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Research Article

Role Of Clinical and Demographic Factors in Urinary Bladder and Renal Cell Cancer Patients Treated with Immune-Oncological Drugs.

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Abstract:
Background: Urinary bladder (UB) and Renal Cell Carcinoma (RCC) are more common in men than women with poor outcomes. Novel immunotherapy (IT) drugs like Immune Check Point Inhibitors (ICIs) are effective but expensive. However, a cost-effective and reliable biomarker to predict response and clinical outcomes is lacking.
Objective: To study the association of histopathological type, grades, number of immunotherapy cycles, and demographic factors (age and gender) with Progression Free Survival (PFS) and Overall Survival (OS) in urinary bladder and renal cell carcinoma patients treated with immune checkpoint inhibitors.
Method: It is a retrospective analysis. We included 89 patients with Urinary bladder and Renal Cell Carcinoma treated with immune checkpoint inhibitors and those registered at Tata Memorial Cente from Jan 2008 to Dec 2019. Clinical evaluation and demographic data were performed as a part of the standard protocol.
Results: When demographic parameters like age and gender were analyzed, there was no significant association with progression-free survival and overall survival of the disease. Also, the progression-free survival and overall survival of the disease were not sustantial in histopathology type (Urinary bladder and Renal Cell Carcinoma) and tumour grade (low and high). Amongst 89 patients, the median immunotherapy cycles were 9 (IQR 5-14) with 61% cases receiving >6 cycles of immunotherapy and 39% cases of <= 6 cycles of immunotherapy. In the cohort, mPFS in<=6 number of immunotherapy cycles was 3.71 months (95% C.I. 2.10- 5.32), and in >6 number of immunotherapy cycles mPFS is 18.37months (95% C.I. 14.32- 22.42) showed significant difference with p value 0.001. Similarly, median OS was 5.62months (95% CI 3.47- 7.76) and 25.27 months (95% CI 21.15-29.38) respectively with p-value 0.001 at<=6 and >6 cycles, with Hazard ratio (HR) for >6 immunotherapy cycles was 0.39(95% CI 0.23 – 0.68) p-value 0.001 and for PFS 0.42 (95% CI 0.25-0.69) p-value of 0.001 which shows a significant decrease in hazards in >6 immunotherapy cycles group. Thus, thepatients who received >= 6 cycles of immunotherapy showed higher median PFS and OS than <6 cycles of immunotherapy.
Conclusion: Among the demographic and clinical factors studied, the number of immunotherapy cycles was significantly associated with progression-free survival and overall survival of the disease.

Keywords: Urinary bladder Cancer, Renal Cell Carcinoma, Immune Checkpoint Inhibitors.

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Introduction:

Genitourinary cancer deals with cancers of the urinary system of men and women and the reproductive organs in men. Urinary cancers result from abnormal neoplastic growth of cells in the prostate, bladder, kidney, adrenal gland, urethra, or other parts of the urinary tract system.

Urinary bladder cancer (BC) is one of the most prevalent urological cancers all around the world; with an increasing rate of morbidity and mortality (1). It is the 9th most commonly diagnosed cancer and the 13th cause of cancer-related mortality worldwide (2). BC cancer begins when healthy most commonly, urothelial cells in the bladder lining, change and grow out of control, forming a mass or tumour. Urothelial cells also line the renal pelvis and ureters. Malignant growth arising in the renal pelvis and ureters is also included in urothelial cancers which are frequently called upper tract urothelial cancer and treated similarly to bladder cancer.

Renal Cell Carcinoma (RCC), the most common and lethal malignant type of kidney tumour, accounts for about 2-3% of all malignant diseases in adults. Worldwide, there are over 400,000 new cases of RCC. Over 170,000 deaths occur annually due to kidney cancer (3). Clear cell RCC (ccRCC) is the most common subtype of RCC, accounting for approximately 70 - 80% of the cases (4).

Sex and gender disparities exist in all facets of healthcare and disease which can arise as a result of several factors, including social, behavioural, and biological determinants of health (5). Biological differences that drive health discrepancies can lead to altered clinical outcomes for male and female subjects. Therefore, it is pivotal to have a thorough understanding of the biological differences between men and women to develop more personalized preventative measures and treatment plans for different diseases.

BC is four times more common in men than women, with a respective occurrence of 9.6/100,000 among men and 2.4/100,000 among women worldwide (6). RCC is approximately two times more common in men than women (7). It can be aggressive and grow faster than other kidney cancers. Several studies have demonstrated sex-related differences in Bladder cancer oncologic outcomes. They are due to genetic, anatomic, hormonal, social, and environmental factor differences that may be operational between males and females (8–10). However, age is also an indicator used to assess prognosis in many solid cancers, especially in clear cell Renal Cell Carcinoma (ccRCC), and is an important risk factor (11, 12). However, we focused on age and gender disparities in bladder cancer and renal cell cancer patients treated with ICIs to identify any difference in survival outcomes.

Bladder cancer cells can also be described as either low-grade or high-grade. Low-grade BC cancer is less likely to grow, spread and come back after treatment. High-grade BC cancer is more likely to grow, spread, and come back after treatment (13-17).

Tumour stage is the key prognostic variable in renal cell carcinoma (RCC). The most accepted and widely used system for grading renal cell carcinoma (RCC) is a nuclear grading system described in 1982 by Fuhrman et al, which synchronously evaluates nuclear size and shape, and nucleolar prominence. However, disagreement and grading imprecision may occur among these three parameters, making the Fuhrman grading irrelevant. In 2012, the International Society of Urologic Pathologists (ISUP) proposed a novel, validated grading system for clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC) which has been implemented by the World Health Organization (WHO) (18-21).

Thus, in this study, we aimed to investigate the clinical utility of histopathological grades, number of immunotherapy cycles, and demographic factors like age and gender with progression-free survival (PFS) and overall survival (OS) in UB and RCC patients treated with ICIs.

Material and Methods:

This is a retrospective study. The patients of urinary bladder and RCC, who were enrolled at TMC from Jan 2008 to Dec 2019 were included. Amongst these 89 patients of the urinary bladder and RCC, the first treatment with ICIs started in November 2016 even though the first patient was registered at TMC in Jan 2008.

The patient's demographic data (age, gender) and treatment history (immunotherapy cycles) were obtained from the Electronic Medical Record (EMR) of Tata Memorial Centre (TMC). The histopathology report (HPR) was obtained from surgical pathology. Low-grade was considered grade 1 and 2**,** whereas high-grade was considered grade 3 and grade 4 for urinary bladder cancer as well as for RCC grade based on Fuhrman grading and ISUP grading.

The combination of two immune checkpoint inhibitors - ipilimumab (Yervoy) and nivolumab (Opdivo) has been approved for the treatment of advanced kidney cancer in first-line therapy. Two combinations of targeted therapy plus an ICI have also been approved for people with advanced kidney cancer in first-line therapy.

- Pembrolizumab (Keytruda), plus the targeted drug axitinib (Inlyta)
- Pembrolizumab plus lenvatinib
- Nivolumab plus cabozantinib

In second-line therapy single agent immunotherapy (Nivolumab) has been used.

For the patients with urinary bladder cancer, Pembrolizumab, Nivolumab or Atezolizumab were used either in first-line or second-line therapy.

Inclusion Criteria:

- Patients diagnosed with urinary bladder and kidney cancer in TMC from Jan 2008 to Dec 2019 and treated in adult medical oncology.
- Patients treated with ICIs in TMC between 2008 to Dec 2019.

Exclusion criteria:

- Patients with inadequate clinical/demographical data available in TMC EMR.

Statistical analysis:

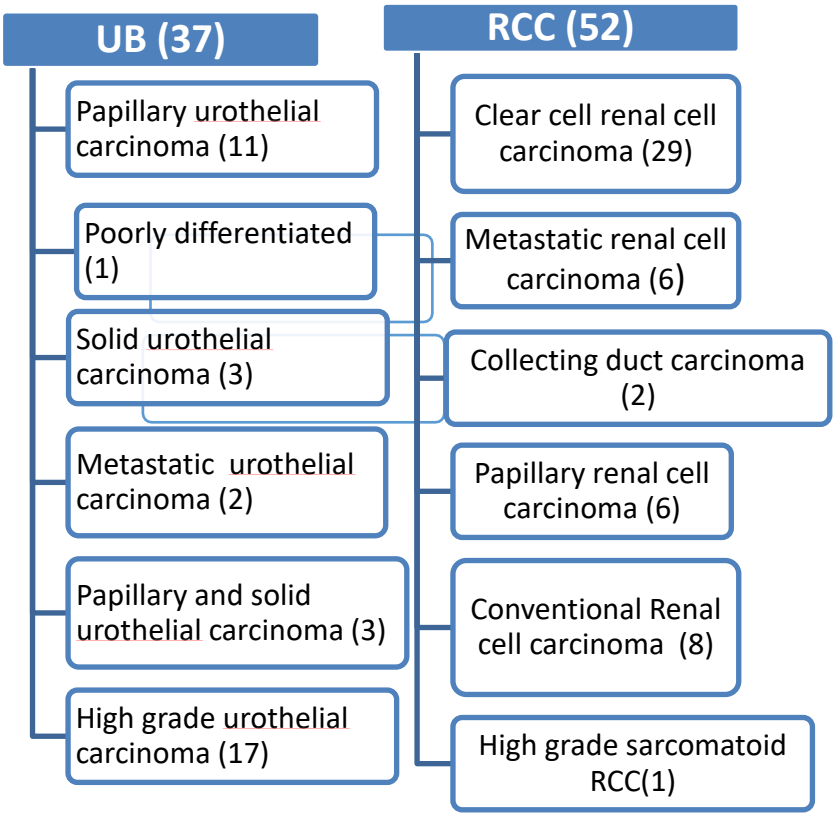
Descriptive statistics were used to summarize the data. Categorical data was summarized using counts and percentages. Continuous data is summarized using Median (IQR). The association between the HPR and grades with progression status was assessed using a chi-square test.

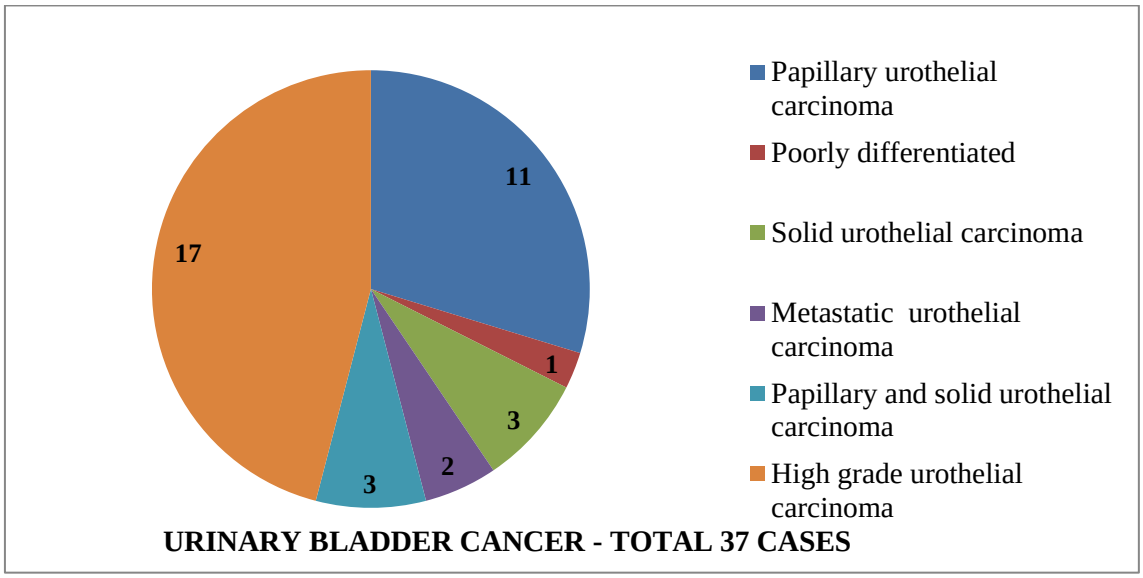
The PFS and OS were estimated between the HPR groups, grades groups, age, gender and number of immunotherapy cycles (<6 and >6 cycles) using the Kaplan- Meier method and the Log-rank test. The Cox Proportional hazards model was used to estimate the Hazard Ratio with 95% CI. A p-value less than 0.05 were considered statistically significant. All statistical analysis was performed in IBM SPSS version 29.

Results:

Within the cohort, tumour histology includes 37 (42%) urinary bladder cancers and 52 (58%) renal cell carcinoma cases treated with immune-oncological drugs. The classification of both cancer cases is shown in Table (1) according to histopathology reports (HPR). Amongst urinary bladder cancer patients, papillary urothelial carcinoma (30%) and high grade urothelial carcinoma (46%) cases were highest. Clear cell renal cell carcinoma patients were around 56% among renal cell cancer patients. (TABLE1) (FIGURE1)

TABLE (1): Classification of Urinary bladder cancer (UB) and Renal cell cancer(RCC) patients.





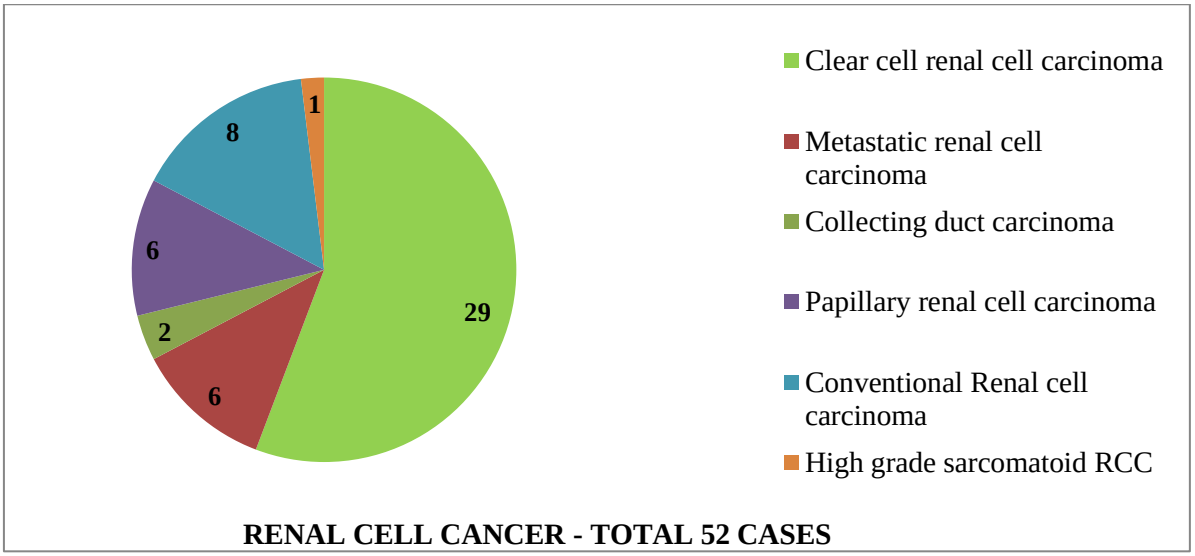


FIGURE (1): Classification of Urinary bladder cancer (UB) and Renal cell cancer (RCC) patients.

In the population of 89 Patients studied, 74(83%) were men and 15(17%) were women.The median age was 64 (IQR 57-71) years with almost equal numbers of <64 (48%) and >= 64(52%) years age patients. Amongst 89 patients, the median immunotherapy cycles were 9 (IQR 5-14) with 61% cases receiving >6 cycles of immunotherapy and 39% cases of <= 6 cycles of immunotherapy. The disease progression in urinary bladder and RCC patients was based on radiology reports. Response was evaluated for 89 patients with computed tomography, positron emission tomography, or magnetic resonance imaging, 58(65%) patients were found to be with disease progression, and 31(35%) patients had no disease progression. The high-grade tumour stage was found in 66(74%) patients and 23(26%) patients had low- grade tumour stage. (TABLE 2)

TABLE (2): Evaluation of demographic and clinical factors in Urinary bladder cancer(UB) and Renal cell cancer (RCC) patients.

GENDER	
Male	74 (83%)
Female	15(17%)
GRADE	
Low grade	23 (26%)
High grade	66 (74 %)
RESPONSE	
Progression	58 (65%)
No progression	31 (35%)
HPR Type	

UB	37 (42%)
RCC	52 (58%)
AGE	Median - 64 (IQR 57-71) Years
	< 64 - 43(48%)
	>= 64 - 46(52%)
IMMUNOTHERAPY CYCLES	Median - 9 (IQR 5 -14) Cycles
	≤ 6 cycles - 35(39%)
	> 6 cycles - 54(61%)

Within the peer of 89 cases, 58 cases had progression of diseases with a medianprogression free survival of 13.6 months (95% CI 6.7 -20.5).

In males out of 74 cases, 46 progressed with median progression-free survival (mPFS) of 15.5 months (95% C.I. 7.73 – 23.36) whereas in females out of 15 cases12 progressed with mPFS of 13.6 months (95% C.I. 0.8 – 26.4) indicating no significant difference in PFS between males and females with p-value 0.586.

Amongst the age group, the mPFS in <64 years was 15.90 months (95% C.I. 5.87- 25.94) and in >=64 years was 13.27 months (95% C.I. 3.99- 22.55) show no significant difference with p-value 0.553.

However in 66 cases with high-grade tumour stage, 43 progressed with mPFS of 15.54 months (95% C.I. 9.24 – 21.84) as compared to 23 low-grade tumour stage,15 cases progressed with mPFS of 9.56 months (95% C.I. 0.0 – 23.11) indicating no significant difference in PFS between the grades with p-value 0.785. In histopathologicaldiagnosed 37 cases of urinary bladder cancer, 29 progressed cases showed mPFS of 7.62 months (95% C.I. 0 - 17.42) whereas 29 progressed out of 52 RCC cases showed mPFS of 18.76 months (95% C.I. 11.58 – 25.94) indicating no significant difference in histopathology category with p-value 0.073.

In the cohort, mPFS in<=6 number of immunotherapy cycles was 3.71 months (95% C.I. 2.10- 5.32) and in >6 number of immunotherapy cycles mPFS is 18.37 months (95% C.I. 14.32- 22.42) showed significant difference with p value 0.001. (TABLE 3), (FIGURE 2)

TABLE (3): Progression-free survival estimates such as Median PFS, 95% CI and p- value, compared with the demographic and clinical factors in Urinary bladder cancer (UB) and Renal cell cancer (RCC) patients using Log-rank test.

Progression Free Survival						
Category	**Total No.**	**No. of Events**	**Median PFS in months**	**95% Confidence Interval**		**P- value**
				Lower Bound	**Upper Bound**	
Overall	89	58	13.6	6.7	20.5	
Gender						
Male	74	46	15.54	7.73	23.36	
Female	15	12	13.60	0.77	26.44	0.586
Grade						
Low grade	23	15	9.56	0	23.11	
High grade	66	43	15.54	9.24	21.84	0.785
HPR						
UB	**37**	**29**	**7.622**	**0**	**17.42**	
RCC	**52**	**29**	**18.76**	**11.58**	**25.94**	**0.073**
No. of immunotherapy cycles						
<=6	35	29	3.71	2.10	5.32	
>6	54	29	18.37	14.32	22.42	**0.001**
Age						
<64	43	28	15.90	5.87	25.94	
>=64	46	30	13.27	3.99	22.55	0.553

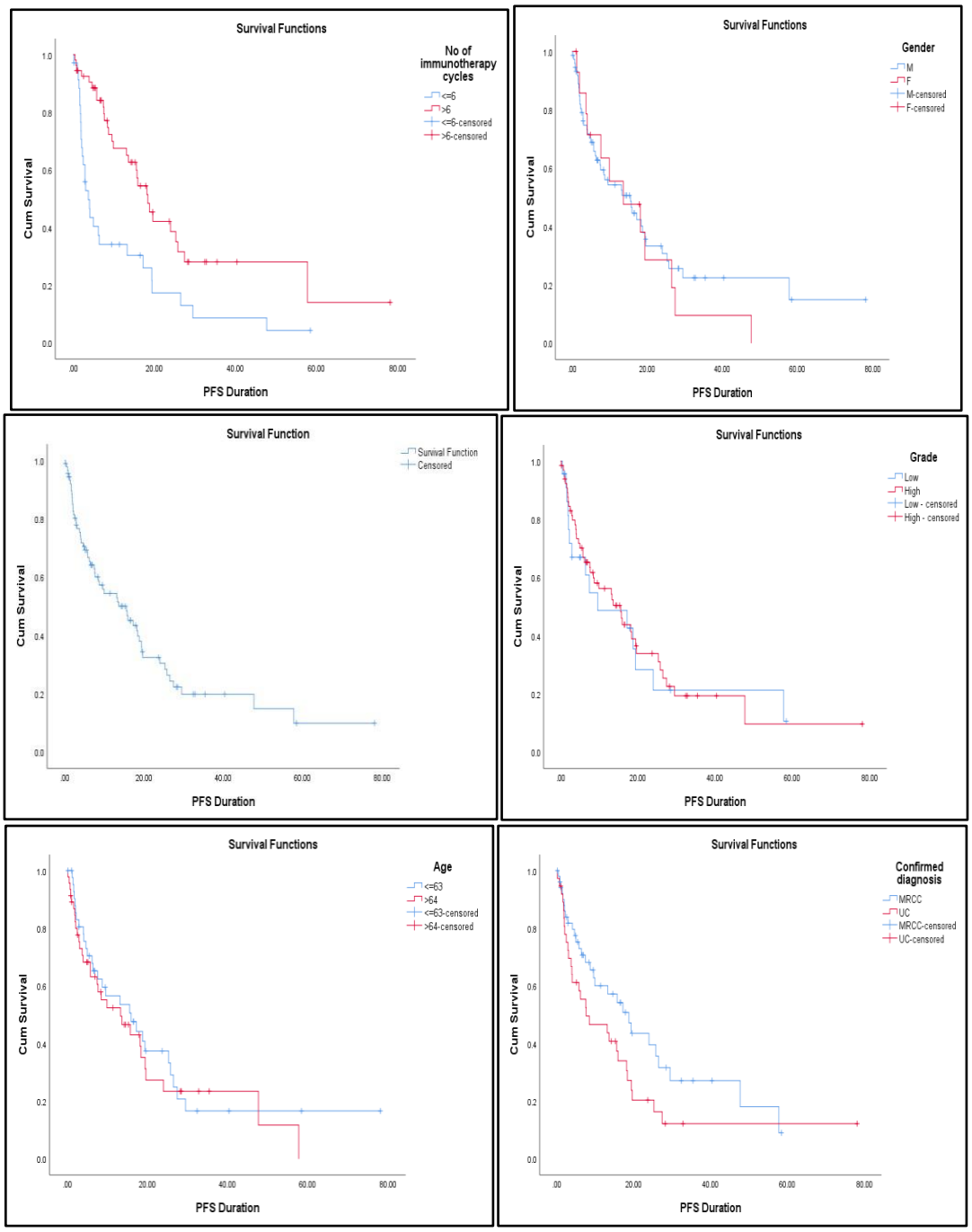


FIGURE 2: Enlisted are the graphs with Kaplan Meier Curves for Progression free survival, the Y-axis indicates the Cumulative survival proportions and the X- axis indicate the PFS duration in Months.

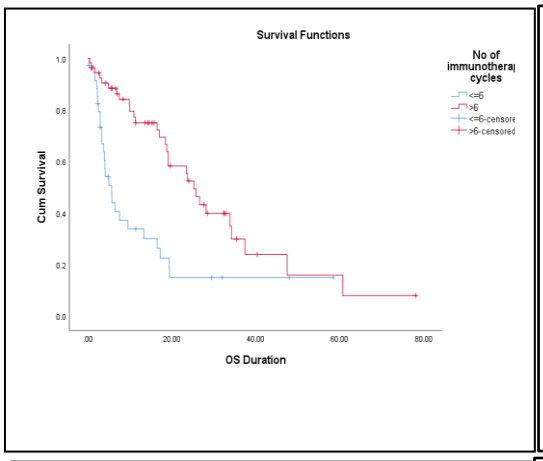
In 74 male patients, 44 patients deceased with median OS of 18.46 months (95% CI15.44- 21.49) whereas in 15 female cases, 11 patients deceased with median OS of 16.46 months (with 95% CI 1.47- 31.45) indicating no significant difference in survival between males and females with p-value 0.668. When age groups categorized at <64 and >=64 years showed no significant difference in median OS 18.46months (95% CI 9.71- 27.22) and 19.06months (95% CI 12.35- 25.76) respectively with P-value 0.848.

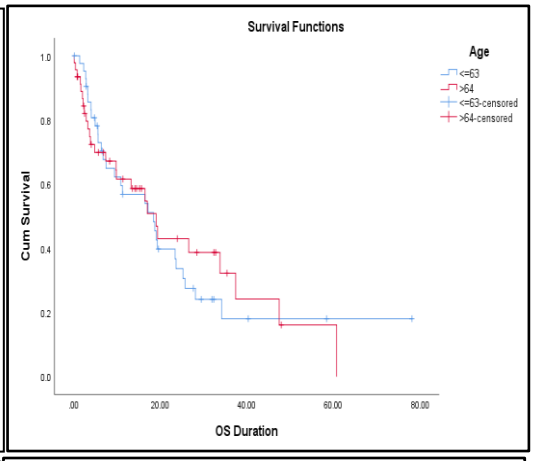
The tumour grade categorized at low and high grade showed no significant difference in median OS 11.27 months (95% CI 0.00- 26.5) and 19.06 months (95% CI 15.63- 22.48) respectively with P-value 0.356.Similarly, the urinary bladder cancer and RCC histological type showed no significant difference in median OS 18.46 months (95% CI 14.84 - 22.09) and 17.22 months (95% CI 9.92 - 24.51) respectively with p –value 0.406.

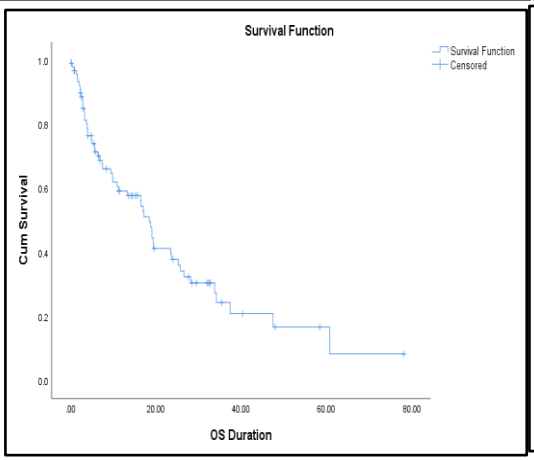
However, the number of immunotherapy cycles categorized at<=6 and >6 cycles showed significant differences in median OS 5.62months (95% CI 3.47- 7.76) and 25.27 months (95% CI 21.15-29.38) respectively with p-value 0.001. (TABLE 4) (FIGURE 3)

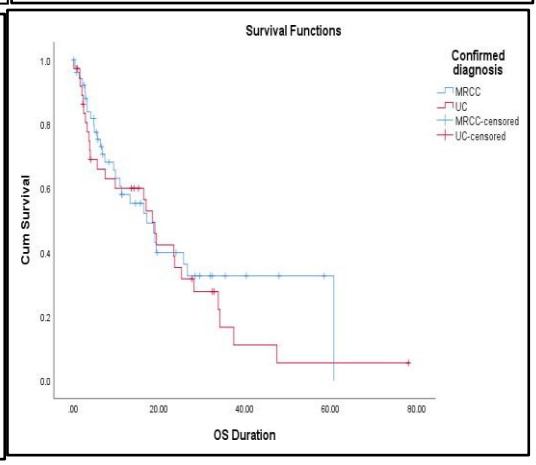
TABLE 4: Overall survival estimates such as Median OS, 95% CI, p-value compared with the demographic and clinical factors in Urinary bladder cancer (UB) and Renal cell cancer (RCC) patients using Log-rank test.

Overall Survival						
				95% Confidence Interval		
Category	Total No.	No. of Events	Median OS in Months	Lower Bound	Upper Bound	P- value
Overall	89	55	18.46	15.87	21.06	
Gender						
Male	74	44	18.46	15.44	21.49	
Female	15	11	16.46	1.47	31.45	0.668
Grade						
Low grade	23	17	11.27	0.00	26.50	
High grade	66	38	19.06	15.63	22.48	0.356
HPR						
UB	37	27	18.46	14.84	22.09	
RCC	52	28	17.22	9.92	24.51	0.406
No. of immunotherapy cycles						
<=6	35	26	5.62	3.47	7.76	
>6	54	29	25.27	21.15	29.38	**0.001**
Age						
<64	43	29	18.46	9.71	27.22	
>=64	46	26	19.06	12.35	25.76	0.848









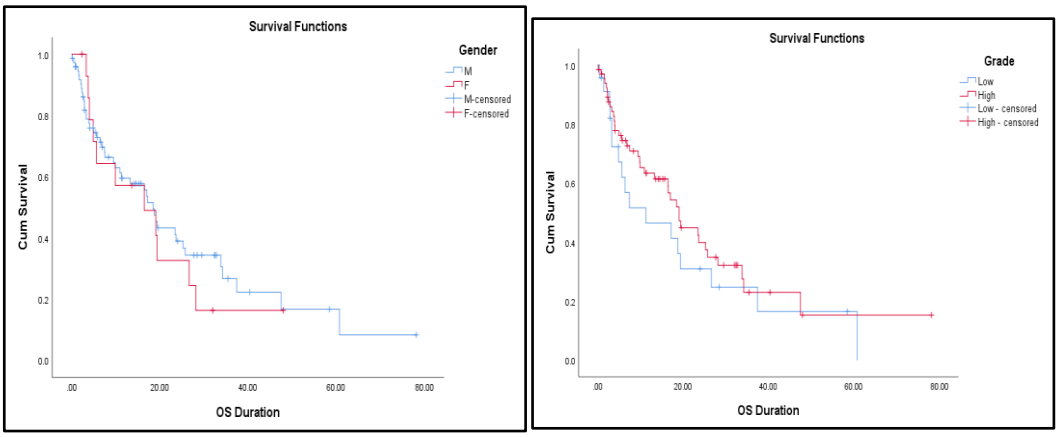


FIGURE (3): Enlisted are the graphs with Kaplan Meier Curves for overall survival, the Y axis indicates the Cumulative survival proportions and the X axis indicates the OS duration in Months.

For overall survival, the Hazard ratio (HR) for >6 immunotherapy cycles was 0.39(95% CI 0.23 – 0.68) with p-value 0.001 and for PFS it was 0.42 (95% CI 0.25-0.69) with p-value of 0.001 which shows significant decrease in hazards in >6 immunotherapy cycles group. However other demographic and clinical factors like age, gender, tumour grade and histopathology type showed no significant association in the hazard ratios.

For OS, the hazard ratio for gender was 1.16 (95% CI 0.59 – 2.24) with p-value 0.669 and for PFS it was 1.19 (95% CI 0.63 – 2.26) with p-value 0.586 showed no significant decrease in hazards in male and female group. Amongst the tumour grades categorized at low and high grade, the hazard ratio for OS was 0.76(95% CI 0.43- 1.36) with p-value 0.358 and for PFS was 0.92 (95% CI 0.51-1.67) and p-value 0.785 had no significant difference. Similarly, there was no significant decrease in hazards of urinary bladder cancer and RCC patients with OS 1.25 (95% CI 0.74-2.13) p-value 0.408 and PFS 1.59 (95% CI 0.95-2.68) with p-value 0.076. The hazard ratio for age groups categorized at <64 and >=64 showed no significant difference with OS 0.95(95% CI 0.56-1.62) with p-value 0.848 and with PFS 1.17 (95% CI 0.69-1.96) P-value of 0.554. (TABLE 5)

TABLE 5: Hazard ratio(HR) for OS and PFS with 95% CI and associated p-value compared with the demographic and clinical factors in Urinary bladder cancer (UB) and Renal cell cancer (RCC) patients. The hazards with >1 are considered increased risk of developing the event of interest.

Hazard Ratios								
Category	**OS**				**PFS**			
	HR	**95.0% CI for HR**		**P-value**	**HR**	**95.0% CI for HR**		**P-value**
		Lower Bound	**Upper Bound**			**Lower Bound**	**Upper Bound**	
Gender								
Male	1	0.59	2.24	0.669	1	0.63	2.26	0.586
Female	1.16				1.19			
Grade								
Low grade	1	0.43	1.36	0.358	1	0.51	1.67	0.785
High grade	0.76				0.92			
HPR								
UB	1	0.74	2.13	0.408	1	0.95	2.68	0.076
RCC	1.25				1.59			
No. of immunotherapy cycles								
<=6	1	0.23	0.68	**0.001**	1	0.25	0.69	**0.001**
>6	0.39				0.42			
Age								
<64	1	0.56	1.62	0.848	1	0.69	1.96	0.554
>=64	0.95				1.17			

Discussion:

In this study, there were more RCC patients (58%) than UB cases (42%). According to a similar study by Bray F. *et al*. (2018) (6), there are over 400,000 new instances of RCC. Approximately 2.1% of all carcinoma deaths are due to urinary bladder cancer and Kidney carcinoma causes more than 170,000 fatalities per year (3). Both ccRCC and urothelial carcinoma were common in this study. An analogous research by Thuy Koll *et al*.(2012) (22), showed that transitional cell carcinoma (TCC) has been the most common cause of metastatic bladder cancer (MBC) upon diagnosis for the past 20 years, the most prevalent kind. Urothelial carcinoma was another name for transitional cell cancer (TCC). Likewise, G. Kristiansen *et al*. (2015) (23) noted that the predominant histological subtype, which makes up over 75% of RCC, is clear cell RCC (ccRCC).

In our analysis, we found that the incidence rates for men in the cohort were about five times greater than those for women. Compared to males, women had a higher rate of illness progression. In a similar vein, Schafer El *et al*. (2023) (24) found that men had two to four times higher incidence and mortality rates of bladder and kidney cancers compared to women. In addition to reflecting genetic, anatomical, hormonal, social, and environmental factors, the gender gap resulted from varied exposure to carcinogens (such as chemicals and smoke). (25)

According to this study, the average age was sixty-four years, indicating a substantial risk factor for old age. Tang F *et al*.(2021) (26) also noted this and demonstrated that age was a significant risk factor for determining prognosis in several neoplasms, including clear cell kidney cancer. Older adults were more likely to deteriorate, had lower survival rates and had worse treatment outcomes than younger adults. This was most likely caused by older people with low levels of physical exerciseor underlying illnesses.

We looked at the possibility that there was no correlation between ages <64 and >= 64 years. Numerous studies have discovered differences between the young and the elderly, but none have documented age group differences and their effect on the prognosis of ccRCC patients (27-29).

Although the tumor stage was not proven to be a predictive factor, this study did demonstrate a notably high number of high-grade illnesses in UB and RCC. Mori K *et al*. (2020) (30) also proposed that tumor stage, grade, and lymph node status are frequent predictive indicators for UB, but that it was difficult to forecast patients' prognoses before treatment alone. On the other hand, Chen *et al*. (2017) (31) built a model and assessed the survival result in individuals with clear cell kidney cancer from T stage, AGR, NLR, and MLR.

In the present study, amongst the demographic and clinical factors, the number of immunotherapy cycles was found to be one of the good prognostic markers. The >= 6 cycles of immunotherapy showed an association with median PFS, OS, and hazard ratio than <6 cycles of immunotherapy.

However, these novel immunotherapy drugs are very costly and less affordable in low and middle-income countries like India. Moreover, data shows that these novel immunotherapy drugs are not effective in a subset of patients. However, it is more relevant to use these expensive therapies in selective patients who will be benefited. Furthermore, a universal prognostic factor that can predict survival regardless of the type of cancer will help to simplify the management of cancer patients.

The current study contains several shortcomings. A bigger cohort size should be used to confirm the findings of our study, because this may be the first report on the clinical utility of parameters like the number of immunotherapy cycles.

Conclusion: Among the demographic and clinical factors studied, the number of immunotherapy cycles was significantly associated with progression-free survival and overall survival of the disease.

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Competing interests statement:

The authors declare no competing interests.

Author contributions:

Mrs. Shilpa Kushte collected, analysed the data, and wrote the paper. Dr. Prashant Tembhare participated in the writing. Dr. Rachna Khatri, Dr. Amit Joshi, Dr. P. G. Subramanian , Dr. Santosh Menon, Dr. Prashant Tembhare assisted in the design of this study. Mr. Akash Pawar ensured the integrity of the data and the accuracy of the data analysis. All authors critically revised the manuscript.

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