Renal Cell Carcinoma in People with HIV- An Analysis of the Postoperative Factors Associated with the Long-Term Survival

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Research Article

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Abstract

Aims: The purpose of the current study is to explore the prognostic factors of the renal cell carcinoma (RCC) in People living with HIV (PLWH), and to evaluate the postoperative factors associated with the survival in PLWH with RCC.

Methods: PLWH with RCC who underwent surgical treatment were retrospectively studied. A single-center analysis was conducted from January 2012 to January 2021. General and postoperative clinical data, including age, gender, smoking and drink history, active antiretroviral therapy (ART), cancer histology, clinical and pathological stage, surgical result, Glasgow Prognostic Score (GPS), the Charlson comorbidity index (CCI), the Karnofsky performance status (KPS), CD4⁺ T cell count, CD4/CD8 ratio and survival time were collected.

Results: A total of 67 patients were included in our study. The Creatine (77.1±18.8 vs 85.7±12.9, P value=0.032), HGB(mg/dL) (113.6±12.6 vs 139.3±20.8, P value=0.694), the CD4/CD8 ratio (0.68±0.40 vs 0.86±0.33, P value=0.006) and overall survival time (months) (74.93±5.249 vs 96.47±3.28, P value=0.009), the progression free survival time (months) (66.47±6.56 vs 90.65±4.82, P value=0.011). The Cox regression analysis showed that the tumor size and the CD4/CD8 ratio were prognostic factors for survival time.

Conclusion: In our retrospective analysis, the survival prognosis of negative group was better than that of PLWH with RCC. The risk factors for overall survival in PLWH with RCC was tumor size and CD4⁺/CD8⁺ ratio. The lower CD4/CD8 ratio was a significant predictive factor for shorter overall survival.

Introduction

By the end of 2017, there were 758610 living with HIV/AIDS patients reported in China, and 134512 HIV/AIDS patients were newly found in that year^[1]. The advent of ART has led to a decreased mortality from opportunistic infectious diseases and improves survival, and HIV-associated illnesses or complications of acquired immunodeficiency syndrome (AIDS) are less frequently observed in PLWH^[2, 3]. PLWH are at elevated risk for developing several cancers. The US Centers for Disease Control (CDC) has defined KS, certain non-Hodgkin lymphomas, and cervical cancer as AIDS-defining cancers (ADCs) since the 1990s^[4]. Prior to the widespread use of antiretroviral therapy (ART), active management of other non-AIDS defining cancers (NADCs) was less frequent and the life expectancy of PLWH was relatively short^[5]. Along with the improved survival, the NADCs has been consistently reported^[6–8]. Compared with the general population, the population of PLWH was at higher risk for cancer incidence^[9].

Renal cell carcinoma (RCC) accounts for 2–3% of all cancers. According to the NCCR of China 2015 annual report, the overall incidence of kidney cancer was 3.35/105 in 2011. Surgery was the main treatment option, whereas the proportion of laparoscopic surgery and nephron-sparing surgery was increasing gradually^[10]. In a large meta-analysis of seven population-based HIV cancer studies, involving

more than 400,000 HIV-positive patients, Grulich et al. ^[11] reported a standardized incidence ratio of 1.50 (95% confidence interval = 1.23–1.83) for RCC in the HIV-positive population. However, most data on NADCs risk are available for Western countries and little data from Asia are available.

The purpose of the current study is to evaluate outcomes of RCC in PLWH referred to the our hospital.

Methods

Patients and Characteristics

This study included PLWH and Negative patients with RCC at Beijing You'an Hospital—Department of Urology—from January 2012 to December 2014, and the follow-up period was up to January 2021. After approval from each institutional ethical committee, patient data were collected from clinical report forms.

Criteria for patients inclusion were as follows—(1) Not limited by age or gender; (2) The PLWH group met the diagnostic criteria for adult HIV/AIDS developed by the Centers for Disease Control and Prevention (CDC); (3) Compliance with TNM staging of RCC in The American Joint Committee on Cancer(AJCC) 2019 revising^[12]; (4) Postoperative pathological diagnosis and the presence of clinical stage I-III of renal cancer; (5) ART has been performed for at least 4 months prior to surgery in PLWH. Criteria for patient exclusion were as follows: (1) Not have ART or not reach the schedual visits; (2) The first time finding RCC but existing metastatic tumor; (3) Do not perform surgery.

After obtaining the approval of Beijing You'an Hospital, clinical characteristics and postoperative data were retrospectively collected, including age, gender, CD4+ T cell count and CD4⁺/CD8⁺ ratio at diagnosis, C-reactive protein (CRP), pathologic features, Glasgow (GPS), the Charlson comorbidity index (CCI), the Karnofsky performance status (KPS). The overall survival time (OS) and progression-free survival (PFS) time was calculated from the date of surgery to the time of death or the last follow-up. We divided the included cases into two groups according to the HIV infection. (Table1).

The GPS was calculated by the level of albumin and CRP according to previous study^[13]. The CCI was scored according to 19 preoperative comorbidities^[14]. The KPS was used to quickly quantify the general health status of the patient population and their ability to perform daily activities^[15, 16].

Data and analysis

Statistical analysis was performed using SPSS 22.0 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY). The statistical significance among distinct groups was determined by an analysis of variance, and the differences between 2 independent groups were evaluated using a Student T test. A P-value <0.05 was considered statistically significant. Survival curves were calculated via the Kaplan-Meier method; differences in survival were assessed using the log-rank test. The variables (P<0.05) in the

univariate and important variable predict the dependent variable were included in multivariate with Cox regression and survival analysis.

Results

Of the 3259 patients managed by the Department of Urology, Beijing Youan Hospital between January 2012 and December 2014, 261 patients with a diagnosis of RCC were identified. Of these, 16 were diagnosed at Stage IV and cannot perform the surgery, 245 were diagnosed at stage I-III. 133 patients cannot collect incomplete data and 16 patients occurred metastasis when were diagnosed. 11 PLWH had no ART before the diagnosis of RCC. The patients at early stage(I-III) were performed surgery. Finally, 33 PLWH and 34 HIV-negative patients with RCC were included in the study. (Figure 1). The demographics, clinical characteristics and univariate analysis are presented in Table 1. PLWH with RCC had used ART for at least 4 months before the diagnosis of RCC. The mean tumor size was 4.33 ± 1.94 (cm). The histological type of RCC was in clear cell carcinoma, The clinical stage of PLWH group and Negative group was no significant statistic difference, cT1(16 vs 18, P value=0.904), cT2(13 vs 12, P value=0.925), cT3(4 vs 4, P value=0.964). However, the pathological stage was slightly different to the clinical stage, no significant statistic difference. A total of 20(7 vs 13) underwent partial resection and 47(26 vs 21) underwent radical resection. We performed the univariate analysis using student T test. The Creatine (77.1 ± 18.8 vs 85.7 ± 12.9 , P value=0.032), HGB(mg/dL) (113.6 ± 12.6 vs 139.3 ± 20.8 , P value=0.694), the CD4/CD8 ratio (0.68 ± 0.40 vs 0.86 ± 0.33 , P value=0.006) and overall survival time (months) (66.7 ± 24.4 vs 80.2 ± 14.4 , P value=0.009) had significant statistical difference in the analysis.

Table 1

General characteristics and Univariate analysis

Feature	total	HIV group	Control	P value
N	67	33	34	
Age at surgery	51±11	51±12	50±11	0.693
BMI	24.8±2.6	24.4±2.2	25.1±2.9	0.228
Gender				
Female/Male	12/55	5/28	7/27	0.562
Creatine	81.4±16.5	77.1±18.8	85.7±12.9	0.032*
CRP	10.92±2.67	7.45±3.78	14.94±30.05	0.160
Albumin	42.5±4.7	41.6±4.8	43.4±4.4	0.132
HGBmg/dL	126.6±21.6	113.6±12.6	139.3±20.8	0.001*
Tumor Size	4.42±2.51	4.52±2.95	4.33±1.95	0.757
CD4 cell count(cell/)	523.3±223.1	401.7±210.1	641.3±166.2	0.195
CD4/CD8 ratio	0.77±0.37	0.68±0.40	0.86±0.33	0.041*
Overall Survival	73.6±21.0	66.7±24.4	80.2±14.4	0.009*
Clinical Stage				
cT1	34	16	18	0.904
cT2	25	13	12	0.925
cT3	8	4	4	0.964
Pathological Stage				
pT1	46	24	21	0.657
pT2	12	5	7	0.794
pT3	10	4	6	0.771
Side				
Left/Right	43/24	19/14	24/10	0.392
GPS				
0	40	20	20	1.000
1	24	11	13	0.870
2	3	2	1	0.534
Histology, n(%)				

Clear cell tumor	58	27	31	0.305
Chromophobe cell tumor	6	5	1	0.105
other	3	1	2	1.000
Positive HBsAg,n(%)	4	3	1	0.278
Positive anti-HCV Ab,n(%)	3	1	2	0.569
CCI	7.58±1.75	6.85±1.18	8.69±1.93	0.694
Baseline ART regimen				
PI-based regimen	14	14	-	
NNRTI-based regimen	18	18	-	
INSTI-based regimen	1	1	-	
Grade				
1	33	21	16	0.874
2	24	8	13	0.215
3	9	4	6	0.524
Surgical approach				0.072
Partial resection	20	7	13	0.126
Radical nephrectomy	47	26	21	0.126
Bleeding(mL)	135.7±77.4	114.0±51.8	169.2±98.5	0.393
Operating Time(h)	1.3±0.4	1.2±0.4	1.4±0.5	0.881
Length of stays	11.7±3.8	11.8±3.8	11.6±3.9	0.856
KPS	90.3±12.8	91.8±13.1	88.8±12.5	0.342
CCI=Chalson Comorbidity index, GPS=Glasgow Prognostic Score; KPS=Karnofsky performance status				

As is shown in Figure 2 and Figure 3, the Kaplan-Meier curves of overall survival and progression-free survival stratified based on the PLWH group and HIV-negative group are shown in Figure 2. The median follow up time was 74.9 and 96.47 in PLWH group and Negative group respectively.

The variables of hemoglobin, serum albumin and creatinine, the CD4/CD8 ratio and tumor size were selected into the Cox regression analysis (Table 2). According to the univariate and Cox logistic regression analyses, the CD4/CD8 ratio (OR=0.037, 95%CI=0.537-0.967, P value=0.029), serum albumin (OR=0.721, 95%CI=0.537-0.967) and clinical tumor size (OR=1.965, 95%CI=1.033-3.737) were significant

risks factor. According to univariate and Cox regression analysis, the tumor size and CD4/CD8 ratio was the significant risk factor for the long-term survival.

Table 2

Multivariate analysis with Cox regression model for overall survival

			Multivariate analysis	
Variables	PLWH group (33 cases)	Negative group (34 cases)	Odds ratio(95% CI)	<i>P</i> -value
CD4/CD8 ratio	0.68±0.40	0.86±0.33	0.09(0.011-0.706)	0.022
Albumin	42.5±4.7	41.6±4.8	0.931(0.837-1.036)	0.190
Hemoglobin	113.6±12.6	139.3±20.8	1.009(0.98-1.04)	0.541
Creatinine	77.1±18.8	85.7±12.9	1.013(0.988-1.038)	0.32
Tumor size	4.33±1.95	4.52±2.95	1.177(1.024-1.352)	0.021

Discussion

With the increase of number of NADCs, cancer screening has become an important health maintenance in HIV clinical practice. And with the increases of RCC screening, the observed prevalence of localized cancers is also likely to increase in PLWH. As we know, the outcomes of RCC in PLWH were rarely reported. Wee^[17] retrospectively reviewed patients with HIV and RCC in a statewide HIV referral center in Australia, seven patients with HIV and RCC were included in this study and they mainly introduced their experience in presentation and management. It is time to establish the safety of the renal carcinoma surgery in PLWH group and decrease the existing disparities in cancer treatment in China. We report a series of PLWH with RCC in a major HIV center in China. While the peak incidence of RCC occurs between the ages 60 and 70 years in the general population^[18], we reported a median age of RCC diagnosis of 51 years. In our study, there were no significant surgical complications. Preoperative serum creatinine and HGB were statistically different between two groups. However, we found no significant difference in multivariate Cox regression analysis. Surgical resection is the only curative treatment with high-quality evidence if all the tumor burden can be removed. Surgical resection for early stage of RCC in PLWH is also potentially curable.

Tumor size has been previously shown to be closely related to outcome to patients with other types of cancers^[19, 20] Mike^[21] found that Five-year cancer specific mortality for treated cases was closely related to tumor size. Kim et.al^[20] retrospectively reviewed 331 patients and found the initial tumor size was

closely related to histologic response and is an important prognostic factor in osteosarcoma. But the conclusion was not consistent in some other studies. Kiatte et.al^[22] performed a study which identified 1208 patients who were treated with nephrectomy for small renal tumors and showed tumor size was not retained as an independent prognostic factor of survival in multivariate analyses. However, in our study, we found tumor size was a risk factor to overall survival time. Tumor size could be a risk factor of OS in the PLWH who were diagnosed as RCC and it should be further studied.

The main factor affecting the prognosis of PLWH may be onset of HIV status. PLWH who are taking ART is similar but not equal to that of uninfected individuals. In our study, the CD4⁺ cell count in PLWH was similar to the Negative group. Previous studies have shown the ratio of CD4⁺ T cells to CD8⁺ T cells (CD4⁺/CD8⁺ ratio) has been used as a surrogate marker of immune status and shown an independent association with NADCs and mortality in PLWH whereas CD4⁺ T cell counts alone do not predict the risk of survival in PLWH with NADCs. ^[23–25] Mariam conducted a cohort study which is to study the association between CD4/CDd8 ratio and morbidity in PLWH on ART, and found that a CD4/CD8 ratio <0.5 could identify patients who require a more intensive strategy of cancer prevention or screening^[23]. These findings further validate prior recommendations advocating surgery for PLWH regardless the CD4⁺ cell count. The CD4⁺/CD8⁺ ratio seems an important prognostic marker in PLWH. In our study, the lower CD4⁺/CD8⁺ ratio in PLWH may predict the worse survival as to general population.

In fact, as we know, there have been no studies about the prognosis of RCC between PLWH and the negative population, Whether HIV infection itself or the tumor itself affects prognosis is unclear. With the similar pathological stage, general status, KPS, GPS and CCI between two groups, the overall survival time and progression free survival time were lower in PLWH. Historically, it has been agreed that PLWH tend to have more advanced cancer stage at diagnosis and poor outcomes. We suspect HIV infection itself may be a greater influence on prognosis of tumor. In our study, a lower CD4/CD8 ratio is likely to reduce survival time in PLWH with RCC and be regarded as an independent risk factor. The findings further validate prior recommendations advocating surgery for PLWH at earlier diagnosis.

This study has several limitations, The sample from Beijing You'an Hospital could be biased because it is a referred center for infectious disease treatment, PLWH admitted by Beijing YouAn Hospital came from all over of China, but the study population cannot be considered a random sample as only who had relatively diseases could come to our hospital. There was another major weakness in our study, to exclude the influence of the non-ART to PLWH, we select the PLWH taking ART for at least 4 months, selection bias may have occurred. We need to collect more data not only from one-single center.

Conclusion

In our retrospective analysis, the survival prognosis of Negative group was better than that of PLWH with RCC. The risk factors for overall survival in PLWH with RCC was tumor size and CD4⁺/CD8⁺ ratio. The lower CD4/CD8 ratio was a significant predictive factor for shorter overall survival.

Declarations

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Contributions

Liang Chen and Wu Menghua contributed equally to this work. All authors reviewed the manuscript.

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Ethics approval and consent to participate

The authors were granted approval from the Human ethics committee of Beijing Youan Hospital. Each participating hospital reviewed and approved the study prior to any enrollment. All the participants provided written informed consent. All methods were carried out in accordance with the relevant guidelines(Human ethics guidelines of Beijing Youan Hospital).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available as they contain protected health information but are available from the corresponding author on reasonable request

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Figures

Figure 1

Flow chart of the patients eligible for this study.

Patient at risk(months)	0	20	40	60	80	100	120	Median(S.E.)	75% survival rate
PLWH	33	31	27	21	14	2	0	74.93(5.24)	43
Negative	34	34	34	31	18	3	4	96.47(3.28)	62

Figure 2

Comparisons of overall survival between PLWH group and Negative group.

Patient at risk (months)	0	20	40	60	80	100	120	Median(S.E.)	75% Survival rate
PLWH	33	26	20	14	7	0	0	66.47(6.56)	30
Negative	34	34	27	18	9	1	0	90.65(4.92)	40

Figure 3

Comparisons of progression free survival between PLWH and Negative.