Analysis of clinical prognostic factors in bladder cancer-associated double primary cancer

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Research Article

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Abstract

Objective: This study aims to explore prognostic factors in bladder cancer-related DPC(double primary cancer).

Method: Patients with bladder cancer admitted to the Department of Urology of the First Affiliated Hospital of Guangxi Medical University from November 2012 to October 2019 were screened. They were divided into simple bladder cancer (n = 27) and bladder cancer-related DPC (n = 27). Differences in sex, average age, smoking history, radiotherapy history, intravenous chemotherapy history, SII, NLR, PLR, PNI, and serum tumor markers between the two groups were analyzed. Factors related to prognosis evaluation were determined.

Results: Smoking history, radiotherapy history, intravenous chemotherapy history, SII, NLR, PLR, and PNI were significantly different between the simple bladder cancer group and the bladder cancer-related DPC group (P<0.05). No significant difference in serum tumor markers CA153, CA199, CA125, CA242, CA724, and CEA, sex, and average age of onset was found between the two groups (P>0.05). In the univariate analysis, patient type, SII, PLR, NLR, and PNI had significant effects on survival rate (P<0.05). Multivariate analysis showed that the type of patient was an independent factor affecting survival. The survival rate of patients with bladder cancer-related DPC was lower than that of patients with simple bladder cancer (P<0.001).

Conclusion: The incidence of DPC associated with bladder cancer is positively correlated with the history of smoking, radiotherapy, and intravenous chemotherapy. Dynamic monitoring of changes in SII, NLR, PLR and PNI after treatment of the first primary cancer is helpful to evaluate the risk of DPC in patients. The prognosis of patients with bladder cancer-related DPC is worse than that of patients with simple bladder cancer.

1. Introduction

The concept of double primary cancer (DPC) was first put forward by Billroth [1]. Bladder cancer-related DPC refers to the simultaneous or successive occurrence of primary malignant tumors in the bladder or other organs of the same patients with bladder cancer. and are two kinds of primary cancers with different pathological types. Global literature reports that the incidence of bladder cancer-related DPC accounts for 1.6%–10.7% of bladder cancer cases [2]. The therapeutic effect on patients with bladder cancer has significantly improved with the continuous development in clinical diagnosis and treatment technology; the survival time has been gradually prolonged, and the number of cases of recurrent malignant tumors in the urinary system and other systems of the body has gradually increased. The diagnosis and treatment of DPC still have deficiencies due to the diversity of clinical features and the complexity of the pathogenesis of the disease. Second primary cancer in chronological patients with DPC is easily misdiagnosed as metastatic cancer, resulting in delayed treatment; similarly, second primary cancer in patients with metachronous DPC may be misdiagnosed as metastatic or recurrent after

treatment, thereby losing the opportunity of radical surgery. Factors affecting the occurrence and prognosis of bladder cancer-related DPC should be explored for precise medical staging and treatment of tumors.

Bladder cancer is a kind of tumor with strong immunogenicity and severe inflammatory reaction[3]. Cancer is closely related to inflammation. The inflammatory reaction of the body is the initiation of the immune protection mechanism, which is used to resist the invasion of pathogens and participate in the repair of tissues and microenvironment. However, in some special cases, inflammatory reaction can lead to changes in the local microenvironment of the body tissue. For example, inflammatory response after long-term chronic inflammatory stimulation can lead to cancer due to the changed microenvironment. The same inflammatory response can rely on cytokines produced to promote tumor neovascularization and participate in the occurrence, development, invasion, and metastasis of cancer. Therefore, a variety of blood-related inflammatory markers have been found and applied to evaluate the prognostic risk of patients with cancer[4-5]. Inflammatory indices such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and systemic immune inflammation index (SII=N*P/L) are prognostic factors used to evaluate many malignant tumors [6-8]. However, whether the expression of blood-related inflammatory markers can reflect the progression of bladder cancer remains unknown [9]. Physical nutrition and immunity are also important factors that affect the prognosis of bladder cancer. Onodera [10] proposed that prognostic nutrition index (PNI= serum albumin (g/L)+5×lymphocyte count ($\times 10^9$/ L)) can be used to evaluate the prognosis of patients with cancer. Blood-related malignant tumor antigen refers to specific substances synthesized by cancer cells and can be detected in the blood of patients with cancer. By monitoring malignant tumor antigens, we can indirectly understand the relevant situation of the tumor, judge the patients' condition, and evaluate their prognosis. Ahmadi[11] reported the correlation between some blood-associated malignant tumor antigens and the prognosis of bladder cancer. The diagnosis of bladder cancer-related DPC often depends on imaging and other examinations, and most patients are in the middle and late stages of the disease when the tumor is detected. Whether it can play a role in the early occurrence and prognosis of bladder cancer and bladder cancer-related DPC through simple and easy to measure blood-related inflammatory indices, prognostic nutrition index, serum tumor markers, and so on remains unclear. The present study aimed to conduct a retrospective analysis to explore the occurrence and prognostic factors of bladder cancer-related DPC. Results can deepen our understanding of bladder cancer-related DPC and guide future clinical work.

2. Materials And Methods

2.1 Clinical data

2.1.1 Inclusion criteria

The classical diagnostic criteria established by Warren and Gates [12] were used in this study: (1) any single tumor must be diagnosed as a malignant tumor; (2) the tumor must have its unique pathological

morphology; (3) the tumor occurs in different parts or organs; and (4) the tumor should not be metastatic and recurrent.

2.1.2 Exclusion criteria

The following exclusion criteria were used: (1) patients with incomplete case data; (2) patients who died in the perioperative period during surgical treatment of primary malignant tumor; and (3) patients whose pathology could not be classified as primary or metastatic tumor.

2.1.3 Source of cases

A total of 1686 patients with bladder cancer diagnosed by operation and pathology were collected from the Department of Urology of the First affiliated Hospital of Guangxi Medical University from November 2012 to October 2019. Twenty-seven cases of bladder cancer-related DPC met the diagnostic criteria and had complete clinical data. Twenty-seven cases of simple bladder cancer were categorized in the control group.

2.2 Research methods

The patients were divided into simple bladder cancer (n=27) and bladder cancer-related DPC (n=27). The sex, average age of onset, history of smoking, history of radiotherapy, history of intravenous chemotherapy, systemic immune disease index (SII=P×N/ L, where P, N and L are platelet, neutrophil, and lymphoid cell in blood routine), neutrophile-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutrition index (PNI=serum albumin (g/L)+5×lymphoid cell count ($\times 10^9$ /L), and peripheral blood tumor markers (CA153, CA199, CA125, CA242, CA724, and CEA) were analyzed.

2.3 Follow-up mode

All patients were followed up through outpatient reexamination and telephone return visit. The follow-up date ended on October 31, 2019.

2.4 Statistical analysis

Statistical analysis was carried out by SPSS26.0 software. Rank sum test was used to compare measurement data, and x^2 test was used to compare counting data. A life table method was used to calculate the survival rate. The COX risk proportional regression model was used in multivariate analysis. Kaplan-Meier method was used to compare survival rate. Values at $P < 0.05$ indicate statistically significant difference.

3. Comparison Of Clinical Data

3.1 Sex, cause of treatment, average age of onset, family history of malignant tumor, history of smoking, history of radiotherapy, and history of intravenous chemotherapy

The history of smoking, radiotherapy, and intravenous chemotherapy were significantly different (P<0.05) between the simple bladder cancer group and the bladder cancer-related DPC group. No significant difference (P>0.05) in sex and average age of onset was found between the two groups (Table 1).

Table 1 Comparison of clinical data

ject	Simple bladder cancer (n=27) (N or M ±QR)	Bladder cancer associated DPC (n=27) (N or M ±QR)	Z/x2	P value
nder			1.964	0.161
le	24(44.4%)	20(37.0%)		
nale	3(5.6%)	7(13.0%)		
erage age of set (years)	62±18	68±14	-1.801	0.072
oking history			27.341	P<0.001*
s	25(46.3%)	21(38.9%)		
ne	2((3.7%)	6(11.1%)		
diotherapy tory			3.527	0.015*
s	0(0%)	7(13.0%)		
ne	27(50.0%)	20(37.0%)		
story of ravenous emotherapy			15.429	P<0.001*
s	0(0%)	12((22.2%)		
ne	27(50.0%)	15(27.8%)		

*** P < 0.05 indicates that it is statistically significant.**

3.2 SII, NLR, PLR, PNI, and serum tumor markers

SII, NLR, PLR, and PNI were significantly different (*P*<0.05) the between simple bladder cancer and the bladder cancer-related DPC. No significant differences (*P*>0.05) in CA153, CA199, CA125, CA242, CA724, and CEA were found between the two groups (Table 2).

Table 2 Comparison of SII, NLR, PLR, PNI, and serum tumor markers

ject	Simple bladder cancer (*n*=27)	Bladder cancer associated DPC (*n*=27)	t	P value
	588.41±66.74	848.27±107.04	-2.060	0.045*
R	2.21±0.16	3.24±0.35	-2.682	0.011*
R	129.89±9.42	195.02±29.54	-2.101	0.044*
I	50.26±0.86	45.08±1.08	3.759	0.000*
153	21.33±9.37	9.11±1.11	1.295	0.207
199	71.54±40.53	38.52±18.79	0.739	0.465
125	13.83±2.73	15.72±2.20	-0.538	0.594
242	28.01±10.69	20.77±7.52	0.555	0.583
724	2.45±0.63	5.92±3.29	-1.036	0.317
A	5.00±1.67	6.01±1.46	-0.458	0.649

4. Correlation Analysis Of Prognosis

4.1 Overview of overall survival rate

The follow-up time of 54 patients was 0–72 months, and the median survival time was 52.09 months. Twenty-three deaths were recorded, with a total mortality rate of 42.59%. The 1-, 3-, and 5-year survival rates were 80.0%, 56.0%, and 39.0%, respectively (Table 3).

Table 3 Survival of 54 patients during follow-up

Total number of cases	Death toll	Total death rate （%）	Survival rate (%)		
			One year	Three years	five years
54	23	42.59	80.0	56.0	39.0

4.2 Analysis of factors affecting the survival rate of 54 patients

4.2.1 Univariate analysis

In the univariate analysis, patient type(Wald2 = 15.291, P < 0.001), SII (Wald2 = 6.131, P = 0.013), PLR (Wald2 = 8.636, P = 0.003), NLR (Wald2 = 8.545, P = 0.003), and PNI (Wald2 = 12.024, P = 0.001) had effects on survival rate (*P*<0.05, Table 4).

Table 4 Univariate analysis of factors affecting the survival rate of 54 patients

Variable	Regression coefficient B	SE	Waldc2	*P*	RR	95%CI of RR	
						Lower limit	Upper limit
Patient type	2.974	0.761	15.291	<0.001	19.570	4.408	86.892
SII	0.001	0.000	6.131	0.013	1.001	1.000	1.002
PLR	0.004	0.001	8.636	0.003	1.004	1.001	1.007
NLR	0.344	0.118	8.545	0.003	1.411	1.120	1.777
PNI	-0.132	0.038	12.024	0.001	0.877	0.814	0.944

4.2.2 Multivariate analysis

Patient type, SII, PLR, NLR, and PNI were included in the multivariate COX proportional hazard regression model. Patient type (Wald 2, 13.533, P < 0.001) was an independent factor that affected the survival rate. The risk of death in patients with bladder cancer-related DPC was 9.713 times higher than that in patients with simple bladder cancer (Table 5).

Table 5 Multivariate analysis of factors affecting the survival rate of 54 patients

Variable		Regression coefficient B	SE	Waldc2	*P*	RR	95%CI of RR	
							Lower limit	Upper limit
Patient type								
Simple bladder cancer		-	-	-	-	1.000	-	-
Bladder DPC	cancer-related	2.273	0.859	7.007	0.008	9.713	1.804	52.293
	SII	0.001	0.001	0.755	0.385	1.001	0.999	1.002
	PLR	0.001	0.002	0.127	0.721	1.001	0.997	1.004
	NLR	0.121	0.243	0.248	0.619	1.129	0.700	1.819
	PNI	-0.061	0.050	1.471	0.225	0.941	0.853	1.038

4.2.3 Comparison of survival rates of different Patient type

Comparison of the survival rates of different Patient type showed that the median survival time of patients with bladder cancer-related DPC was 13 months, and that of patients with simple bladder cancer was 65 months; the difference was statistically significant (Log Rankc2 = 28.620, P < 0.001). The survival rate of patients with bladder cancer-related DPC was lower than that of patients with simple bladder cancer (Table 6 and Figure 1).

Table 6 Comparison of survival rates of different Patient type

Patient type	Median survival time (months)	Standard error	95% confidence interval		Median survival time (months)	Standard error	95% confidence interval	
			Lower limit	Upper limit			Lower limit	Upper limit
Simple bladder cancer	64	4.966	54.675	74.141	65	9.581	46.221	83.779
Bladder cancer-related DPC	18	2.746	13.021	23.787	13	5.284	2.644	23.356
Total	46	4.85	36.852	55.863	55	12.159	31.168	78.832

5. Discussion

In this study, significant differences (*P*<0.05) in the history of smoking, radiotherapy, and intravenous chemotherapy were found between the simple bladder cancer and the bladder cancer-related DPC. Patient

type, SII, NLR, PLR, and PNI had significant effects (P<0.05) on survival rate. The survival rate of patients with bladder cancer-related DPC was lower than that of patients with simple bladder cancer (P<0.001).

At present, the cause and mechanism of DPC remain unclear, and no statistical significance has been found in the comparison of age and sex of onset. Considering the overall comparison of bladder cancer and its related DPC between the two groups, it may be related to insufficient number of cases. In the present study, the occurrence of DPC may be related to the following factors.(1).Smoking history may be a risk factor for bladder cancer-related DPC. Tabuchi[13] reported that smoking have 59% higher risk of DPC than non-smoking patients with cancer; smoking causes genetic mutations in the body, and tobacco components, such as aromatic amines and tar, are likely to cause cancer.(2).Medical therapeutic factors, such as history of radiotherapy and intravenous chemotherapy, were higher in the bladder cancer-related DPC than those in the simple bladder cancer. A large number of studies have found that patients with malignant tumors develop DPC after radiotherapy [14-16]. Radiotherapy and intravenous chemotherapy are routine methods for treatment of malignant tumors; although these methods can kill cancer cells, they can also cause the carcinogenesis of normal cells.

Inflammation runs through the occurrence, development, and metastasis of cancer [17-19].(1).Systemic immune inflammation index (SII) is closely related to the inflammation and immune system of the body. Neutrophils interact with cancer cells by secreting vascular endothelium growth factor(VEGF). Platelets in the inflammatory microenvironment can also secrete VEGF to affect tumor neovascularization and increase the permeability of neovascularization, which is related to the metastasis and spread of cancer cells [20-21]. Mantovani [22] found that lymphocytes in the blood system are important immune cells and can control the proliferation, variation, and metastasis of cancer cells through cellular immunity and humoral immunity.(2).Abnormalities in blood routine indices, such as neutrophil/lymphocytes ratio (NLR), are often found in patients with advanced tumor; this condition is characterized by an increase in the absolute number of neutrophils and a decrease in the absolute number of lymphocytes. Lymphocytes are an important part of the body's immune system. The decrease in the absolute number of lymphocytes indicates the decline of patients' immunity and the ability to resist tumor. Therefore, changes in NLR calculated by neutrophils and lymphocytes can also reflect the immune function of the body and guide the determination of the prognosis of malignant tumors.Bhindi [21] speculated that NLR is the best inflammatory index of blood-related malignant tumor for predicting the prognosis of cystectomy for bladder cancer.Gondo[23] conducted univariate and multivariate analyses of 189 patients with bladder cancer. The results showed that high NLR was significantly correlated with poor prognosis and could be an independent risk factor for tumor prognosis.(3).For platelet/lymphocyte rate (PLR), studies have shown that the number of platelets and the absolute value of lymphocytes in patients with bladder cancer are closely related to their condition and prognosis [24-25]. Therefore, by comparing and analyzing PLR calculated using platelets/lymphocytes, we can judge the prognosis of malignant tumors. Zhang[26] studied the prognostic value of PLR in 124 patients with bladder malignant tumors and found that the prognosis of the high-value PLR was worse than that of the low-value PLR. The results of this study show that increases in SII, NLR, and PLR are important clinical features of bladder cancer-related DPC. Dynamic

monitoring of SII, NLR, and PLR after treatment of first primary cancer is helpful to evaluate the risk of DPC in the patients. When the values of SII, NLR, and PLR continue to increase after the treatment of the first primary cance, the possibility of DPC also increases. The prognosis of the bladder cancer-related DPC was found to be worse than that of the simple bladder cancer.

At present, prognostic nutrition index (PNI) has been widely used to evaluate the prognosis of patients with cancer.Cui [27] analyzed the clinical data of 329 patients with non-muscular invasive bladder cancer and reported that PNI was an independent risk factor for recurrence-free survival; the prognosis of patients with low PNI was worse than that of patients with high PNI. PNI also indicates the nutritional status and immunity of the body. Poor condition of the body will lead to poor prognosis. The results of this study suggest that low PNI is another important clinical feature of bladder cancer-related DPC. Changes in PNI should be monitored dynamically after the treatment of the first primary cancer. This strategy helps not only evaluating the risk of developing DPC but also on determining the prognosis of patients.

Cox univariate analysis showed that patient type, SII, PLR, NLR, and PNI influenced the survival rate. Cox multivariate analysis showed that DPC was an independent risk factor for survival. Kaplan–Meier analysis also showed that the survival time of patients with bladder cancer-related DPC was shorter than that of patients with simple bladder cancer. The values of SII, NLR, and PLR were significantly higher, whereas the PNI value was significantly lower in the bladder cancer-related DPC than those in the simple bladder cancer. In summary, the preoperative values of SII, NLR, PLR, and PNI in patients with bladder cancer-related DPC have important clinical significance in evaluating prognosis.

In this study, no significant differences in blood-related malignant tumor antigens CA153, CA199, CA125, CA242, CA724, and CEA were found between the simple bladder cancer and the bladder cancer-related DPC. The reason for this may be compared with the overall data of bladder cancer and bladder cancer-related DPC cases. It may also be related to CA153, CA199, and other malignant tumor antigens that are not specific to bladder cancer.

We analyzed and summarized factors related to the occurrence and prognosis of bladder cancer-related DPC. Results provide guidance for future clinical work. However, this study has some shortcomings and limitations. First, this study is retrospective and completed in a single institution and has relatively small sample size. Further multicenter, prospective study with large sample size should be conducted to confirm the findings. Second, SII, NLR, PLR,and PNI were not analyzed by Cox proportional hazard model in the bladder cancer-related DPC due to the limited number of patients.

Our conclusions are as follows. (1). A positive correlation existed between the occurrence of bladder cancer-related DPC and the history of smoking, radiotherapy, and intravenous chemotherapy. (2). Significant differences in preoperative SII, NLR, PLR, and PNI were found between patients with bladder cancer-related DPC and patients with simple bladder cancer. No significant difference in traditional tumor

markers such as CA153, CA199, CA125, CA242, and CA724 were detected. (3).The prognosis of patients with bladder cancer-related DPC was found to be worse than that of patients with simple bladder cancer.

Declarations

1.Ethics approval and consent to participate：This paper belongs to clinical retrospective research type, non-basic experimental type, We mainly collect the related indexes of patients' hospitalization examination and analyze them after follow-up, without violating ethics, and get the informed consent of patients.This study was approved and fully supported by the First Affiliated Hospital of Guangxi Medical University.

2.Consent for publication：All authors participating in this article agree to publish.

3.Availability of data and materials：We guarantee that the collected data are true and reliable, and they are the true results of patients included in the clinical diagnosis and treatment process.

4.Competing interests：there is no conflict of interest in any aspect.

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6.Authors' contributions：Zhang and Yang made equal contributions in this study, followed up and collected the research data, and wrote the paper after analysis. Mo and Li were responsible for analyzing the rationality of the audit data and participating in the writing of the paper. Cheng, the correspondent author, proposed the overall design of the paper, participated in the writing of the paper, and put forward guiding opinions on the paper, which was finally finalized.

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We confirm that all methods are implemented in accordance with relevant guidelines and regulations.This study was approved and fully supported by the First Affiliated Hospital of Guangxi Medical University,and confirm that we have obtained the informed consent of all subjects.

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Figures

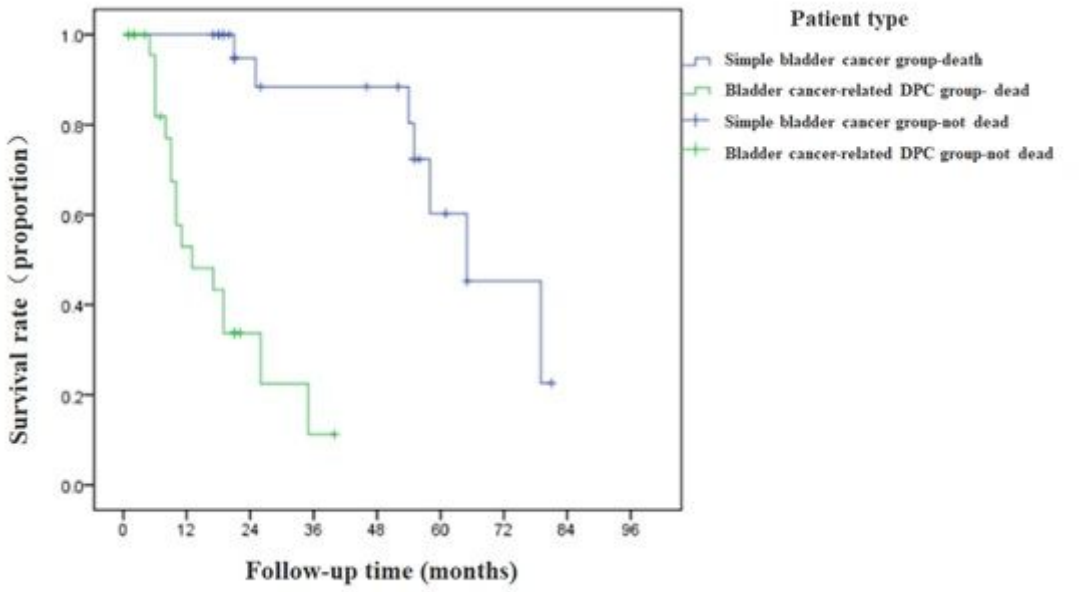

Figure 1

Comparison of survival rates of different Patient type