found that black CC patients were more likely to have distant metastases, consistent with previously reported results (16). Previous studies have demonstrated a lack of awareness of screening guidelines in general and in African American men in particular (17, 18).

Furthermore, black patients with metastatic colorectal cancer are less likely to get chemotherapy or have liver metastasectomy, and they are less likely to discuss or contemplate participating in studies (19, 20). During the multivariate analysis of this study, no racial differences in OS were observed. Previous studies have shown that no racial difference in survival was observed among patients aged 50 years or older; however, among younger patients, non-Hispanic Blacks experienced worse survival than non-Hispanic Blacks(21). The effect of racial differences on female patients remains to be studied. The primary location of the tumor is strongly associated with patient prognosis, as reported in different types of cancer (22–24).In the same vein, Ishihara et al. (25) found that proximal indolent cell carcinoma is considered a distinct subgroup with a good tumor prognosis in colon cancer. Our analysis from a gender perspective showed that the primary tumor location of FCC was more often located in the right colon than MCC, which is consistent with previous reports (4). However, both were more likely to metastasize in the left colon than the right colon. In patients with colon cancer, researchers developed a nomogram that predicted risk variables for liver and lung metastasis, with tumor site being an independent risk factor for metastasis (26). As we mentioned earlier, women have a higher rate of incomplete colonoscopy (12). In addition, some women tend to have a more extended colon cross-section and smaller bowel diameter, making standard colonoscopy equipment usually unsuitable for this group of women (27). Therefore, we recommend that women need to choose a thinner colonoscopy device for a complete colonoscopy when undergoing colon cancer screening to reduce the number of missed right colon cancer due to the device and physiological configuration.

The preference for chemotherapy and radiation therapy over surgery in advanced cancers may also explain why patients with metastatic FCC rarely undergo surgery. However, we found that the risk ratio of primary site resection and primary site resection combined with metastasectomy was much smaller than that of non-surgical patients. Therefore, it is necessary to actively accept surgical treatment for colon cancer patients. Treatment of stage IV colon cancer remains challenging, and despite recent advances in chemotherapy and other palliative treatment modalities, the best treatment options for colon cancer with unresectable metastases remain to be elucidated. Interestingly, the number of patients treated with radiation is more than 5% for male and female patients. Adjuvant external beam radiation is usually not recommended due to the difficulty of targeting and the

proximity of critical surrounding structures (e.g., small intestine), as these factors can limit the dose that can kill the tumor. Recent findings show that adjuvant radiotherapy can significantly prolong OS in patients with advanced local disease (pT4) and positive cut margins (28, 29); therefore, adjuvant therapy for CC patients should not be abandoned due to the limitations of RT. Hypodifferentiated versus undifferentiated colon cancer is more likely to develop distant metastases, and there is no difference between men and women.

Although modern research has been able to elucidate the pathogenesis of CC and provide effective screening strategies, the prevalence of CC is still increasing. A better understanding of the occurrence, progression, and metastasis of CC can help develop molecular markers for early detection and risk stratification methods to improve clinical care for CC patients. We compared distant metastasis patterns in patients with MCC and FCC in depth using the SEER database to understand the survival differences between patients with different metastasis patterns. Single-site metastases occurred in more than three-quarters of the total number of patients. Overall, the liver and brain were the most common and least common sites of solitary metastases in patients with CC, respectively, consistent with prior reports (29). Due to the blood-brain barrier, fewer patients had brain metastases alone (0.3% vs. 0.5%), but when combined with metastases from other sites, brain metastases exceeded 1% in both sexes.

Similarly, when lung metastases were combined with liver metastases, the number of patients was much higher than that of patients with lung metastases alone. We believe that once a tumor develops distant metastasis in one organ, it may accelerate metastasis in other sites, although brain metastasis alone is uncommon when it has metastasis in other sites. Interestingly, FCC was more likely to have a single lung metastasis than MCC, yet we found no significant difference in their OS.

The clinicopathological characteristics and metastatic patterns of metastatic MCC and FCC were different in the present study. Multivariate Cox regression showed that in patients with FCC, advanced age, primary site in the right colon, higher pathological grade, tumor size > 2cm, positive CEA level, and distant organ metastasis were independent risk factors affecting the prognosis of patients with FCC (Table 3). The most common site of distant metastasis in patients with CC is the liver, but we found differences in prognosis by gender, and the survival of patients with single liver metastasis in FCC was significantly lower than that of MCC in the same group (P = 0.012), especially in the first 36 months. Once the tumor metastasized, patient survival decreased, and the OS decreased more with increasing metastatic sites, and the same results have been reported in other tumors (30, 31). Liver and lung are the two most common sites of solitary metastases in FCC (32), but there are differences in OS in patients with these two metastases. The OS of patients with solitary lung metastasis was significantly higher than that of patients with solitary liver metastasis. Reasons for the difference still need further exploration. However, there are some limitations which worth further research in this study; firstly, the data source used in this study was the SEER database. We were only able to study this with the available information on four organ metastases, namely liver, lung, bone, and brain, due to the inability to obtain data on other metastasis sites, we can not conduct a more comprehensive study. Secondly, there are differences in metastatic patterns between males and females, but we could not determine which factors are associated with them. That said, further research to clarify the rationale underlying these differences is necessary. Finally, our conclusions may apply only to patients from the United States.

Conclusion

Our population-based analysis of 135503 CC patients found that older women were diagnosed with colon cancer and that advanced age at diagnosis (>60 years) significantly predicted worsening OS. The primary site of FCC was more likely to be in the right colon. Female patients may be more likely to have pulmonary metastases; although the most common distant sites of metastasis for both FCC and MCC are liver and lung, patients with liver metastases from FCC have a worse prognosis than their MCC counterparts, and we also found that patients with liver metastases from FCC have a worse prognosis than those with pulmonary metastases. The results of this study have some reference value for clinicians in dealing with CC patients, who should pay attention to colon cancer screening in women and should actively receive treatment for FCC patients with liver metastases and lung metastases to improve their prognosis.

Abbreviations

CC: Colon cancer; FCC: Female colon cancer; MCC: Male colon cancer; SEER: Surveillance, Epidemiology, and End Results; CoC: Commission on Cancer; ICD-O-3: International Classification of Diseases for Oncology, Third Edition; AJCC: American Joint Committee on Cancer; OS: Overall survival.

Declarations

Acknowledgments

Not applicable.

Author contributions

Liu YR, Kang RB, Zheng HD, and Xu JH designed the study. Wang PC, Jiang WX, and Xiong B contributed to the literature search. Liu YR, Jiang WX, and Chen JT extracted and analyzed the data. Liu YR and Kang RB wrote the paper. Liu YR and Kang RB contributed equally to this work and should be considered as co-first authors. All authors contributed to the article and approved the submitted version.

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Availability of data and materials

The data supporting this study's results are available from the corresponding author on request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* (2020) 70: 7–30. doi: 10.3322/caac.21590
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin (2018) 68: 394–424. doi: 10.3322/caac.21492
3. Oliver JS, Martin MY, Richardson L, Kim Y, Pisu M. Gender differences in colon cancer treatment. J Womens Health (Larchmt) (2013) 22: 344–51. doi: 10.1089/jwh.2012.3988
4. Schmuck R, Gerken M, Teegen EM, Krebs I, Klinkhammer-Schalke M, Aigner F, et al. Gender comparison of clinical, histopathological, therapeutic and outcome factors in 185,967 colon cancer patients. Langenbecks Arch Surg (2020) 405: 71–80. doi: 10.1007/s00423-019-01850-6
5. Fanipakdel A, Hosseini S, Javadinia SA,Farzin Afkhami Jeddi,Mostafa Vasei. The Prognostic Role of Body Mass Index in Survival of Non-metastatic Postoperative Patients with Colorectal Cancer. International Journal of Cancer Management(2021) 14.doi: 10.5812/ijcm.110257

6. Majek O, Gondos A, Jansen L, Emrich K, Holleczek B, Katalinic A, et al. Sex differences in colorectal cancer survival: population-based analysis of 164,996 colorectal cancer patients in Germany. PLoS One (2013) 8: e68077. doi: 10.1371/journal.pone.0068077
7. Gupta P, Chiang SF, Sahoo PK, Mohapatra SK, You JF, Onthoni DD, et al. Prediction of Colon Cancer Stages and Survival Period with Machine Learning Approach. Cancers (Basel) (2019) 11. doi: 10.3390/cancers11122007
8. Recio-Boiles A, Cagir B. Colon Cancer. *StatPearls*. Treasure Island (FL): StatPearls Publishing (2022). p.
9. National Cancer Institute SEER Taining Models. Cancer Patients Follo-up: Requirements of CoC/Governing Agencies. https://training.seer.cancer.gov/followup/intro/requirements.html. AccessedJanuary 16, 2020.
10. SEER*Stat Databases: November 2015 Submission. Case Listing and Frequency Sessions: https://seer.cancer.gov/data-software/documentation/seerstat/nov2015/Surveillance, Epidemiology, and End Results Program. AccessedJuly 31, 2019.
11. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol (2010) 17: 1471–4. doi: 10.1245/s10434-010-0985-4
12. Berian JR, Benson AB, 3rd, Nelson H. Young Age and Aggressive Treatment in Colon Cancer. Jama (2015) 314: 613–4. doi: 10.1001/jama.2015.9379
13. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin(2019) 69(3): 184–210. doi: 10.3322/caac.21557. Epub 2019 Mar 15.
14. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer (2015) 136: E359-86. doi: 10.1002/ijc.29210
15. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol (2019) 16: 713–32. doi: 10.1038/s41575-019-0189-8
16. Rutter CM, Knudsen AB, Lin JS, Bouskill KE. Black and White Differences in Colorectal Cancer Screening and Screening Outcomes: A Narrative Review. Cancer Epidemiol Biomarkers Prev (2021) 30: 3–12. doi: 10.1158/1055-9965.Epi-19-1537
17. Rogers CR, Goodson P, Foster MJ. Factors Associated with Colorectal Cancer Screening among Younger African American Men: A Systematic Review. J Health Dispar Res Pract (2015) 8: 133–56. doi:
18. Carnahan LR, Jones L, Brewer KC, Watts EA, Peterson CE, Ferrans CE, et al. Race and Gender Differences in Awareness of Colorectal Cancer Screening Tests and Guidelines Among Recently Diagnosed Colon Cancer Patients in an Urban Setting. J Cancer Educ (2021) 36: 567–75. doi: 10.1007/s13187-019-01666-4
19. Senft N, Hamel LM, Manning MA, Kim S, Penner LA, Moore TF, et al. Willingness to Discuss Clinical Trials Among Black vs White Men With Prostate Cancer. JAMA Oncol (2020) 6: 1773–7. doi: 10.1001/jamaoncol.2020.3697
20. Bliton JN, Parides M, Muscarella P, Papalezova KT, In H. Understanding Racial Disparities in Gastrointestinal Cancer Outcomes: Lack of Surgery Contributes to Lower Survival in African American Patients. Cancer Epidemiol Biomarkers Prev (2021) 30: 529–38. doi: 10.1158/1055-9965.Epi-20-0950
21. Andaya AA, Enewold L, Zahm SH, Shriver CD, Stojadinovic A, McGlynn KM,et al. Race and colon cancer survival in an equal-access health care system. Cancer Epidemiol Biomarkers Prev. (2013) 22(6): 1030–1036. doi:10.1158/1055-9965.EPI-13-0143
22. Mygatt JG, Cullen J, Streicher SA, Kuo HC, Chen Y, Young D, et al. Race, tumor location, and disease progression among low-risk prostate cancer patients. Cancer Med (2020) 9: 2235–42. doi: 10.1002/cam4.2864
23. Shan Q, Li Z, Lin J, Guo J, Han X, Song X, et al. Tumor Primary Location May Affect Metastasis Pattern for Patients with Stage IV NSCLC: A Population-Based Study. J Oncol (2020) 2020: 4784701. doi: 10.1155/2020/4784701
24. Wu S, Zhou J, Ren Y, Sun J, Li F, Lin Q, et al. Tumor location is a prognostic factor for survival of Chinese women with T1-2N0M0 breast cancer. Int J Surg (2014) 12: 394–8. doi: 10.1016/j.ijsu.2014.03.011
25. Ishihara S, Watanabe T, Akahane T, Shimada R, Horiuchi A, Shibuya H, et al. Tumor location is a prognostic factor in poorly differentiated adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma of the colon. Int J Colorectal Dis (2012) 27: 371–9. doi: 10.1007/s00384-011-1343-0

26. Gaitanidis A, Machairas N, Alevizakos M, Tsalikidis C, Tsaroucha A, Pitiakoudis M. Predictive Nomograms for Synchronous Liver and Lung Metastasis in Colon Cancer. J Gastrointest Cancer (2020) 51: 925–31. doi: 10.1007/s12029-019-00325-7
27. Saunders BP, Fukumoto M, Halligan S, Jobling C, Moussa ME, Bartram CI, et al. Why is colonoscopy more difficult in women? Gastrointest Endosc (1996) 43: 124–6. doi: 10.1016/s0016-5107(06)80113-6
28. Wegner RE, Abel S, Monga D, Raj M, Finley G, Nosik S, et al. Utilization of Adjuvant Radiotherapy for Resected Colon Cancer and Its Effect on Outcome. Ann Surg Oncol (2020) 27: 825–32. doi: 10.1245/s10434-019-08042-y
29. Huang Y, Gu X, Ge K, Fu G, Chu J, Wei W. The survival benefit of adjuvant radiotherapy for pathological T4N2M0 colon cancer in the Modern Chemotherapy Era: evidence from the SEER database 2004–2015. Artif Cells Nanomed Biotechnol(2020) 48(1): 834–840. doi: 10.1080/21691401.2020.1770270.
30. Wang J, Li S, Liu Y, Zhang C, Li H, Lai B. Metastatic patterns and survival outcomes in patients with stage IV colon cancer: A population-based analysis. Cancer Med (2020) 9: 361–73. doi: 10.1002/cam4.2673
31. Wang R, Zhu Y, Liu X, Liao X, He J, Niu L. The Clinicopathological features and survival outcomes of patients with different metastatic sites in stage IV breast cancer. BMC Cancer (2019) 19: 1091. doi: 10.1186/s12885-019-6311-z
32. Riihimäki M, Hemminki A, Fallah M, Thomsen H, Sundquist K, Sundquist J, et al. Metastatic sites and survival in lung cancer. Lung Cancer (2014) 86: 78–84. doi: 10.1016/j.lungcan.2014.07.020

Figures

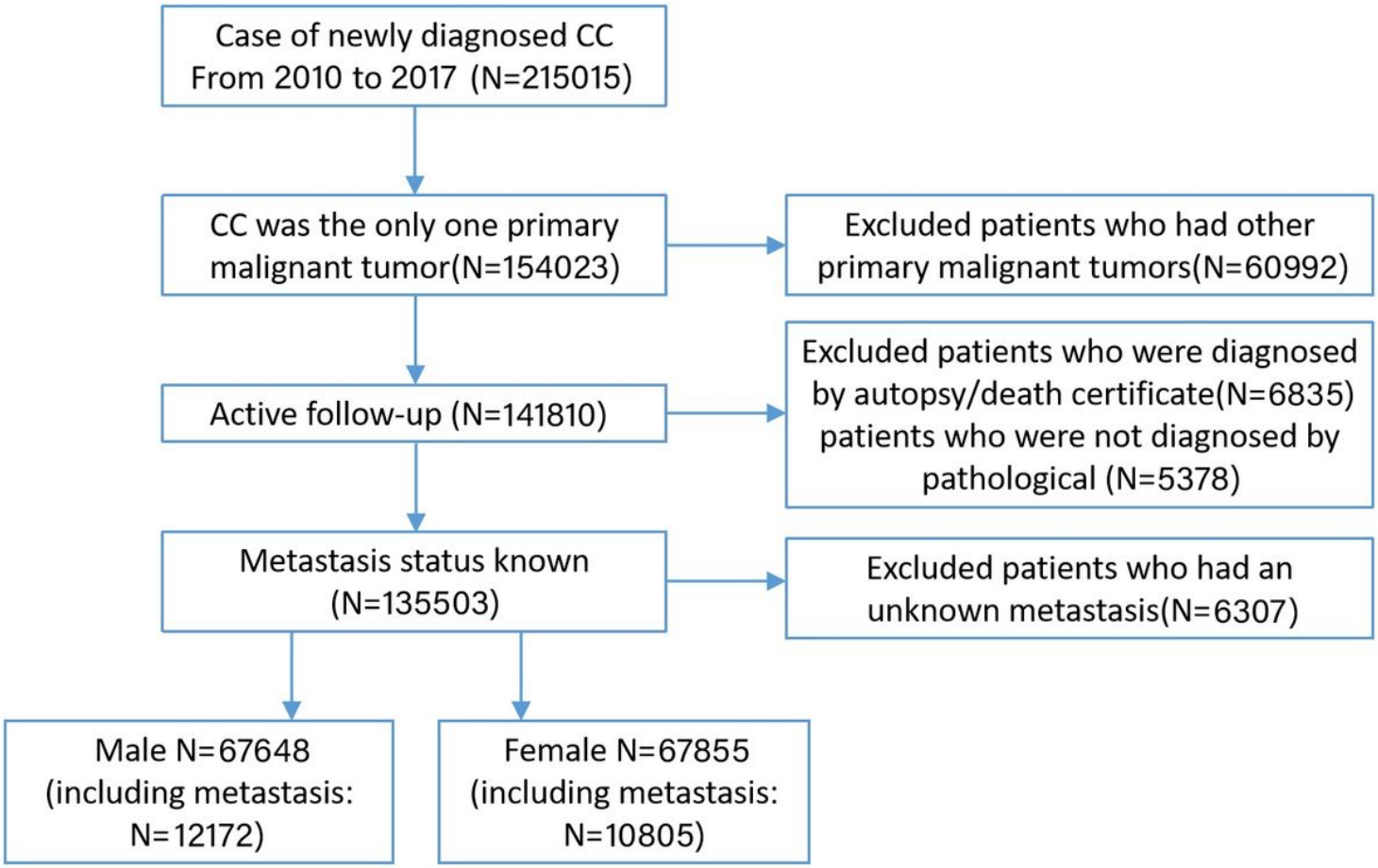

Figure 1

Flowchart of selection of patients with metastatic colon cancer used the SEER database. SEER=surveillance epidemiology and end results.

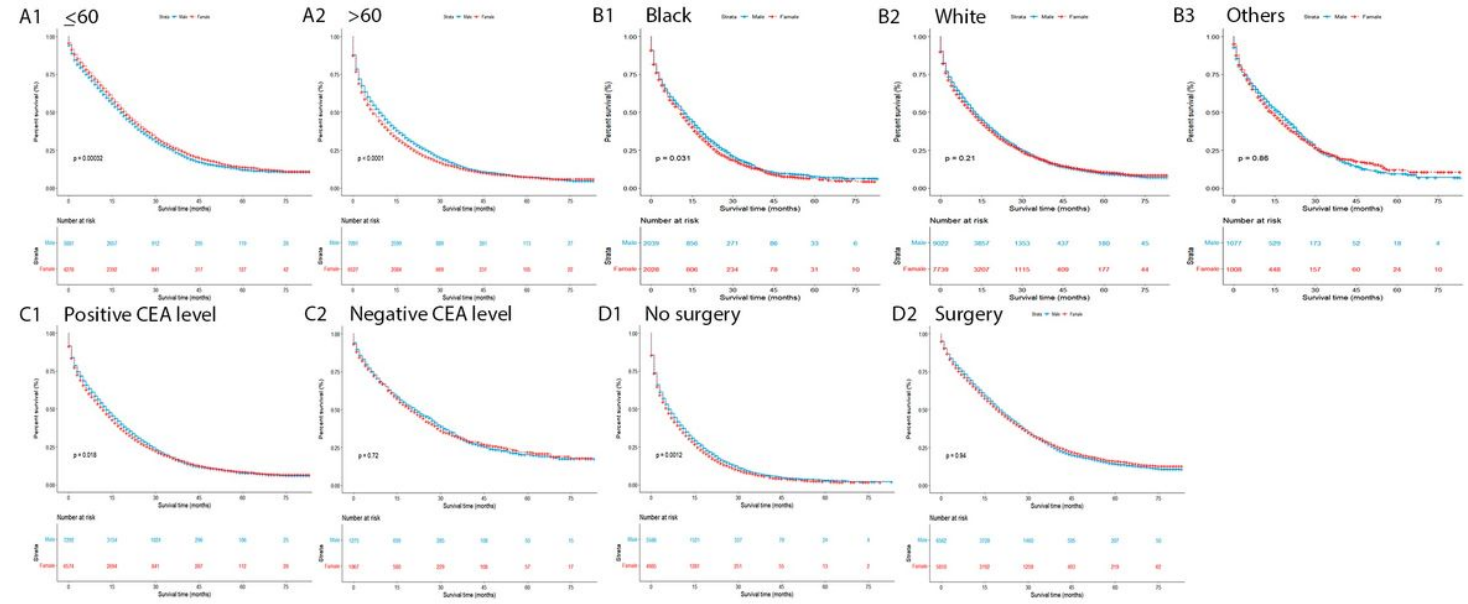

Figure 2

Changes in OS rate of metastatic MCC and metastatic FCC patients for each specific age, race, serum CEA level and surgery group. (A1-A2): OS rate of metastatic MCC andd metastatic FCC patients across subgroups of age at diagnosis. (B1-B3): OS rate of metastatic MCC and metastatic FCC patients across subgroups of race. (C1-C2) :OS rate of metastatic MCC and metastatic FCC patients across subgroups of serum CEA levels. (D1-D2) :OS rate of metastatic MCC and metastatic FCC patients across subgroups of surgery.

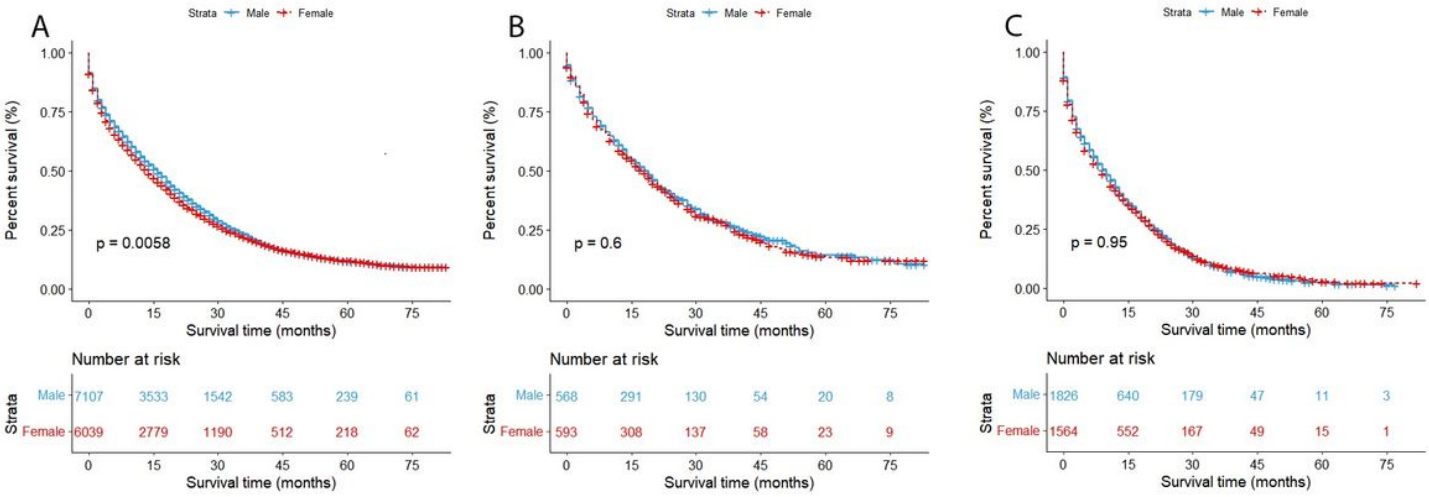

Figure 3

OS rate of MCC and FCC patients at different metastasis sites. (A) OS of liver alone metastasis between MCC and FCC patients; (B) OS of lung alone metastasis between MCC and FCC patients; (C) OS of both liver and lung metastasis between MCC and FCC patients. FCC=female colon cancer, MCC=male colon cancer, OS=overall survival.

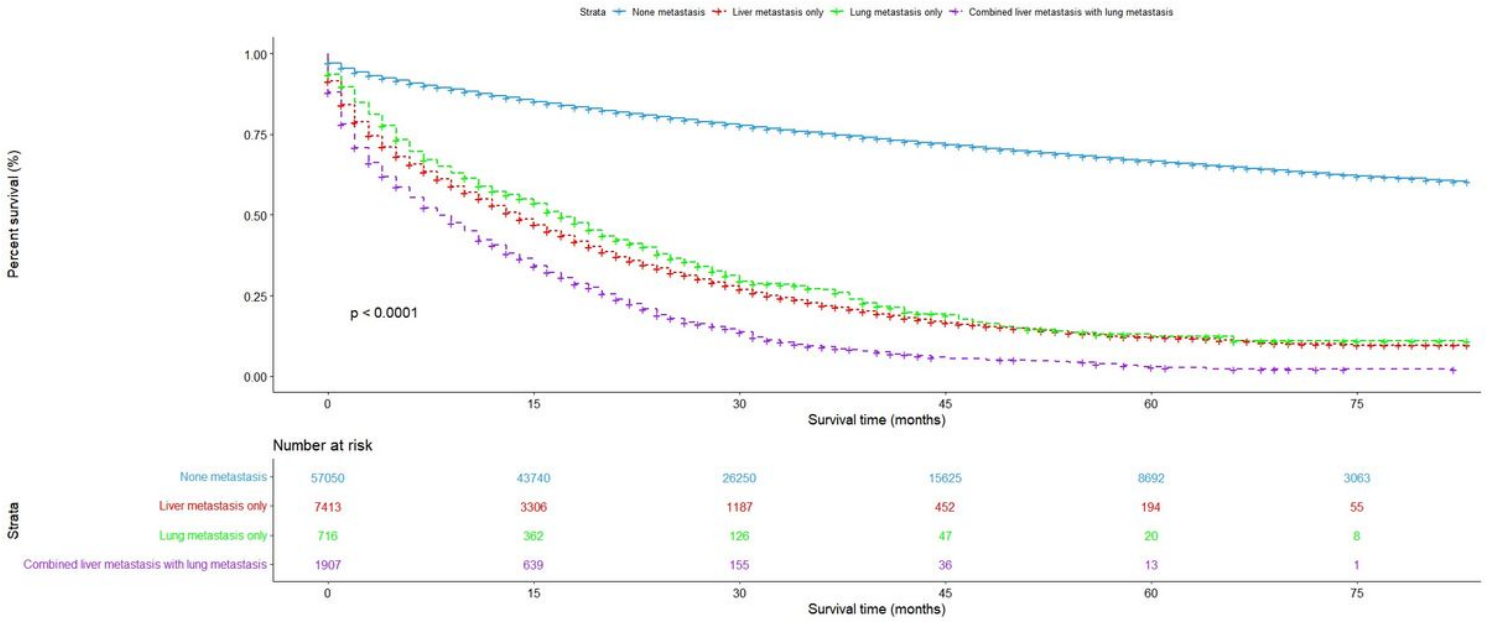

Figure 4

The survival difference among the different metastasis sites in FCC patients. FCC=female colon cancer.

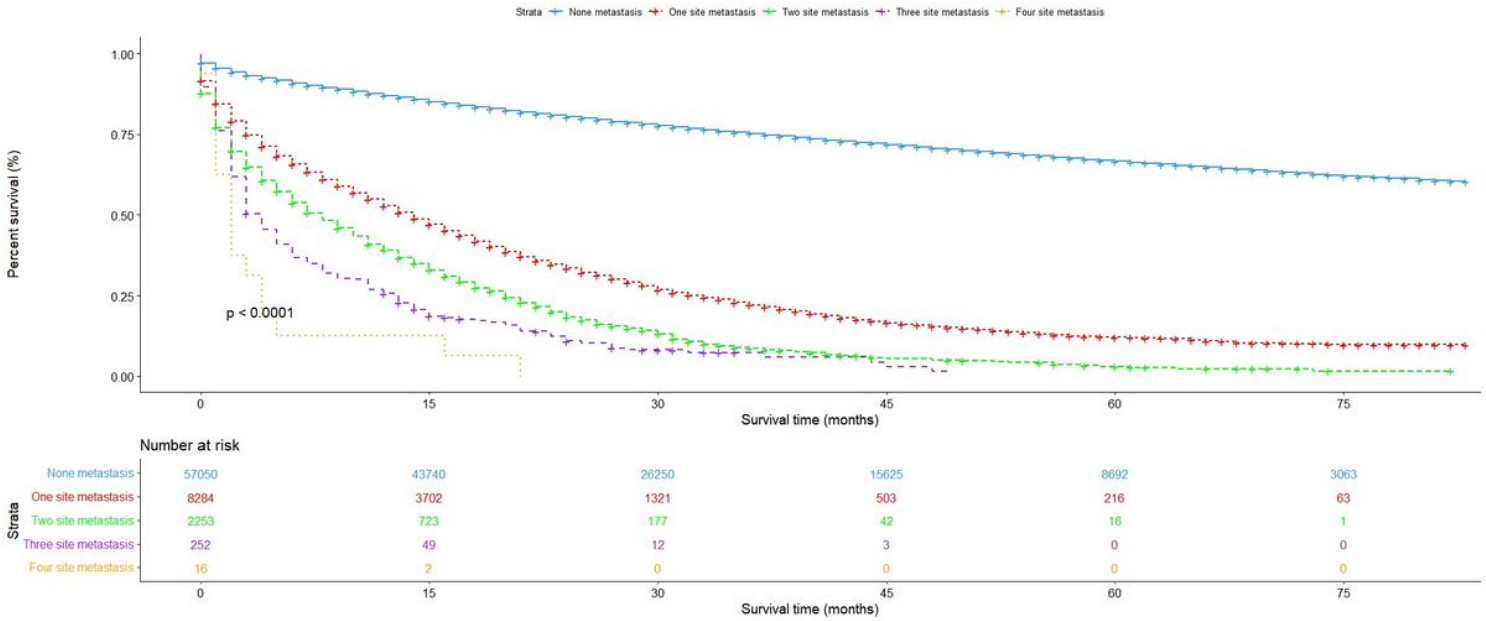

Figure 5

The survival difference among the different number of metastasis sites in FCC patients. FCC=female colon cancer.