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The survival of the prostate cancer patients with secondary colorectal cancer: a study based on a SEER database from southern China

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Abstract. – OBJECTIVE: To evaluate the prognosis of prostate cancer patients with secondary colorectal cancer.

PATIENTS AND METHODS: The study included men with prostate cancer who developed colorectal cancer after radical prostatectomy in the Surveillance, Epidemiology, and Outcomes (SEER) database. After adjusting the age at first diagnosis, the prostate-specific antigen (PSA) level and Gleason score, the influence of the occurrence of secondary colorectal cancer on the prognosis of patients was evaluated.

RESULTS: A total of 66,955 patients were included in the present study. The median follow-up was 12 years. There were 537 patients with the incidence of the secondary colorectal cancer. The results of the three survival analysis methods all showed that the secondary colorectal cancer greatly increased the mortality risk of prostate cancer patients. Cox analysis results showed the hazard ratio (HR) is 3.79 (3.21-4.47), the Cox model with time-dependent covariates was introduced, and the result was 6.15 (5.19-7.31). When the Landmark time point is set to 5 years, the HR is 4.99 (3.85-6.47).

CONCLUSIONS: This study provides an important theoretical basis for evaluating the effect of secondary colorectal cancer on the prognosis of prostate cancer patients.

Key Words:
Prostate cancer, Colorectal cancer, Survival analysis.

Introduction

Prostate cancer is an epithelial malignant tumor that occurs in the prostate[1,2]. In 2012, the incidence of prostate cancer in China's tumor registration areas was 9.92/100,000, ranking sixth in the incidence of male malignant tumors. The age of onset was at a low level before the age of 55, and gradually increased after the age of 55T. The incidence rate increased with age, and the peak age was 70-80 years old. For the familial hereditary type of prostate cancer, the onset age of prostate cancer was always young, with 43% of patients aged ≤ 55 years old. With the improvement of early diagnosis and treatment of cancer, the 5-year survival rate of prostate cancer has reached 97%. The incidence of secondary colorectal cancer in patients has increased, gradually attracting people's attention[3,4]. Radical prostatectomy is a cure treatment for prostate cancer recommended by the guidelines. Age is associated with the risk stratification of prostate cancer, which has an influence on the choice of treatment. Colorectal metastases were the most common secondary cancer for prostate cancer patients. The lesion location and the histological type of the secondary colorectal cancer were different from those of primary cancer and did not include the metastases and recurrences of primary cancer in the same individual. Since the main treatment strategy for prostate cancer patients is still surgery, it is necessary to study the prognosis of these patients in order to provide a theoretical basis for improving the survival of patients[5,6].

We have hypothesized that there was an increased risk of mortality from prostate cancer due to colorectal metastases. In this study, patients undergoing radical prostatectomy from the SEER database in the United States were included in the study to explore the impact of secondary colorectal cancer on the prognosis of patients with prostate cancer.

Patients and Methods

The Study Population

All of the population for study were screened from the SEER database. The SEER database is

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a large oncology patient registry developed by the National Cancer Institute, covering approximately 28% of cancer patients in the United States. This study included Caucasian patients diagnosed with prostate adenocarcinoma (ICD-O-3 codes 8140, 8480, 8490, 8550) from 2004 to 2009.

Inclusion criteria were patients who received radical prostatectomy; aged between 18 and 79 years; if patients with the secondary tumor occurred, the tumor type was limited to colorectal cancer. Exclusion criteria were cancer confirmed by autopsy; cancer pathological type of non-adenocarcinoma; secondary colorectal cancer diagnosed less than 2 months after diagnosis of prostate cancer; missing main indicators.

The Outcome

The primary outcome of this study was overall survival (OS), which was defined as the time from prostate cancer diagnosis to death, loss to follow-up, or December 31, 2015. The patients were grouped according to whether the secondary colorectal cancer occurred. The survival process was described by Kaplan-Meier (K-M) survival curve, and the differences between groups were analyzed by log-rank test. Covariates included in the analysis included age at diagnosis, prostate-specific antigen (PSA) level, and Gleason score. In order to explore whether the occurrence of secondary colorectal cancer has an effect on OS and considering that the time of occurrence of secondary colorectal cancer in patients may have an impact on OS, the following three methods were used for analysis.

The Cox Regression Analysis

In the Cox regression model, the secondary colorectal cancer was used as a prognostic factor, and the patients were divided into two groups according to whether the secondary colorectal cancer occurred, and the survival of the patients was compared. In this study, none of the prostate cancer patients included in the analysis had secondary colorectal cancer at time 0. With the increase of follow-up time, some patients were diagnosed with secondary colorectal cancer, so theoretically this analysis strategy will be biased.

The Time-Dependent Cox Regression Analysis

According to Cox regression analysis, patients who died due to various reasons would be directly assigned to the group without secondary colorectal cancer, resulting in poor survival in this group. In this model, the occurrence of secondary colorectal cancer was considered as a time-dependent covariate, and patients were treated as not having secondary colorectal cancer until they were diagnosed with secondary colorectal cancer. Analysis was performed as the occurrence of secondary colorectal cancer after diagnosis. Cox models can be extended to include time-dependent covariates. This approach does not introduce the bias that arises when analyzing secondary colorectal cancer as a time-fixed covariate. At this time, in order to accurately describe the state of patients at different time points, the data adopt the format of counting process.

Landmark Analysis

The Landmark method defines the data set for the next analysis, namely the Landmark analysis set, according to whether the patient has an outcome event before a specific time point (i.e., the Landmark time point). Patients who were lost to follow-up or died before the Landmark time point were not included in the analysis, and patients who developed secondary colorectal cancer after this time point were assigned to the group without secondary colorectal cancer. At this time, the Landmark time point was defined as the starting point of survival time.

Statistical Analysis

All the statistical analyses were conducted with SPSS version 22.0 (IBM Corp., Armonk, NY, USA) as well as the SEER*Stat program version 8.3.6 (available at: https://seer.cancer.gov/seerstat/). Kaplan-Meier (K-M) analysis was used to compare the overall survival of patients. Continuous variables were expressed in mean ± standard deviation or median (range) as appropriate. Differences between subgroups were analyzed using χ^2 or Fisher's exact test for categorical parameters and Student *t*-test for continuous parameters as appropriate. Statistical significance was declared with a two-sided p-value < 0.05.

Results

The Included Patients

A total of 66,955 patients were included in the present study. The median follow-up was 12 years. There were 537 patients with the incidence of the secondary colorectal cancer. We divided patients into two groups, one group with the secondary colorectal cancer and the other group without the secondary colorectal cancer.

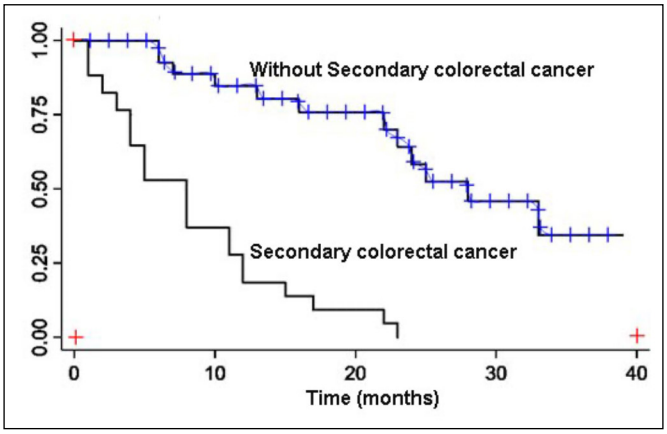

Figure 1. The Kaplan-Meier curve on secondary colorectal cancer.

As showed in the Table I, we compared the baseline characteristics of patients from the two groups. Patients with secondary colorectal cancer had an older age, and higher PSA and Gleason score.

We performed the survival analysis; the Kaplan-Meier curve was presented in the Figure 1. We found a significantly worse survival in patients with secondary colorectal cancer.

The Cox Regression Model

We analyzed the clinical risk factors that were associated with the survival of the patients. The results based on the Cox regression analysis were presented in Table II. In the multivariate analysis, the age of patients, the PSA, Gleason score and also the secondary colorectal cancer were evaluated to be independently associated with overall survival of patients.

The Time-Dependent Cox Regression Model

We next explored the prognostic clinical factors by the time-dependent Cox regression model. The results were presented in the Table III. The age, the PSA, Gleason score and also the secondary colorectal cancer were still the independent risk factors of the survival of the patients. Patients with secondary colorectal cancer had a significantly decreased overall survival [hazard ratio (HR) and 95% CI: 6.15 (5.19-7.31)].

Landmark Analysis

The Landmark time point was defined as 5 years after prostate cancer diagnosis, when 64,537 patients were included in the Landmark analysis set, of which 271 developed secondary colorectal cancer. Multivariate analysis showed that the HR (95% CI) for the occurrence of sec-

Table I. The baseline characteristics of the included patients.

	All patients	Secondary colorectal cancer		
Variables	N = 66,955	No = 66,418	Yes = 537	*p*-value
Age				<0.001
18-55	13,313 (19.9)	13,260 (20.0)	53 (9.9)	
55-70	47,229 (70.5)	46,833 (70.5)	396 (73.7)	
70-79	6,413 (9.6)	6,325 (9.5)	88 (16.4)	
PSA				0.004
<10	57,271 (85.5)	56,842 (85.6)	429 (79.9)	
10-20	7,266 (10.9)	7,181 (10.8)	85 (15.8)	
≥20	2,418 (3.6)	2,395 (3.6)	23 (4.3)	
Gleason Score				0.004
≤7	60,292 (90.0)	59,829 (90.1)	463 (86.2)	
8-10	6,663 (10.0)	6,589 (9.9)	74 (13.8)	
SCRC				-
No	66,418 (99.2)	-	-	
Yes	537 (0.8)	-	-	

PSA, prostate specific antigen; SCRC, secondary colorectal cancer.

Table II. The survival analysis by Cox regression analysis.

Variables	HR and 95% CI	*p*-value
Age		<0.001
18-55	Reference	
55-70	1.71 (1.54-1.88)	
70-79	3.65 (3.25-4.09)	
PSA		<0.001
<10	Reference	
10-20	1.60 (1.48-1.73)	
≥20	2.17 (1.94-2.43)	
Gleason Score		<0.001
≤7	Reference	
8-10	2.95 (2.75-3.17)	
SCRC		<0.001
No	Reference	
Yes	3.79 (3.21-4.48)	

HR, hazard ratio; CI, confidence interval; PSA, prostate specific antigen; SCRC, secondary colorectal cancer.

ondary colorectal cancer within 5 years after diagnosis was 4.99 (3.85-6.47) (Table IV). In addition, in order to study whether the choice of Landmark time point had an effect on the conclusion, we set the time point as 3 years, 4 years and 6 years respectively, and performed a multivariate analysis again with the results when the time point was set at 5 years. The results showed that the hazard ratio of death from second primary colorectal cancer at different time points was slightly different, about 5 times that of patients without secondary tumor.

Analysis After Propensity Score Matching

We performed a propensity matching based on the age, PSA level and Gleason score in patients with and without secondary colorectal cancer with ratio of 1:1. The baseline characteristics of the patients after matching was presented in the Table V. When we performed the survival analysis, patients with secondary colorectal cancer still had a significantly worse survival than patients without secondary colorectal cancer.

Table IV. The Landmark multivariate analysis.

Variables	HR and 95% CI	*p*-value
Age		<0.001
18-55	Reference	
55-70	1.84 (1.61-2.10)	
70-79	4.13 (3.56-4.80)	
PSA		<0.001
<10	Reference	
10-20	1.54 (1.39-1.72)	
≥20	2.04 (1.76-2.38)	
Gleason Score		<0.001
≤7	Reference	
8-10	2.75 (2.51-3.02)	
SCRC		<0.001
No	Reference	
Yes	4.99 (3.85-6.47)	

HR, hazard ratio; CI, confidence interval; PSA, prostate specific antigen; SCRC, secondary colorectal cancer.

Table III. The survival analysis by the time-dependent Cox regression analysis.

Variables	HR and 95% CI	*p*-value
Age		<0.001
18-55	Reference	
55-70	1.70 (1.54-1.88)	
70-79	3.64 (3.24-4.08)	
PSA		<0.001
10	Reference	
10-20	1.60 (1.47-1.74)	
≥20	2.16 (1.94-2.42)	
Gleason Score		<0.001
≤7	Reference	
8-10	2.94 (2.74-3.16)	
SCRC		<0.001
No	Reference	
Yes	6.15 (5.19-7.31)	

HR, hazard ratio; CI, confidence interval; PSA, prostate specific antigen; SCRC, secondary colorectal cancer.

Discussion

Prostate cancer is the most common male tumor in Western countries, and the number of newly diagnosed prostate cancer patients in the United States in 2019 is expected to reach 175,000, ranking first in male cancer[7-9]. In recent years, with the

Table V. The baseline characteristics of the included patients after propensity matching.

Variables	HR and 95% CI	*p*-value
Age		0.066
18-55	85 (15.8)	53 (9.9)
55-70	377 (70.2)	396 (73.7)
70-79	75 (14.0)	88 (16.4)
PSA		0.083
<10	401 (74.6)	429 (79.9)
10-20	68 (12.7)	85 (15.8)
≥20	68 (12.7)	23 (4.3)
Gleason Score		0.197
≤7	411 (76.5)	463 (86.2)
8-10	126 (23.5)	74 (13.8)

PSA, prostate specific antigen.

improvement of surgical techniques, serious complications brought about by surgery are no longer a limiting factor for radical prostatectomy. The survival of patients is almost the same as that of the normal population. However, studies[10,11] have shown that patients undergoing radical prostatectomy have a higher risk of developing colorectal cancer than the general population, which may have an adverse effect on patients' overall survival. Therefore, this study aimed to analyze patients who received radical prostatectomy to explore the influence of the secondary colorectal cancer on the prognosis of patients.

After treatment, the mortality rate of colorectal cancer is higher than that of prostate cancer, and the higher tumor burden leads to an increased risk of death in patients. The current follow-up strategy for prostate patients only monitors the recurrence and metastasis of prostate cancer, and the time is concentrated within 5 years after surgery[12,13]. However, the results of this study showed that the incidence of secondary colorectal cancer was concentrated in the 2-8 years after prostate cancer treatment, and even in more than 10 years after surgery in some patients. The lack of follow-up strategies for secondary colorectal cancer leads to misdiagnosis or missed diagnosis in clinical diagnosis and treatment, which affects the choice of treatment plan, delays the best time for diagnosis and treatment, and thus affects the survival of patients. How to rationally use fecal occult blood test and colonoscopy to regularly check the high-risk group of secondary colorectal cancer is an important research direction that improves the survival of patients. In addition, some influencing factors of colorectal cancer, such as diet, living habits, etc., shown by current research[14,15], also provide ideas and references for strengthening prevention and improving the survival rate of prostate cancer patients.

The prognostic factors of prostate cancer patients are multi-faceted. Based on the adjustment of the main influencing factors (diagnosis age, PSA level and Gleason score), this paper focuses on the influence of the occurrence of secondary colorectal cancer[16,17]. When the traditional Cox model is established, all variables are regarded as time-fixed covariates, and the value of some variables may be changed during the follow-up period without considering the situation that the result may produce eternal time bias. For example, the results of the first analysis of this study showed that the risk of death in patients with secondary colorectal cancer was approximately 3.8 times of patients without secondary colorectal cancer. However, through Cox model analysis with time-dependent covariates, it was found that the mortality risk of patients with secondary colorectal cancer was about 6.5% that of patients without secondary colorectal cancer. The risk of death is therefore underestimated using conventional analytical strategies.

Conclusions

This study provides an important theoretical basis for evaluating the effect of secondary colorectal cancer on the prognosis of prostate cancer patients. Based on this, we should strive to improve doctors' and patients' understanding of secondary colorectal cancer, provide effective prevention and follow-up strategies, achieve early detection and early treatment, and contribute to improving the long-term survival of prostate cancer patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The data were taken from public dataset; therefore, the ethics approval was not applicable.

Informed Consent

The data were taken from public dataset; therefore, the informed consent of patients was not applicable.

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