

Risk Factors for Death from Heart Disease in Elderly Colon Cancer Patients with Liver Metastasis

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Abstract

Background: Colon cancer is one of the most frequently diagnosed cancers worldwide. The study aimed to identify the risk factors of death from heart disease in the elderly colon cancer patients with liver metastasis. **Methods:** All data of the retrospective study were retrieved from database of the Surveillance, Epidemiology, and End Results between 2000 and 2020. Odds ratio (OR) and the corresponding 95% confidence intervals (CIs) were calculated by using logistic regression model. **Results:** A total of 14322 elderly colon cancer patients with liver metastasis were identified. Out of them, 288 cases died of heart diseases, and 2001 cases were alive. In multivariate logistic analysis, the significant predictors for heart disease death were old age (OR = 1.06, $p = 0.000$), other histologic type besides adenocarcinoma (OR = 1.68, $p = 0.004$) and tumor size ≥ 5 cm (OR = 1.89, $p = 0.000$). The protective factors were metastases besides liver (OR = 0.70, $p = 0.027$), surgery (OR = 0.64, $p = 0.001$) and chemotherapy (OR = 0.23, $p = 0.000$). **Conclusion:** Among elderly colon cancer with liver metastases, it is crucial to identify the risk factors and adopt preventive methods and appropriate treatment, which may enhance the quality of patient care and prolong patients' survival.

Keywords: Death from heart disease- elderly colon cancer- liver metastasis

Asian Pac J Cancer Prev, 25 (12), 4217-4221

Introduction

Colon cancer is one of the most frequently diagnosed cancers worldwide. More than half of colon cancer patients develop distant metastases, and most of these patients have unresectable liver metastasis [1]. With the advancement of cancer diagnosis and therapy, the survival time of colon cancer patients has been considerably prolonged. A higher incidence of cardiovascular disease and mortality of heart disease was also observed with the longer life expectancy [2]. Colon cancer patients, especially among the elderly, are a high-risk group for developing cardiovascular diseases [3].

A systematic review showed that men had higher rates of advanced colorectal neoplasia across different age groups [4]. Usually, due to the protection of estrogen, women have a lower risk of developing cardiovascular disease compared to men [5]. In addition to age and gender, other cancer-related factors such as tumor stage, tumor size and treatment may be associated with the death cause of heart disease. Different treatment, such as cytotoxic chemotherapy and targeted therapy, are associated with cardiotoxicity, which contributed a significant mortality in patients with early breast cancer [6]. Radiotherapy was reported to be associated with more death from cardiovascular disease in patients with lung

cancer and bladder cancer [7].

With longer follow-up time, cancer-related deaths in over 65-year patients with colorectal cancer tend to decline, whereas deaths due to cardiovascular disease and lung diseases increased [8]. However, studies that concentrate on death from heart disease in elderly colon cancer patients with liver metastasis remain rare. To investigate high-risk factors resulting in death of heart disease and guide prevention and surveillance, we performed the multivariate analysis of the patients in a cancer database of the Surveillance, Epidemiology, and End Results (SEER) between 2000 and 2020. The study aimed to identify the risk factors of death from heart disease in the elderly colon cancer patients with liver metastasis.

Materials and Methods

Patients and methods

Data source

All data of the present study were retrieved from the SEER database (<https://seer.cancer.gov/>) using SEER*Stat software (version 8.4.3). The database of SEER Research Data, 17 Registries, Nov 2022 Sub (2000-2020) was chosen. Since the study was based on a publicly available database, informed consent and institutional review board

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approval are not required.

Study population

The study was a retrospective analysis of a national population. Patient eligibility was as follows: (1) histological confirmation of colon cancer as the only primary cancer; (2) combined with liver metastasis; (3) age at diagnosis over 65 years old; (4) diagnosed between 2000 and 2020; (5) causes of death: alive or death from diseases of heart. Patients with reporting from autopsy only or death certificate only were excluded. Patients with other causes of death, such as cerebrovascular diseases, lung and bronchus, and septicemia, were excluded. Demographic characteristics included age and gender. Clinical characteristics included tumor site, histologic type, T stage, N stage, tumor size, other metastases besides liver, surgery, chemotherapy, radiotherapy, vital status, survival months and causes of death.

Statistical analysis

The categorical and continuous variables were described as median and frequency (percentage), respectively. Patient characteristics were analyzed by chi-square or rank sum test. Multivariate analyses were performed with logistic regression model. Odds ratio (OR) and the corresponding 95% confidence intervals (CIs) were calculated. All analyses were conducted using SPSS 24.0 software (IBM, Armonk, NY, USA). Two-tailed $p < 0.05$ indicates statistical significance.

Results

Patient characteristics

A total of 14,322 elderly colon cancer patients with liver metastasis were identified between 2000 and 2020. Out of them, 288 cases died of heart diseases (Death due to heart disease group), and 2001 cases were alive (Alive group). The patient characteristics were presented in Table 1. The median age of Death due to heart disease group was 77 years, higher than that of Alive group (72 years, $p = 0.000$). There was no gender difference between the two groups (female, 46.9% vs. 47.5%, $p = 0.848$). Compared to Alive group, the primary tumors of Death due to heart disease group were more likely to be located in the right half colon (63.9% vs. 57.2%, $p = 0.032$). Death due to heart disease group had fewer adenocarcinomas than Alive group (79.9% vs. 88.7%, $p = 0.000$). Regarding T stage and N stage, there was no difference between the two groups. Besides liver metastasis, less patients of Death due to heart disease group had other distant metastases (22.5% vs. 29.3%, $p = 0.025$). The tumor size in Death due to heart disease group were larger than those in Alive group (66.7% of patients had larger tumors, compared to 51.1% in Alive group, $p = 0.000$). As opposed to Alive group, less patients of Death due to heart disease group underwent surgery (51.0% vs. 63.3%, $p = 0.000$), and chemotherapy (38.2% vs. 78.7%, $p = 0.000$). Both group received little radiation therapy, with no notable difference (0.7% vs. 2.3%, $p = 0.070$).

Risk factors of death from heart disease

The association between individual characteristics and death from heart disease is shown in Table 2. A logistic regression including only the significantly different factors was applied. As shown, with increasing age, the risk of dying from heart diseases rose (OR = 1.06, $p = 0.000$). Additionally, patients with other histologic types were at a higher risk for heart diseases death (OR = 1.68, $p = 0.004$) than those with adenocarcinoma. Large tumor size was also associated with an increment in the odds of death from heart disease (OR = 1.89, $p = 0.000$). As for death from heart disease, the odds of patients with other metastases

Table 1. Patient Characteristics

Characteristics	Death due to heart disease group	Alive group	P value
Number	288 (100%)	2001 (100%)	
Age, median	77 (IQR, 71-84)	72 (IQR,68-77)	0.000
Gender			
Female	135 (46.9%)	950 (47.5%)	0.848
Male	153 (53.1%)	1051 (52.5%)	
Tumor site			0.032
Left	104 (36.1%)	856 (42.8%)	
Right	184 (63.9%)	1145 (57.2%)	
Histologic type			0.000
Adenocarcinoma	230 (79.9%)	1774 (88.7%)	
Others	58 (20.1%)	227 (11.3%)	
T stage			0.482
T0/Tis	2 (0.7%)	11 (0.5%)	
T1	23 (8.0%)	114 (5.7%)	
T2	5 (1.7%)	66 (3.3%)	
T3	96 (33.3%)	739 (36.9%)	
T4	66 (22.9%)	456 (22.8%)	
Tx	96 (33.3%)	615 (30.7%)	
N stage			0.386
N0	99 (34.4%)	647 (32.3%)	
N1	77 (26.7%)	530 (26.5%)	
N2	56 (19.4%)	397 (19.8%)	
Nx	56 (19.4%)	427 (21.3%)	
Metastases besides liver			0.025
No	222 (77.1%)	1415 (70.7%)	
Yes	66 (22.9%)	586 (29.3%)	
Tumor size			0.000
<5cm	96 (33.3%)	979 (48.9%)	
≥5cm	192 (66.7%)	1022 (51.1%)	
Surgery			0.000
No	141 (49.0%)	735 (36.7%)	
Yes	147 (51.0%)	1266 (63.3%)	
Chemotherapy			0.000
No	178 (61.8%)	427 (21.3%)	
Yes	110 (38.2%)	1574 (78.7%)	
Radiation			0.070
No	286 (99.3%)	1954 (97.7%)	
Yes	2 (0.7%)	47 (2.3%)	
Follow-up time, median, months	3(IQR, 1-12)	15 (IQR, 5-34)	0.000

Table 2. Multivariable Logistic Regression Analysis: odds of death from heart diseases

Patient characteristic	Multivariate analysis		
	OR	95% CI	P value
Age	1.06	1.04-1.08	0.000
Tumor site			
Left		Reference	
Right	1.31	0.99-1.73	0.055
Histologic type			
Adenocarcinoma		Reference	
Others	1.68	1.18-2.39	0.004
Metastases besides liver			
No		Reference	
Yes	0.7	0.51-0.96	0.027
Tumor size			
<5cm		Reference	
≥5cm	1.89	1.44-2.50	0.000
Surgery			
No		Reference	
Yes	0.64	0.48-0.84	0.001
Chemotherapy			
No		Reference	
Yes	0.23	0.18-0.31	0.000

were 30% lower than those without other metastases (OR = 0.70, $p = 0.027$). Furthermore, compared to those without surgery, patients who underwent surgery had a 36% decreased risk of death from heart diseases (OR = 0.64, $p = 0.001$). And similarly, patients who received chemotherapy had a 77% decreased risk of death from heart diseases (OR = 0.23, $p = 0.000$).

Discussion

The present study focused on risk factors and death from heart disease among elderly colon cancer with liver metastasis. In multivariate logistic regression analysis, the significant predictors for heart disease death were old age, other histologic type besides adenocarcinoma and tumor size ≥ 5 cm. The protective factors were metastases besides liver, surgery and chemotherapy.

The long-term cardiovascular disease incidence was evaluated in high-risk stage II-III colorectal cancer patients in Hong Kong [9]. The age of cancer diagnosis was correlated with the occurrence of cardiovascular (hazard ratio (HR) per 5-year increase: 1.16; 95% CI 1.08-1.24). In a Korean retrospective study, multivariate analysis showed that age was a significantly predictive factor for cardiovascular disease (HR:1.062, $p < 0.001$) among colorectal cancer patients who survived at least 5 years [10]. Our study showed that age was associated with the increased risk of heart disease death in elderly advanced colon cancer, possibly due to the higher occurrence of cardiovascular disease in this patient population with colorectal cancer.

In a retrospective cohort study of stage III colon cancer [11], patients with mucinous adenocarcinoma

had significantly worse disease-free and overall survival compared to those without mucinous adenocarcinoma. In a systematic review and meta-analysis [12], the overall survival of patients with mucinous adenocarcinoma was significantly poorer than non-specific adenocarcinoma (HR: 1.23, $p < 0.01$). In our study, compared to non-specific adenocarcinoma, other histologic types, including mucinous adenocarcinoma, were also associated to an increased risk of death from heart diseases.

The prognosis of tumor size in colon cancer is controversial. In stage II colon cancer, both small and large tumor sizes have been reported to be associated with a poorer disease-free survival [13]. In a retrospective study of 593 colorectal cancer patients, tumor size ≥ 5 cm was a statistically significant risk factor in terms of overall survival [14]. However, no literature has reported an association between tumor size of colon cancer and heart disease death. In our study, compared to those with small tumor size, patients with tumor size ≥ 5 cm had an 89% increased risk of death from heart diseases.

As is well known, the more organs cancer metastasizes to, the worse the prognosis is [15, 16]. Surprisingly, our study revealed that the presence of metastases to organs other than liver can actually reduce the risk of heart disease death in elderly colon cancer patients. We speculate that patients with multiple organ metastases, often having extremely poor prognosis, tend to die of cancer itself, whereas patients who die of other causes may be long-term survivors who have responded well to treatment.

In a retrospective Japanese study of 2017 colorectal cancer patients, one severe cardiac infarction occurred after minimally invasive surgery [17]. Compared to cancer-free cohort, HR for incident heart failure was 1.53 (95% CI 1.02-2.28) in another stage I-III colorectal cancer group that underwent elective surgery [18]. Although surgery poses a risk of heart disease in colorectal cancer, in our study, surgery reduced the risk of death from heart disease. Among our elderly advanced cancer patients, those who were eligible for surgery may have a relatively low tumor load and better performance status, so the risk of death from heart disease was lower.

The odds of experiencing heart disease were not consistent regarding chemotherapy. In a retrospective Chinese study of 2085 colorectal cancer patients, the risk of cardiovascular complications was higher in patients who underwent chemotherapy (adjusted HR: 1.84, 95% CI 0.70-1.86) [19]. In a long-term colorectal cancer survivor cohort study, history of chemotherapy was recognized as independent risk factor for ischemic heart disease (HR: 0.636, 95% CI 0.443-0.912) [10]. In our elderly colon cancer patients with liver metastasis, chemotherapy was also identified as independent favorable risk factor reducing the risk of heart disease death. The role of chemotherapy in risk of heart diseases requires further research.

There are several limitations in the current study. Firstly, the retrospective nature of the study introduces selection and recall bias and does not allow for the determination of causal relationships. Secondly, patients' comorbidities and lifestyle behaviors are closely related to the occurrence and deterioration of heart disease.

Unfortunately, these risk factors were not available in SEER database. Thirdly, data regarding molecular subtypes, specific chemotherapeutic drugs used, whether targeted or immunotherapy was performed, were lacking in the SEER database. Therefore, it is not feasible for us to further analyze the risk of these cancer-related factors in elderly advanced colon cancer patients.

In conclusion, among elderly colon cancer patients with liver metastases, old age, histologic type besides adenocarcinoma and large tumor size were associated with increased risk of death from heart diseases. Conversely, the presence of other metastases, surgery and chemotherapy reduced the risk. It is crucial to identify the risk factors and adopt preventive methods and appropriate treatment, which may enhance the quality of patient care and prolong patients' survival.

Author Contribution Statement

Wu Y collected the data, and drafted the work; Zhou MH performed the design of the work, analyzed the data and revised the work. All authors read and approved the final manuscript.

Acknowledgements

Since the study was based on a publicly available database, informed consent and institutional review board approval are not required.

It was not approved by any scientific body, nor is it part of an approved student thesis.

Data Availability

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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