Urologia Internationalis

Research Article

Urol Int 2023;107:698–705
DOI: 10.1159/000531080

Received: September 17, 2022
Accepted: February 6, 2023
Published online: June 2, 2023

The Influence of Preoperative Hydronephrosis on the Prognosis after Radical Cystectomy among Patients with Different Pathological Stages of Bladder Cancer

Jingwei Du Hui Zhan Jian Chen Jiansong Wang Shi Fu Mingxia Ding Ting Luan Hairong Wei Chengcai Yang

Department of Urology, The Second Affiliated Hospital, Kunming Medical University, Kunming, China

Keywords
Bladder urothelial carcinoma · Radical cystectomy · Preoperative hydronephrosis · Overall survival

Abstract

Introduction: Preoperative hydronephrosis is closely associated with the prognosis of patients with bladder cancer. This study assesses the effect of preoperative hydronephrosis on the prognosis after radical cystectomy (RC) among patients with different pathological stages of bladder urothelial carcinoma. ***Methods:*** We retrospectively analyzed the clinical data of 231 patients who underwent RC because of bladder urothelial carcinoma at our institution from January 2013 to December 2017. The overall survival (OS) in patients with or without preoperative hydronephrosis was followed up and compared, and the prognostic role that preoperative hydronephrosis played in patients with different pathological stages of bladder cancer was analyzed. Multivariate analysis was performed with the help of Cox proportional hazards regression models, the postoperative survival was analyzed with the help of Kaplan-Meier plots and log-rank test, and the p values of multiple testing were corrected using the Bonferroni correction. ***Results:*** Of 231 patients, 96 were patients with preoperative hydronephrosis and 115 patients had died by the end of the follow-up. Survival analysis found the 3- and 5-year survival rates after radical surgery of patients with preoperative hydronephrosis were significantly lower than those of patients without preoperative hydronephrosis ($p < 0.001$). Multivariate analysis found preoperative hydronephrosis, T stage of tumor, and lymphatic metastasis were independent influencing factors of postoperative OS ($p < 0.05$). Survival analysis of subgroups according to pathological stages found in $pT_{3-4}N_0M_0$ patients had a significant difference in postoperative survival between the group with preoperative hydronephrosis and the group without preoperative hydronephrosis ($p < 0.0001$). ***Conclusion:*** The results indicate that preoperative hydronephrosis mainly affects postoperative OS in the patients whose pathological stage of bladder cancer is $pT_{3-4}N_0M_0$.

Introduction

Radical cystectomy (RC) with pelvic lymph node dissection remains the mainstay of treatment for patients with muscle-invasive and high-risk nonmuscle-invasive bladder urothelial carcinoma [1–4]. The factors influencing postoperative survival are important to estimate prognosis, develop follow-up protocols, and select

karger@karger.com
www.karger.com/uin

Correspondence to:
Hui Zhan, zhanhui77@126.com

adjuvant treatment for patients after radical surgery. The TNM pathological staging (pTNM) system proposed by the American Joint Committee on Cancer/Union for International Cancer Control (UICC) is the main prognostic indicator for bladder cancer patients [5]. Besides the pTNM stage, many studies have found that preoperative hydronephrosis had a significant influence on the survival of patients after RC for bladder cancer [6–17]. For example, Georg C. Bartsch et al. reported in 2007 [18] that preoperative hydronephrosis is an independent prognostic factor for recurrence-free survival of bladder cancer patients after radical surgery. Berkan Resorlu et al. reported in 2009 [19] that the presence of hydronephrosis before RC is a significant prognostic parameter associated with poor cancer-specific survival (CSS) and advanced disease stage. Manuel S. Eisenberg et al. [11] also found that preoperative hydronephrosis was significantly associated with the risk of bladder cancer death.

It is the consensus that preoperative hydronephrosis is a risk factor for the survival of patients after RC [6–19], but to our knowledge, whether preoperative hydronephrosis can affect the postoperative survival of patients with different pathological stages of bladder cancer is still rarely reported, and little attention has been paid to the value of this problem. Therefore, in this study, with the help of Cox proportional hazards regression models, Kaplan-Meier plots, and the log-rank test, we explored the relationship between preoperative hydronephrosis and the overall survival (OS) after RC of patients with different pathological stages of bladder urothelial carcinoma within our institutional dataset.

Materials and Methods

Patient Cohort

Our research enrolled patients with bladder urothelial carcinoma who underwent radical surgical treatment between January 2013 and December 2017 at the Department of Urology, the Second Affiliated Hospital of Kunming Medical University (Kunming, China). Eligible cases met the following criteria: (1) had accepted RC and pelvic lymphadenectomy for bladder cancer at our institution; (2) the postoperative pathological diagnosis was urothelial carcinoma; (3) there were imaging data (ultrasound, intravenous urography, CT, MRI, etc.) within 2 weeks before the surgery to suggest the presence of hydronephrosis; (4) preoperative comorbid hydronephrosis was due to bladder neoplasm and had excluded nonneoplastic pathogenic reasons such as urinary calculi, inflammatory stricture, congenital malformations, benign prostatic hyperplasia, and ureteral injury; (5) postoperative survival was at least 3 months. Also excluded were patients who were lost in follow-up, refused to cooperate with the investigation, had a history of tumors coming from other visceral organs, or combined with upper urinary tract tumors.

Follow-Up

Follow-up visits included outpatient reviews, phone calls, and short messages. Patients were offered reviews every 3 months for the first 1–2 years after surgery, every 6 months for years 2–3, and yearly after that if no recurrence occurred. The follow-up continued until the cutoff time of the study or patient death, whichever occurred first. We calculated the OS as the time from operation to the point of death or the last time of follow-up. Patients still alive at the end point of follow-up were treated as censored data. The factors employed for research included age, gender, Eastern Cooperative Oncology Group (ECOG) score, history of TURBT, body mass index, comorbid disease, preoperative hydronephrosis, pathological grade and T stage of the tumor, lymph node metastasis, history of adjuvant chemotherapy, surgical approach (open surgery or laparoscopic surgery), urinary diversion (cutaneous ureterostomy or orthotopic neobladder), and estimated glomerular filtration rate (eGFR). We diagnosed the pathological staging according to the 8th edition of the TNM staging method issued by the UICC in 2017 and diagnosed the pathological grading according to the 2004/2016 grading system of the World Health Organization. If the patient had distant metastases within a short time (<3 months) after radical surgery, we considered the metastasis had occurred before the surgery. The end of the study was January 2021.

Statistical Analyses

IBM SPSS statistical software version 21.0 (IBM Corp.) and GraphPad Prism 9 (GraphPad Software) were employed for data analysis and statistical mapping. The survival curves were exhibited with the help of Kaplan-Meier curves. The differences in OS were calculated using the log-rank test. Independent influencing factors on OS after radical surgery were identified using the Cox proportional hazards regression analysis. The hazard ratio (HR) and 95% confidence interval (CI) were calculated finally. The p value for multiple testing was corrected using the Bonferroni correction.

Results

A total of 231 patients with bladder urothelial carcinoma were included in the study, namely, 202 males and 29 females (detailed data for each patient have been submitted to the journal as an online suppl. material; for all online suppl. material, see https://doi.org/10.1159/000531080). There were 96 patients (41.6%) who had preoperative hydronephrosis. The clinical characteristics of all patients are shown in Table 1. The median follow-up time was 47 months (interquartile range 25–68 months). The 3-year OS of patients with and without preoperative hydronephrosis were 62.5% ± 4.9% and 74.8% ± 3.7% ($p < 0.001$), respectively. The 5-year OS of patients with and without preoperative hydronephrosis were 38.5% ± 5% and 66.8% ± 4.1% ($p < 0.001$), respectively (shown in Fig. 1).

Table 1. Patient characteristics

Characteristics	Total $N = 231$	With hydronephrosis ($n = 96$)	Without hydronephrosis ($n = 135$)	p values
		n (%)	*n* (%)	
Median follow-up time, month	47 (25, 68)	36.5 (10, 59.5)	56 (38, 70)	<0.001
Gender				
Male	202 (87.4)	83 (86.5)	119 (89.1)	0.702
Female	29 (12.6)	13 (13.5)	16 (11.9)	
Age				
<65 years	128 (55.4)	50 (52.1)	78 (57.8)	0.391
≥65 years	103 (44.6)	46 (47.9)	57 (42.2)	
BMI				
Normal	140 (60.6)	54 (56.2)	86 (63.7)	0.253
Abnormal	91 (39.4)	42 (43.8)	49 (36.3)	
Comorbid disease				
Yes	60 (26.0)	23 (24.0)	37 (27.4)	0.556
No	171 (74.0)	73 (76.0)	98 (72.6)	
Surgical approach				
Open	78 (33.8)	45 (46.9)	33 (24.4)	<0.001
Laparoscopy	153 (66.2)	51 (53.1)	102 (75.6)	
Urinary diversion				
Cutaneous ureterostomy	97 (42.0)	50 (52.1)	47 (34.8)	0.009
Orthotopic neobladder	134 (58.0)	46 (47.9)	88 (65.2)	
Adjuvant chemotherapy				
Yes	28 (12.1)	13 (13.5)	15 (11.1)	0.577
No	203 (87.9)	83 (86.5)	120 (88.9)	
ECOG-PS				
≤1	195 (84.4)	81 (84.4)	114 (84.4)	0.989
≥2	36 (15.6)	15 (15.6)	21 (15.6)	
History of TURBT				
Yes	46 (19.9)	17 (17.7)	29 (21.5)	0.479
No	185 (80.1)	79 (82.3)	106 (78.5)	
Pathological grade				
Low level	45 (19.5)	12 (12.5)	33 (24.4)	0.024
High level	186 (80.5)	84 (87.5)	102 (75.6)	
T stage				
T1–2	143 (61.9)	46 (47.9)	97 (71.9)	<0.001
≥T3a	88 (38.1)	50 (52.1)	38 (28.1)	
Lymph node metastasis				
N+	20 (8.7)	10 (10.4)	10 (7.4)	0.423
N–	211 (91.3)	86 (89.6)	125 (92.6)	
eGFR, mL/min/1.73 m^2				
≤60	15 (6.6)	11 (11.8)	4 (2.9)	<0.01
>60	214 (93.4)	82 (88.2)	132 (97.1)	

ECOG-PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; eGFR, estimated glomerular filtration rate.

The univariate analysis found that patient age, surgical approach, urinary diversion, preoperative hydronephrosis, adjuvant chemotherapy, ECOG score, pathological grade, T stage of the tumor, and lymph node metastasis were significantly associated with OS of patients after RC (shown in Table 2). The multivariate analysis showed that preoperative hydronephrosis (HR = 2.059, 95% CI: 1.401–3.025, $p < 0.001$), tumor T stage (HR = 3.479, 95% CI: 2.237–5.411, $p < 0.001$), and lymph node metastasis (HR = 2.978, 95% CI: 1.704–5.203, $p < 0.001$) were independent prognostic factors of OS after RC (shown in Table 2).

Of the 231 patients, 96 were classified into the hydronephrosis group and 135 were classified into the no hydronephrosis group. Subsequently, the patients were

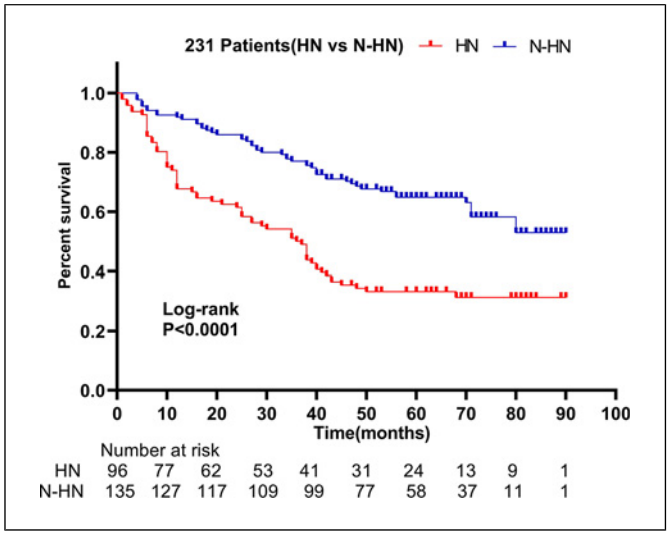

Fig. 1. Overall survival of patients stratified by preoperative hydronephrosis.

hydronephrosis group was 12.2% ± 5.1% and 7.3% ± 4.1%, respectively. The difference in OS between the hydronephrosis group and the no hydronephrosis group was significant ($p < 0.001$) (shown in Fig. 5). In $pT_xN_+M_x$ patients ($n = 20$), the difference in OS between the hydronephrosis group and no hydronephrosis group was insignificant ($p = 0.518$) (shown in Fig. 6). The corrected p values using the Bonferroni correction showed that there was a significant difference in OS between the hydronephrosis group and no hydronephrosis group of $pT_{3-4}N_0M_0$ patients.

Discussion

It is well known that preoperative hydronephrosis affects the prognosis of bladder cancer patients undergoing radical surgery. A meta-analysis reported by

Table 2. Multivariate analysis of variables affecting the OS of patients after RC for bladder cancer

Variable	Cutoff	Univariate p value	Multivariate		
			HR	95% CI	p value
Gender	Male versus female	0.604			
Age, years	<65 versus ≥ 65	0.032	1.197	0.819–1.749	0.353
BMI	Normal versus abnormal	0.711			
Comorbid disease	Yes versus no	0.604			
Surgical approach	Open operation versus laparoscopy	0.025	1.803	0.730–1.606	0.692
Urinary diversion	Cutaneous ureterostomy versus orthotopic neobladder	0.001	0.816	0.538–1.239	0.34
Hydronephrosis	Yes versus no	<0.001	2.059	1.401–3.025	<0.001
Adjuvant chemotherapy	Yes versus no	0.041	0.945	0.557–1.603	0.833
ECOG-PS	≤1 versus ≥2	0.040	1.51	0.942–2.420	0.087
History of TURBT	Yes versus no	0.911			
Pathological grade	Low level versus high level	<0.001	1.797	0.855–3.776	0.122
T stage	T1–2 versus ≥T3a	<0.001	3.479	2.237–5.411	<0.001
Lymph node metastasis	N+ versus N–	<0.001	2.978	1.704–5.203	<0.001

ECOG-PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index.

divided into eight subgroups according to the TNM stage for subgroup analysis (shown in Fig. 2). As shown in Figure 3, in $pT_1N_0M_0$ patients ($n = 64$), no statistical difference ($p = 0.980$) in OS was found between the hydronephrosis group and the no hydronephrosis group. In $pT_2N_0M_0$ patients ($n = 76$), the difference in OS between the hydronephrosis group and the no hydronephrosis group was significant ($p = 0.050$) (shown in Fig. 4). In $pT_{3-4}N_0M_0$ patients ($n = 71$), the 3- and 5-year OS of the no hydronephrosis group was 63.3% ± 8.8% and 40.2% ± 9.5%, respectively. The 3- and 5-year OS of the

Zhaowei Zhu et al. [9] found that preoperative hydronephrosis significantly affected OS and CSS in patients after RC, and the CSS was worse in patients with bilateral hydronephrosis. Another systematic review by Jong Jin Oh et al. [10] reached similar conclusions. However, the conclusions of different studies on the question of whether preoperative hydronephrosis can affect the postoperative prognosis of patients with different pathological stages of bladder cancer remain confusing and even contradictory. For example, in the research by Huan-yi Lin et al.[20], 3-year recurrence-free survival rates of the

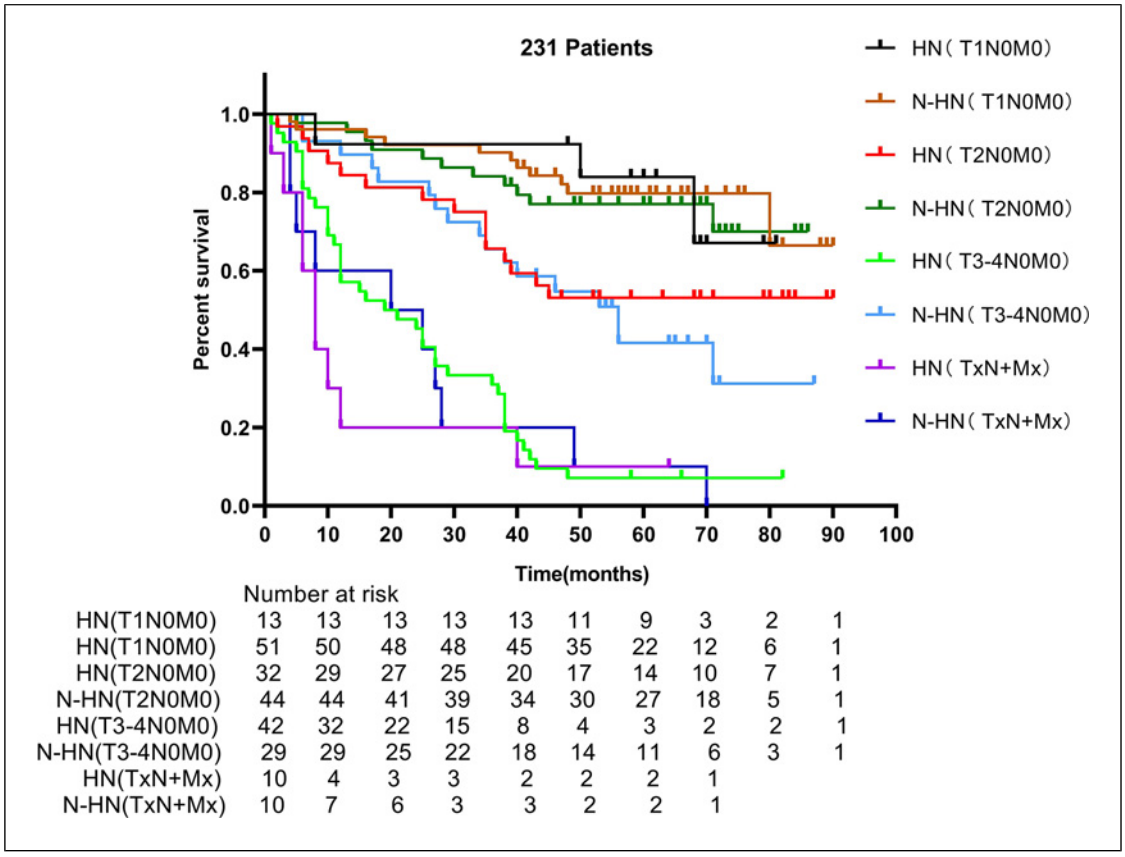

Fig. 2. Overall survival of patients stratified by pTNM stages and preoperative hydronephrosis.

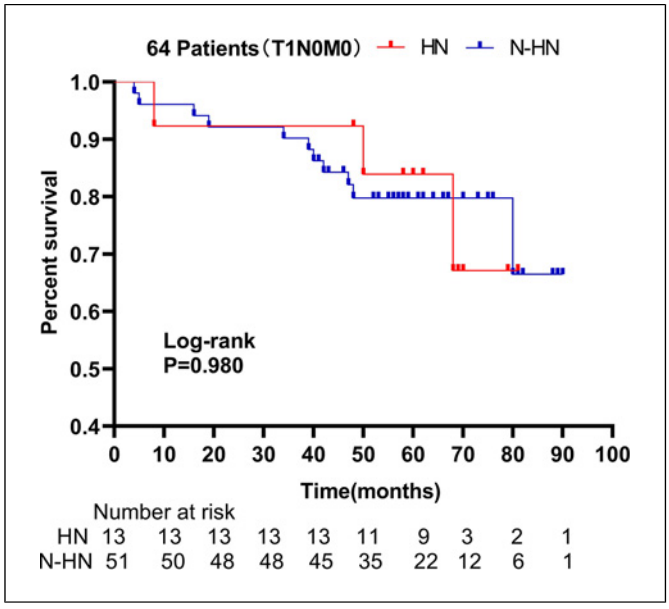

Fig. 3. Overall survival of T1N0M0 patients stratified by preoperative hydronephrosis.

subgroups of stage $pT_{3a}N_0M_0$ were 75.0% ± 21.7% for patients without hydronephrosis and 22.2% ± 12.6% for patients with hydronephrosis, which differed significantly, but no significant difference was found in patients with other pTNM stages. In another study, Thomas Hofner et al. [13] reported that there was no significant difference in CSS rates between patients with and without preoperative hydronephrosis across pTNM stages.

In this study, we found that preoperative hydronephrosis had a significant impact on postoperative OS in bladder cancer patients with tumor stage $pT_{3-4}N_0M_0$. To our knowledge, this is the first study to examine the effect of preoperative hydronephrosis on postoperative OS in patients with different pathological stages of bladder cancer. According to our study, preoperative hydronephrosis could divide $pT_{3-4}N_0M_0$ bladder cancer patients into two risk groups, those with preoperative hydronephrosis being the high-risk group and those without preoperative hydronephrosis being the opposite, with patients in the high-risk group having significantly lower postoperative survival rates than those in the low-risk group. Therefore, preoperative hydronephrosis

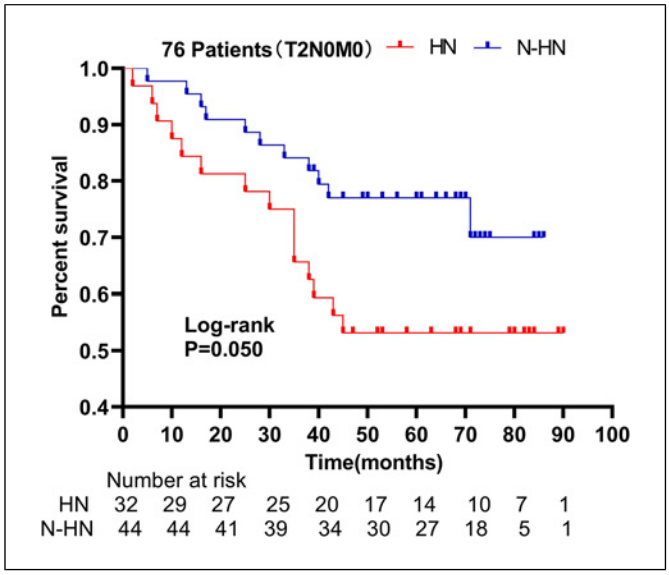

Fig. 4. Overall survival of T2N0M0 patients stratified by preoperative hydronephrosis.

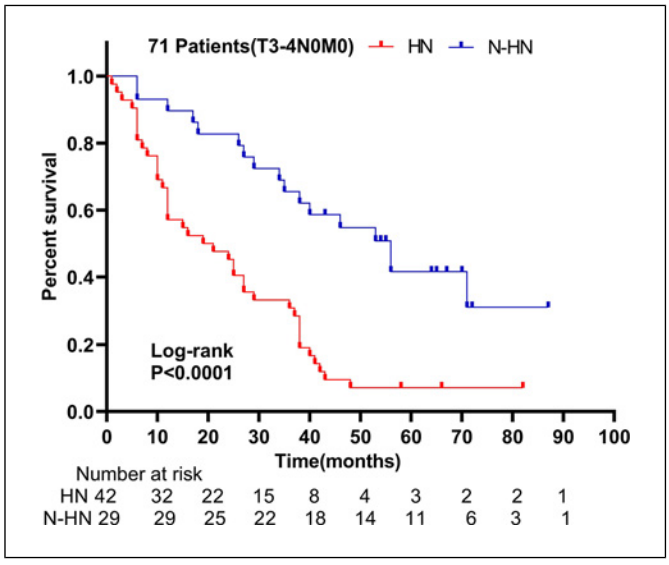

Fig. 5. Overall survival of $T_{3-4}N0M0$ patients stratified by preoperative hydronephrosis.

is an influencing factor for risk stratification of patients after radical surgery for $pT_{3-4}N_0M_0$ bladder cancer.

Studies have found that the causes of hydronephrosis due to bladder cancer include bladder tumors growing near the ureteral orifice, combined ureteral tumors, and advanced bladder tumors that compress or invade the ureter [18–23]. In patients with early pathological stages ($pT_1N_0M_0$ and

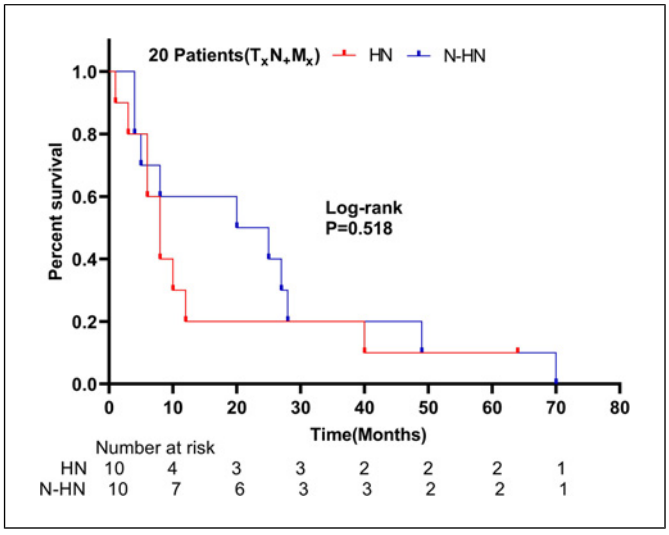

Fig. 6. Overall survival of TxN+Mx patients stratified by preoperative hydronephrosis.

$pT_2N_0M_0$) of bladder cancer, the presence of hydronephrosis is due to bladder tumor growth near the ureteral orifice rather than advanced tumor compression or invasion of the ureter, so preoperative hydronephrosis has no impact on patient survival postoperatively [6, 24, 25]. In patients with $pT_xN_+M_x$ bladder cancer, poor prognosis due to advanced tumor stage may override the impact of preoperative hydronephrosis on survival after radical surgery. Therefore, preoperative hydronephrosis has no significant impact on postoperative survival in patients with $pT_xN_+M_x$ bladder cancer.

Preoperative renal insufficiency is also an important factor influencing the long-term survival of patients after radical bladder cancer surgery. Itsuto Hamano et al. [26] reported that preoperative chronic kidney disease predicts poor oncological outcomes after RC in patients with muscle-invasive bladder cancer, and preoperative chronic kidney disease was significantly associated with poor PFS, CSS, and OS after RC. Dai Koguchi et al. [27] also found that severely reduced preoperative eGFR was an independent risk factor for worse PFS and worse CSS in patients after RC. Because hydronephrosis is one of the mechanisms for the development of renal insufficiency, we observed the preoperative eGFR of patients included in the study. It was found that the percentage of patients with preoperative hydronephrosis whose preoperative eGFR was no more than 60 mL/min/1.73 m^2 reached 11.8%, which was significantly higher than that of patients without preoperative hydronephrosis (Table 1); there was an obvious correlation between preoperative hydronephrosis and renal insufficiency. Therefore, we believe that renal insufficiency is a

mediator between preoperative hydronephrosis and the survival outcomes of patients after radical surgery. To avoid the occurrence of multicollinearity, we did not look at preoperative eGFR as an influencing factor in the present study. In addition, it has been found that renal insufficiency is also associated with various factors such as age, diabetes mellitus, and hypertension [28–30], so that preoperative renal insufficiency in patients undergoing RC may have complex mechanisms of occurrence. Further studies are necessary to investigate the relationship between preoperative hydronephrosis, renal insufficiency, and survival prognosis after radical surgery for bladder cancer.

Our study has several limitations: data in this study were collected retrospectively, patients were from a single institution, and the effects of grade of hydronephrosis, unilateral, and bilateral hydronephrosis were not included in the study. These shortcomings would have affected the statistical testing power of this study.

Conclusions

Preoperative hydronephrosis mainly affects postoperative OS in bladder cancer patients with a pathological stage of $pT_{3-4}N_0M_0$. Because patients with $pT_{3-4}N_0M_0$ bladder cancer complicated by preoperative hydronephrosis have a poorer prognosis, a more aggressive treatment strategy may be beneficial for them. However, further studies are needed to validate the results of this study.

Acknowledgments

We thank *Medjaden* Inc. for scientific editing of this manuscript.

Statement of Ethics

This study protocol was in accordance with the 1964 Helsinki Declaration and its later amendments and was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University, approval number SPJK-2022-18. Written informed consent was obtained from all of the participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The work was not supported by any funding.

Author Contributions

Conceptualization, study design, and project administration were provided by Hui Zhan and Jian Chen. Material and data collection was performed by Jingwei Du, Mingxia Ding, and Hairong Wei. Data analysis and interpretation were provided by Jiansong Wang, Chengcai Yang, and Ting Luan. The first draft of the manuscript was written by Jingwei Du, Hui Zhan, and Shi Fu. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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