Causes of Death After Rectal Cancer Diagnosis: A population-based study

Yanyan Jin (✉ 651099063@QQ.COM)

Wenzhou Medical University <https://orcid.org/0000-0001-9974-1287>

GuiRong Tan

Wenzhou Medical University

Yifan Xia

Wenzhou Medical University

Lijun Wu

Wenzhou Medical University <https://orcid.org/0000-0003-0772-5189>

Research Article

Keywords: rectal cancer, SEER, causes of death, survivorship

Posted Date: October 20th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-993404/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

BACKGROUND

The focus on non-rectal cancer causes of death in patients with rectal cancer remains superficial. The purpose of the current study was to review the causes of death in rectal cancer survivors.

METHODS

We used the population-based Surveillance, Epidemiology, and End Results (SEER) cancer registry data to evaluate the causes of death in rectal cancer patients. We summarized characteristics of patients after diagnosis and survival outcomes, using Kaplan–Meier analysis and multivariate Cox proportional hazard regression analysis for survival analysis.

RESULTS

The study included 121742 patients who were diagnosed with rectal cancer, of whom 72,007 (59.1%) died during follow-up. Most deaths occurred from rectal cancer (n =31,505, 43.80%), and the number of rectal cancer deaths decreased as more years passed after diagnosis. >10 years after diagnosis, the most common causes of death were heart disease followed by rectal cancer. The 5-year overall survival rate, rectal cancer-specific survival rate, and non-rectal cancer-specific survival rate were 32.0%, 17.3% and 56.6%, respectively. And the 10-year overall survival rate, rectal cancer-specific survival rate and non-rectal cancer-specific survival rate were 14.6%, 4.4% and 31.8%, respectively. On multivariate analysis, factors associated with heart disease-specific survival among rectal cancer survivors include white race, female, married, grade I, earlier stages, surgery and chemotherapy.

CONCLUSIONS

Rectal cancer is the most common cause of death after diagnosis, however, the proportion of non-rectal cancer causes increases with longer survival. Routine follow-up care for rectal cancer survivors should be given more attention than ever.

Introduction

Colorectal cancer is the fifth most common malignant neoplasm and the fifth main cause of cancer death in the world in 2020. (Sung, Ferlay et al. 2021) In 2021, an estimated 45,230 new cases of rectal cancer will occur in the United States (26,930 in men; 18,300 in women), and an estimated 52,980 people will die of rectal and colon cancer combined. (Siegel, Miller et al. 2021) Nowadays, a lot of scholars focus on the diagnosis, staging and treatment of rectal cancer.(Horvat, Carlos Tavares Rocha et al. 2019, Keller, Berho et al. 2020) A large number of retrospective and population-based studies have discussed specific mortality in patients with colorectal cancer.(Li, Wu et al. 2015, Benitez Majano, Di Girolamo et al. 2019, Aguiar Junior, Oliveira et al. 2020) It is inevitable that the increasing survival rate raises crucial questions about the actual causes of death in rectal cancer patients. However, there is still little information focused on non-rectal cancer causes of death from rectal cancer. It is difficult to assess such information in prospective studies, therefore, population-based databases of high quality are significant to provide answers to these questions. And they have been used effectively to solve similar problems about other malignant tumors.(Baxi, Pinheiro et al. 2014, Afifi, Saad et al. 2020) Similarly, the aim of this study is to review the causes of death in rectal cancer patients registered within the surveillance, epidemiology and end results (SEER) database, and to provide preliminary insights for guiding long-term follow-up strategies. At the same time, we investigated not only the variety of causes of death over the course of time after diagnosis of rectal cancer but also the distribution of causes of death in patients with rectal cancer according to age, sex, race, marital status, SEER stage, grade, treatment modalities, for the purpose of guiding treatment and surveillance policies.

Materials And Methods

Data Source

Our study used data from the surveillance, epidemiology and end results (SEER) database submission of December 2020. The information was retrieved using the SEER*Stat software Version 8.3.8 .

Selection of the study cohort

We included patients diagnosed with rectal cancer from 1975 to 2016 for the study. Other inclusion criteria included (1) diagnostic Confirmation being Positive histology (2) complete information of Grade (3) complete information of stage (4) type of follow-up expected being active follow-up (5) complete basic information (race, sex, survival months, age at diagnosis) (6) no previous history of other malignant diseases

Data extracted for this study included age, sex, race, marital status, SEER stage, grade, treatment modalities, survival time, survival status and causes of death. Age was divided into five groups during statistics: < 50, 50–59, 60–69, 70–79, and ≥ 80 years. We defined marital status as married (both cohabit and married), single (never married, divorced, separated or widowed), as well as unknown. Causes of death were classified as (1) rectal cancer; (2) second primary cancer; (3) diseases of heart; (4) pulmonary causes, including chronic obstructive pulmonary disease & allied cond, pneumonia and influenza; (5) other non-cancer causes of death.

Statistical analysis

Generate survival curves were performed using Kaplan–Meier analysis. Cox proportional hazards regression was used to multivariate survival analyses of the patient population (95% CI confidence intervals). For multivariate analysis, the evaluated factors included: age, sex, race, marital status, SEER stage, grade and treatment modalities. A two-tailed P value <0.05 was considered to be statistically significant. All the statistical analyses were performed using the Statistical Product and Service Solutions 19.0.

Results

We reviewed 121,742 patients diagnosed with rectal cancer between 1973 and 2018. The great masses of patients were older than 60 years. Patients aged 60-69 accounted for 26.9%, and the proportion of patients aged 50-59 was 23.5%; the great majority of patients were white (82.3%), married (58.3%), and diagnosed with localized rectal cancer (45.1%). During the follow-up period, of the included patients (n=72,007, 59.1%) died, it was highest that the number of deaths due to rectal cancer (n =31,505, 43.80%) was. In the meanwhile, 17,150 deaths (23.80%) occurred within 1 year of rectal cancer diagnosis, 12,672 deaths (17.60%) occurred within 5 to 10 years, 5,593 deaths (7.80%) occurred within 10 to 15 years of rectal cancer diagnosis, and 5,087 deaths (7.10%) occurred more than 15 years after rectal cancer diagnosis. Table 1 listed all patients diagnosed with rectal cancer, grouping the characteristics of deaths based on time of death after diagnosis.

Table 1

baseline characteristics of all patients with rectal cancer and patients who died according to the time of death after diagnosis

Timing of Deaths After Diagnosis							
Characteristic	Total No. of Patients	all deaths	<1 Year	1-5 Years	5-10Years	10-15Years	≥15 Years
		No. of Patients (%)	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)
	121742(100)	72007(100)	17150(23.8)	31505(43.8)	12672(17.6)	5593(7.8)	5087(7.1)
Age at diagnosis,y							
<50 years	16938(14.0)	6537(9.1)	1350(20.6)	3625(55.5)	999(15.3)	249(3.8)	314(4.8)
50-59 years	28595(23.5)	12207(17.0)	2296(18.8)	5876(48.1)	2062(16.9)	747(6.1)	1226(10.0)
60-69 years	32775(26.9)	19023(17.0)	3851(20.2)	7944(41.8)	3325(17.5)	1705(9.0)	2198(11.6)
70-79 years	27463(22.6)	20579(28.6)	4917(23.9)	8186(39.8)	4057(19.7)	2186(10.6)	1233(6.0)
80 years+	15971(13.1)	13661(19.0)	4736(34.7)	5874(43.0)	2229(16.3)	706(5.2)	116(0.8)
sex							
Female	50780(41.7)	29479(40.9)	7167(24.3)	12543(42.5)	5087(17.3)	2338(7.9)	2344(8.0)
Male	70962(58.3)	42528(50.1)	9983(23.5)	18962(44.6)	7585(17.8)	3255(7.7)	2743(6.4)
race							
Black	10074(8.3)	5847(8.10)	1618(27.7)	2825(48.3)	854(14.6)	296(5.1)	254(4.3)
White	100220(82.3)	60519(84.0)	14259(23.6)	26009(43.0)	10878(18.0)	4915(8.1)	4458(7.4)
other	11448(9.4)	5641(7.8)	1273(22.6)	2671(47.3)	940(16.7)	382(6.8)	375(6.6)
grade							
Grad I	16561(69.5)	8389(11.7)	1582(18.9)	3217(38.3)	1693(20.2)	877(10.5)	1020(12.2)
Gra II	84638(13.6)	48973(68.0)	10224(20.9)	22039(45.0)	9279(18.9)	4009(8.2)	3422(7.0)
Gra III	18989(15.6)	13593(18.9)	4821(35.5)	5859(43.1)	1606(11.8)	689(5.1)	618(4.5)
Gra IV	1554(1.3)	1052(1.50)	523(49.7)	390(37.1)	94(8.9)	18(1.7)	27(2.6)
stage							
Localized	54917(45.1)	27463(38.1)	3831(13.9)	9803(35.7)	6876(25.0)	3555(12.9)	3398(12.4)
Regional	47558(39.1)	27894(38.7)	4880(17.5)	14159(50.8)	5279(18.9)	1953(7.0)	1623(5.8)
Distant	19267(15.8)	16650(23.1)	8439(50.7)	7543(45.3)	517(3.1)	85(0.5)	66(0.4)
Surgery							
No	15907(13.1)	11372(15.8)	5940(52.2)	4866(42.8)	461(4.1)	97(0.9)	8(0.1)
Yes	71799(58.9)	30083(41.8)	5103(17.0)	17079(50.1)	7124(23.7)	2425(8.1)	352(0.2)
Unknown	34036(28)	30552(42.4)	6107(20.0)	11560(37.8)	5087(16.7)	3071(10.1)	4727(15.5)
Radiotherapy							
NO	64588(53.1)	41179(57.2)	11360(27.6)	15812(38.4)	6908(16.8)	3466(6.9)	3633(8.8)

Timing of Deaths After Diagnosis							
YES	57154(46.9)	30828(42.8)	5790(18.8)	15693(50.9)	5764(18.7)	2127(6.9)	1454(4.7)
Chemotherapy							
No/Unknown	63569(52.2)	41627(57.8)	10914(26.2)	15214(36.5)	7453(17.9)	3855(9.3)	4191(10.1)
Yes	58173(47.8)	30380(42.2)	6236(20.5)	16291(53.6)	5219(17.2)	1738(5.7)	896(2.9)
Marital status							
marry	70946(58.3)	39723(55.2)	7763(19.5)	17368(43.7)	7535(19.0)	3483(8.8)	3574(9.0)
single	45841(37.7)	29950(41.6)	8713(29.1)	13126(43.8)	4770(15.9)	1951(6.5)	1390(4.6)
unknown	4955(4.1)	2334(3.2)	674(28.9)	1011(43.3)	367(15.7)	159(6.8)	123(5.3)

It was found that the major causes of death were rectal cancer, heart disease, second primary cancer, and pulmonary causes in descending order. Among all the patients, rectal cancer was the most common cause of death (n= 45072, 62.6%). A large quantity of rectal cancer deaths occurred during the 1-5 years after diagnosis (n = 31505, 43.8%). The leading cause was heart disease (n = 9302, 12.9%) and pulmonary causes (n = 2533, 3.5%), among the most common non-cancer causes of death. During the follow-up, 4410 patients (5.7%) were died from primary tumors other than rectal cancer. Table 2 listed the baseline characteristics for all patients diagnosed with rectal cancer based on the causes of death.

Table 2
baseline characteristics for all patients diagnosed with rectal cancer based on the causes of death

Causes of death					
Characteristic	Other Cause of Death	Rectal cancer	Second primary cancer	Diseases of Heart	pulmonary causes
	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)
All deaths	986(13.7)	45072(62.6)	4140(5.7)	9302(12.9)	2533(3.5)
Timing of Deaths After Diagnosis					
<1 Year	1379(8.0)	13218(77.1)	316(1.8)	1619(9.4)	423(2.5)
1-5 Years	2675(8.5)	23888(75.8)	1120(3.6)	2661(8.4)	712(2.3)
5-10Years	2312(18.2)	5963(47.1)	1266(10.0)	2293(18.1)	630(5.0)
10-15Years	1697(30.3)	1249(22.3)	772(13.8)	1360(24.3)	416(7.4)
≥15 Years	1798(35.3)	754(14.8)	666(13.1)	1369(26.9)	352(6.9)
Age at diagnosis,y					
<50 years	375(5.7)	5613(85.9)	182(2.8)	195(3.0)	32(0.5)
50-59 years	1129(9.3)	9091(74.5)	751(6.2)	832(6.8)	216(1.8)
60-69 years	2545(13.4)	11910(62.6)	1404(7.4)	2234(11.7)	606(3.2)
70-79 years	3429(16.6)	11111(54.0)	1317(6.4)	3418(16.6)	1013(4.9)
80 years+	2383(17.5)	7347(53.8)	486(3.6)	2623(19.2)	666(4.9)
sex					
Female	4368(14.9)	18362(62.3)	1577(5.3)	3758(12.7)	961(3.3)
Male	5493(12.9)	26710(62.8)	2563(6.0)	5544(13.0)	1572(3.7)
race					
Black	650(11.1)	4109(70.3)	317(5.4)	609(10.4)	103(1.8)
White	8562(14.1)	37205(61.5)	3513(5.8)	8144(13.5)	2260(3.7)
other	649(11.5)	3758(66.6)	310(5.5)	549(9.7)	170(3.0)
grade					
0.0					
Grad I	1549(18.4)	4079(48.6)	648(7.7)	1562(18.6)	381(4.5)
Gra II	6935(14.2)	30020(61.3)	2928(6.0)	6548(13.4)	1803(3.7)
Gra III	1313(9.7)	10120(74.5)	534(3.9)	1116(8.2)	330(2.4)
Gra IV	64(6.1)	853(81.1)	30(2.9)	76(7.2)	19(1.8)
stage					
Localized	6105(22.3)	10988(40.0)	2515(9.2)	5800(21.1)	1600(5.8)
Regional	3316(11.9)	18789(67.4)	1474(5.3)	3082(11.0)	816(2.9)

Causes of death					
Distant	440(2.6)	15295(91.9)	151(0.9)	420(2.5)	117(0.7)
Surgery					
No	641(5.7)	9628(84.7)	185(1.6)	567(5.0)	176(1.5)
Yes	4562(15.2)	18398(61.2)	1899(6.3)	3663(12.2)	1097(3.6)
Unknown	4658(15.2)	17046(55.8)	2056(6.7)	5072(16.6)	1260(4.1)
Radiotherapy					
NO	6534(15.9)	23138(56.2)	2494(6.1)	6620(16.1)	1751(4.3)
YES	3327(10.8)	21934(71.1)	1646(5.3)	2682(8.7)	782(2.5)
Chemotherapy					
No/Unknown	7149(17.2)	21932(52.7)	2773(6.7)	7220(17.3)	1896(4.6)
Yes	2712(8.9)	23140(76.2)	1367(4.5)	2082(6.9)	637(2.1)
Marital status					
marry	5413(13.6)	24667(62.1)	2640(6.6)	5051(12.7)	1341(3.4)
single	4138(13.9)	18972(63.3)	1364(4.6)	3943(13.2)	1083(3.6)
unknown	310(13.3)	1433(61.4)	136(5.8)	308(13.2)	109(4.7)

As the number of years after diagnosis increases, a growing number of patients died from causes other than rectal cancer, especially after 10 years. Meanwhile, more patients died from heart disease instead of rectal cancer. At the same time, the proportion of different causes of death varied by age of diagnosis as survival increased. For patients diagnosed under 50 years of age, rectal cancer remained the main cause of death as survival increased, and heart disease was the second cause of death. For patients over 50 years of age, heart disease became the main cause of death with a longer survival time, and the proportion of rectal cancer decreased significantly (Figure 1).

The 5-year, 10-year and 15-year overall survival (OS) rate were 32.0%, 14.6% and 7.0%, respectively. 5-year, 10-year and 15-year rectal cancer specific survival (RCSS) rate were 17.3%, 4.4% and 1.7%, respectively. 5-year, 10-year and 15-year non-rectal cancer specific survival (NRCSS) rate were 56.6%, 31.8% and 15.9%, respectively. (Figure2)

Multivariate analyses were performed to evaluate the three primary endpoints, illustrated in Table 3 and 4. Cox proportional hazard regression analysis showed that sex, race, marital status, grade, stage, surgery, radiotherapy and chemotherapy were the significant prognostic factors for patients who died of rectal cancer. Black patients showed a slightly higher risk of death compared to white—being male and single likewise had a higher risk of death. The factors associated with other primary cancers survival in multivariate analyses included sex, race, marital status, stage, surgery and chemotherapy. There were sex, race—marital status, stage, surgery and chemotherapy associated with heart disease-specific survival in multivariate analyses. Compared with patients who died from rectal cancer, radiotherapy and grade were no longer specific survival-related factors for other primary cancers and heart disease.

Table 3
Multivariate analysis of factors affecting primary rectal cancer-specific survival in patients with rectal cancer survivors

Factor		rectal cancer HR	P	95.0% CI	
				Lower	Upper
Sex	Female	Reference			
	Male	1.021	0.05	1.002	1.041
Race	Black	Reference			
	White	0.954	0.05	0.923	0.985
	other	0.934	0.05	0.893	0.976
Grade	Grad I	Reference			
	Gra II	1.058	0.001	1.023	1.093
	Gra III	1.482	0.001	1.428	1.538
	Gra IV	1.971	0.001	1.830	2.123
stage	Localized	Reference			
	Regional	1.457	0.001	1.421	1.494
	Distant	3.002	0.001	2.917	3.090
Surgery	No	Reference			
	Yes	0.543	0.001	0.529	0.558
	Unknown	0.500	0.001	0.486	0.515
Radiotherapy	NO	Reference			
	YES	0.956	0.001	0.935	0.977
Chemotherapy	No/Unkno	Reference			
	Yes	0.690	0.001	0.673	0.707
Marital status	marry	Reference			
	single	1.231	0.001	1.207	1.255
	unknown	1.188	0.001	1.126	1.254

Table 4

Multivariate analysis of factors affecting heart disease-specific and second primary cancer-specific survival in patients with long-term (>5 years) bladder cancer survivors

Factor		Disease of heart HR	P	95.0% CI		Second primary cancer HR	P	95.0% CI	
				Lower	Upper			Lower	Upper
Sex	Female	Reference				Reference			
	Male	1.187	0.001	1.135	1.240	1.129	0.001	1.057	1.205
Race	Black	Reference	0.101			Reference	.101		
	White	0.915	0.05	0.842	0.994	0.860	0.05	0.766	0.966
	other	0.904	0.089	0.805	1.015	0.782	0.05	0.668	0.915
Grade	Grad I	Reference				Reference			
	Gra II	1.049	0.094	0.992	1.110	0.991	0.847	0.909	1.081
	Gra III	1.108	0.05	1.025	1.198	1.000	1.000	0.889	1.125
	Gra IV	1.206	0.112	0.957	1.520	0.951	0.789	0.658	1.374
stage	Localized	Reference				Reference			
	Regional	1.180	0.001	1.126	1.236	1.149	0.001	1.070	1.234
	Distant	2.815	0.001	2.535	3.126	2.209	0.001	1.856	2.629
Surgery	No	Reference				Reference			
	Yes	0.506	0.001	0.461	0.555	0.442	0.001	0.378	0.518
	Unknown	0.225	0.001	0.204	0.248	0.168	0.001	0.142	0.198
Radiotherapy	NO	Reference				Reference			
	YES	0.940	0.051	0.883	1.000	0.967	0.470	0.882	1.059
Chemotherapy	No/Unkno	Reference				Reference			
	Yes	0.832	0.001	0.776	0.893	0.870	0.05	0.787	0.962
Marital status	marry	Reference				Reference			
	single	1.231	0.001	1.207	1.255	1.237	0.001	1.155	1.325
	unknown	1.188	0.001	1.207	1.255	1.163	0.088	0.978	1.384

Discussion

At the beginning, death from rectal cancer was the most pervasive cause of death after diagnosis. However, its position was replaced by non-rectal cancer causes of death with the extension of survival time. Deaths from heart disease, second primary cancer and lung diseases are increasing in frequency in particular.

The prognosis and overall survival of patients with rectal cancer have significantly improved in the US over the past few decades.(Siegel, Miller et al. 2020) The standard treatment models led to tumor downstaging, improved living quality, as well as lowered relapse rate.(Ludmir, Palta et al. 2017) At the same time, emerging total neoadjuvant therapy provided good results for locally advanced rectal cancer.(Liu, Jiang et al. 2021) Therefore, non-rectal cancer causes play an increasingly important

role as the time after diagnosis continues to increase; simultaneously, it is crucially important to be concerned about non-rectal cancer causes when providing advice about prognosis and subsistence for patients.

Cardiotoxicity is a rare, but relevant side effect of 5-FU and capecitabine.(Polk, Vaage-Nilsen et al. 2013) It comprehends a wide spectrum of side effects, from electrocardiogram changes to myocardial infarction and cardiogenic shock.(de Forni, Malet-Martino et al. 1992, Dyhl-Polk, Vaage-Nilsen et al. 2020) Although some of the influence factors are well known, the mechanism which is responsible for the effects mentioned above remains poorly defined. The main reasons discussed in the literature are ischemia and drug-related myocardial toxicity.(Becker, Erckenbrecht et al. 1999, Yung and McCrea 2009, Sara, Kaur et al. 2018) In Table 2, we also found that the proportion of patients who died of heart disease after chemotherapy was higher than that of patients who did not receive chemotherapy. There is a study(Hillreiner, Baumeister et al. 2020) that looked at cardiorespiratory fitness and colorectal cancer. In this prospective study of nearly 60,000 women and men followed for up to 5 years, higher cardiorespiratory fitness was associated with a lower risk of rectal cancer. This significant burden of cardiac deaths should also raise a concern about the cardiac disease risk factors, such as cigarette smoking, hyperlipidemia and diabetes mellitus.(Johnson, Davis et al. 2016)

Based on the database analysis, we found that rectal cancer survivors were susceptible to developing second primary cancers such as lung, breast, kidney and uterine cancer. Primary malignancies other than rectal cancer became more frequent as causes of death, from 1.8% within 1 year after diagnosis to 13.8% 10-15 years after diagnosis(Table 2). It highlights the significance for rectal cancer patients following appropriate screening and preventive measures for other malignant tumors.

Men were more likely than women to develop and die from rectal cancer. First of all, estrogen takes a protective part in the etiology of rectal cancer(Nanda, Bastian et al. 1999), and the use of estrogen can reduce the risk of rectal cancer. (Grodstein, Newcomb et al. 1999) Furthermore, when it comes to lifestyle and health, women no doubt is generally better than men. Many men have smoke, drink, lack dietary fiber and other bad habits.(Bardou, Montembault et al. 2002, Liang, Chen et al. 2009) But it is not clear to figure out the underlying mechanism of this result.

The ethnic difference also affects treatment decisions in general, white patients have a relatively low risk of rectal cancer death in black patients and this may be related to dietary differences between ethnic groups.(Satia-Abouta, Galanko et al. 2004)

Married rectal cancer patients have longer survival times than single patients. Spouses can be spiritual pillars. Married patients have better compliance than unmarried, such as timely seeking medical advice and receiving chemotherapy or radiotherapy. (Schone and Weinick 1998) Furthermore, researchers(Uchino 2006) have revealed that social support could reduce stress responses, for example, the effect of social support on decreasing the risk of cardiovascular events and down-regulating cortisol reactivity to mental stress was supported by laboratory settings. A study(Stimpson, Wilson et al. 2012) has found that married people were more likely than unmarried people to go through colon endoscopy to enable early detection and treatment of patients.

Conclusions

The methodologic advantages of our study included high numbers of samples and detailed information in the SEER database. There were the limitations of our study that inherent investigations based on data from cancer registries, including the lack of specific treatment plans for radiotherapy and chemotherapy, as well as no information on relapse therapy. In addition, we lacked individual-level information on variables such as smoking habits, drinking habits, medication use, and obesity, which may increase the risk of death from both rectal cancer and non-rectal cancer causes.

In conclusion, our data illustrated that deaths from non-rectal cancer caused account for a significant proportion of deaths in patients with rectal cancer during follow-up after diagnosis. Among them, heart disease, second primary cancer and lung disease were three of the most common causes. Long-term survivors of rectal cancer are a heterogeneous group who face an increased risk of death from a variety of causes, these factors vary by demographic, health status, lifestyle, and disease

characteristics including time since diagnosis. Rectal cancer is a global health issue, with an increasing incidence in younger populations.(Connell, Mota et al. 2017) thus it can be seen, It is important to elucidate optimal guidelines for long-term screening and possible interventions in order to reduce death rates from heart disease, second primary cancer and lung diseases. Our study, using a large study sample, contributes evidence that supports further investigation of long-term management in rectal cancer patients.

Declarations

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: There is no funding.

Author Contributions

Yanyan Jin: Conceptualization, Writing - Original Draft, Methodology

Guirong Tan: Formal analysis, Visualization

Yifan Xia: Data Curation, Investigation

Lijun Wu: Writing - Review & Editing, Supervision, Project administration

References

- Afifi AM, Saad AM, Al-Husseini MJ, Elmeharth AO, Northfelt DW, Sonbol MB (2020) "Causes of death after breast cancer diagnosis: A US population-based analysis. " *Cancer* 126(7):1559–1567
- Aguiar Junior S, Oliveira MM, Silva D, Mello CAL, Calsavara VF, Curado MP (2020) "Survival of Patients with Colorectal Cancer in a Cancer Center. " *Arq Gastroenterol* 57(2):172–177
- Bardou M, Montembault S, Giraud V, Balian A, Borotto E, Houdayer C, Capron F, Chaput JC, Naveau S (2002) Excessive alcohol consumption favours high risk polyp or colorectal cancer occurrence among patients with adenomas: a case control study. *Gut* 50(1):38–42
- Baxi SS, Pinheiro LC, Patil SM, Pfister DG, Oeffinger KC, Elkin EB (2014) Causes of death in long-term survivors of head and neck cancer. *Cancer* 120(10):1507–1513
- Becker K, Erckenbrecht JF, Haussinger D, Frieling T (1999) "Cardiotoxicity of the antiproliferative compound fluorouracil" *Drugs* 57(4):475–484
- Benitez Majano S, Di Girolamo C, Rachet B, Maringe C, Guren MG, Glimelius B, Iversen LH, Schnell EA, Lundqvist K, Christensen J, Morris M, Coleman MP, Walters S (2019) Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden: a population-based study. *Lancet Oncol* 20(1):74–87
- Connell LC, Mota JM, Braghiroli MI, Hoff PM (2017) The Rising Incidence of Younger Patients With Colorectal Cancer: Questions About Screening, Biology, and Treatment. *Curr Treat Options Oncol* 18(4):23
- de Forni M, Malet-Martino MC, Jaillais P, Shubinski RE, Bachaud JM, Lemaire L, Canal P, Chevreau C, Carrie D, Soulie P et al (1992) "Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study". *J Clin Oncol* 10(11):1795–1801
- Dyhl-Polk A, Vaage-Nilsen M, Schou M, Vistisen KK, Lund CM, Kumler T, Appel JM, Nielsen DL (2020) "Incidence and risk markers of 5-fluorouracil and capecitabine cardiotoxicity in patients with colorectal cancer". *Acta Oncol* 59(4):475–483

- Grodstein F, Newcomb PA, Stampfer MJ (1999) "Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis". *Am J Med* 106(5):574–582
- Hillreiner A, Baumeister SE, Sedlmeier AM, Finger JD, Schlitt HJ, Leitzmann MF (2020) "Association between cardiorespiratory fitness and colorectal cancer in the UK Biobank". *Eur J Epidemiol* 35(10):961–973
- Horvat N, Carlos Tavares Rocha C, Clemente Oliveira B, Petkovska I, Gollub MJ (2019) "MRI of Rectal Cancer: Tumor Staging Imaging Techniques Management" *Radiographics* 39(2):367–387
- Johnson CB, Davis MK, Law A, Sulpher J (2016) "Shared Risk Factors for Cardiovascular Disease and Cancer: Implications for Preventive Health and Clinical Care in Oncology Patients". *Can J Cardiol* 32(7):900–907
- Keller DS, Berho M, Perez RO, Wexner SD, Chand M (2020) The multidisciplinary management of rectal cancer. *Nat Rev Gastroenterol Hepatol* 17(7):414–429
- Li P, Wu H, Zhang H, Shi Y, Xu J, Ye Y, Xia D, Yang J, Cai J, Wu Y (2015) Aspirin use after diagnosis but not prediagnosis improves established colorectal cancer survival: a meta-analysis. *Gut* 64(9):1419–1425
- Liang PS, Chen TY, Giovannucci E (2009) "Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis". *Int J Cancer* 124(10):2406–2415
- Liu S, Jiang T, Xiao L, Yang S, Liu Q, Gao Y, Chen G, Xiao W (2021) "Total Neoadjuvant Therapy (TNT) versus Standard Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer: A Systematic Review and Meta-Analysis. " *Oncologist* 26(9):e1555–e1566
- Ludmir EB, Palta M, Willett CG, Czito BG (2017) "Total neoadjuvant therapy for rectal cancer: An emerging option. " *Cancer* 123(9):1497–1506
- Nanda K, Bastian LA, Hasselblad V, Simel DL (1999) "Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis". *Obstet Gynecol* 93(5 Pt 2):880–888
- Polk A, Vaage-Nilsen M, Vistisen K, Nielsen DL (2013) "Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: a systematic review of incidence, manifestations and predisposing factors". *Cancer Treat Rev* 39(8):974–984
- Sara JD, Kaur J, Khodadadi R, Rehman M, Lobo R, Chakrabarti S, Herrmann J, Lerman A, Grothey A (2018) 5-fluorouracil and cardiotoxicity: a review. *Ther Adv Med Oncol* 10:1758835918780140
- Satia-Abouta J, Galanko JA, Martin CF, Ammerman A, Sandler RS (2004) "Food groups and colon cancer risk in African-Americans and Caucasians". *Int J Cancer* 109(5):728–736
- Schone BS, Weinick RM (1998) "Health-related behaviors and the benefits of marriage for elderly persons. " *Gerontologist* 38(5):618–627
- Siegel RL, Miller KD, Fuchs HE, Jemal A (2021) "Cancer Statistics, 2021". *CA Cancer J Clin* 71(1):7–33
- Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA, Jemal A (2020) "Colorectal cancer statistics, 2020". *CA Cancer J Clin* 70(3):145–164
- Stimpson JP, Wilson FA, Watanabe-Galloway S, Peek MK (2012) "The effect of marriage on utilization of colorectal endoscopy exam in the United States. " *Cancer Epidemiol* 36(5):e325–e332
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021) "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries". *CA Cancer J Clin* 71(3):209–249

Uchino BN (2006) "Social support and health: a review of physiological processes potentially underlying links to disease outcomes". J Behav Med 29(4):377–387

Yung LT, McCrea WA (2009) "Capecitabine induced acute coronary syndrome." BMJ Case Rep 2009

Figures

Figure 1

Causes of death in colorectal cancer survivors of different ages

a Causes of death in rectal cancer survivors in the whole cohort

b Causes of death in rectal cancer survivors who were younger than 50 years

c Causes of death in rectal cancer survivors aged 50-59

d Causes of death in rectal cancer survivors aged 60-69

e Causes of death in rectal cancer survivors aged 70-79

f Causes of death in rectal cancer survivors 80 years or older

Figure 2

The curves of overall survival(OS), rectal cancer specific survival(RCSS) and non-rectal cancer specific survival(NRCSS) of the patients