ORIGINAL ARTICLE

SURVIVAL AND PROGRESSION AFTER RADICAL NEPHRECTOMY IN A COHORT OF NON-METASTATIC RENAL CELL CARCINOMA TREATED WITH CURATIVE INTENT

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Background: Radical nephrectomy (RN) is a standard treatment of cure for non-metastatic renal cell carcinoma (NMRCC). Long-term outcome data are limited for Pakistani population. Our aim was to assess the long-term outcomes of RCC treated with curative intent with radical nephrectomy (RN) and to study the 5 & 10years survival outcomes in patients with NMRCC who underwent radical nephrectomy. **Methods**: This is a retrospective review and analysis of the data between December 2006 and February 2017. We included all the adult patients (age ≥18 years) with NMRCC from both genders irrespective of their histologic subtypes who underwent radical nephrectomy (RN) with a curative intent. The data was analysed for overall survival and recurrence rates at 5- and 10-years using Kaplan-Meier survival analysis. Multivariate analysis was performed using Cox-regression to identify risk factors associated with poor overall outcome in terms of recurrence and mortality. **Results**: Three hundred and forty-four patients with 195 (55.5%) males and 149 (44.2%) females with a mean age of 53.5±14.1 years were monitored for a mean follow-up of 31.1±26.77 months (range: 3–132 months). Overall there were 46 (13.4%) deaths. Forty-nine 14.2%) cases had disease recurrence with 33 (9.5%) deaths from disease progression. The 5-year progression-free survival was 37% (95% CI: 49.04–72.76) with the median time to recurrence of 33 months (95% CI: 27.6–38.4) and the median overall survival was 103.7 months (95% CI: 95.7–111.7). The 5-year overall survival was 76.1% (95% CI: 75.2–77) while 10-year survival was 70.8%. There was a significant median survival difference for cases with and without recurrence (log-rank χ^2: 117.5, p<0.001), T stage, Fuhrman's grade, and early postoperative recurrence. **Conclusion**: Radical nephrectomy offers the best survival for non-metastatic renal cell carcinoma patients with excellent postoperative survival and progression-free profile. Although renal cell cancer presents in younger age group but the long-term survival after radical nephrectomy in Pakistani population is similar to the rest of the world.

Keywords: Renal cell carcinoma; Radical nephrectomy; Recurrence; Survival

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INTRODUCTION

The incidence of renal cancer is on the rise; globally more than 338,000 new cases of renal cancer are diagnosed each year with an estimated increase of 22% by 2020.[1] The gap in mortality rate between developed and developing countries appears to be widening.[2] Renal cell carcinoma (RCC) is one of the most lethal cancers of the genitourinary tract and one-third of the diagnosed with RCC die of progression of the disease.[3] RCC most commonly presents in sporadic form, 3–25% present as multifocal in the sporadic forms and 1–2% as known familial syndromes, such as von Hipple-Lindau disease.[4–6]

Radical nephrectomy has remained the best treatment for large renal tumours for >50 years and is the standard against which all other treatments for renal cell carcinoma are compared. Greater than 60% of renal tumours are now detected incidentally.[7] As a result, there is a decrease in stage and tumour size at presentation.[8] This has shifted the management of small renal tumours from radical nephrectomy to nephron sparing surgery (NSS).

About 20% of solid enhancing T1 tumours of the kidneys are benign and as a result their management varies from active surveillance to radical nephrectomy depending on the circumstances. Radical nephrectomy (RN) remains gold standard treatment for localized T2 tumours or larger and in selected T1 tumours which are not amenable to nephron sparing surgery (NSS).[9–11]

Several studies have been conducted on radical nephrectomy role in the management of RCC in Pakistan but the studies regarding the long-term outcomes of RN in Renal Cell carcinoma in Pakistani population is scanty. The main aim of this study is to assess the long-term outcomes of RN in localized RCC in Pakistani population.

MATERIAL AND METHODS

The data, from December 2006 till February 2017, was collected after hospital IRB approval. We included all the adult patients (age ≥18 years) with non-metastatic renal cell carcinoma (NMRCC) from both genders irrespective of their histologic subtypes who underwent radical nephrectomy (RN) with a curative intent. All the procedures were performed in a single institute by different surgeons. The tumours were staged with CT scans and type assessed with histopathology reports however the final T stage and N stage were recorded from histopathology reports. American Joint Committee on Cancer (AJCC) TNM Staging System for Kidney Cancer (2010) was used for TNM staging. Age, gender, kidney involved, presenting complaints were recorded preoperatively. Histological variant, Fuhrman's grade, surgical margins, neurovascular invasion were recorded post operatively. Haemoglobin (Hb) was recorded before and after operation while creatinine (Cr) was recorded before and after surgery. All the patients were followed post operatively at 1 month then at 3 and 6 months with ultrasound abdomen, creatinine and X-ray chest. Followed by alternation of ultrasound and CT scan at 6 months' intervals for 5 years. Those cases with metastatic disease M1 stage on presentation, age less than 18 years, patients with incomplete data, histopathology other than RCC, perioperative mortality (within 3 months of surgery) and those who lost to follow before 3 months were excluded from the study. The data was analysed for overall survival and recurrence rates at 5- and 10-years using Life table and Kaplan-Meier survival analysis. Multivariate analysis was performed using Cox-regression to identify risk factors associated with poor overall outcome in terms of recurrence and mortality.

RESULTS

The general characteristics of patients are shown in table 1. 344 patients with 195 (56.7%) males and 149 (43.3%) females with an overall mean age of 53.5±14.1 years (range: 18–89 years) underwent radical nephrectomy (RN) between December 2006 and February 2017 diagnosed as cases of non-metastatic RCC (NMRCC).

There were 58 (16.9%) diabetics and 18 (5.2%) hypertensive patients. A large proportion of patients (n=186, 54.1%) were diagnosed incidentally, 131 (32.8%) patients had flank pain, 89 (25.90%) had haematuria, 15 (4.4%) had lower urinary symptoms, 11 (3.2%) fever and 22 (6.4%) had weight loss on presentation as shown in figure-1. One hundred and ninty-one (55.5%) patients had tumours on the right and 153 (44.5%) had on their left side. Twenty-seven (7.8%) of patients had renal vein thrombosis on initial workup. The mean length of stay (LOS) was 4.8±1.9 days (range: 3–30 days). The mean length of follow-up was 31±26.7 months (range: 3–131 months).

The characteristics are summarised in table 2 and 3. Clear cell variant of RCC was the most common histopathological entity encountered in our surgical specimens which was followed by papillary RCC, chromophobe RCC, sarcomatoid RCC and other rare forms such as multiloculated RCC, eosinophilic variant and small cell carcinoma. One hundred and sixty-six (48.3%) patients had T stage 1 disease, 82 (23.8%) had T2, 83 (24.1%) had T3 and 9 (2.6%) had T4 disease with 328 (95.3%) patients in N0 and 15 (4.4%) in N1 stage. The most common Fuhrman's grade was grade 2 (n=186, 54.1%), followed by grade 3 (n=65, 18.9%), grade 4 (n=55, 16%), and grade 1 (n=37, 10.8%). Fifty (14.5%) patient had tumour with renal sinus extension, 27 (7.9%) had vascular invasion and 23 (6.7%) had capsular invasion. We observed involvement of the ipsilateral adrenal gland in 5 (1.5%) patients.

Post RN the important clinical findings are summarised in table-4. The most common complication after surgery at follow-up was an incision hernia in 7 (2.0%), chronic incision site pain in 2.7%, weight loss, ascites and hydrocele in one patient each. Wound infection was observed in 6 (1.7%) patients which responded to antibiotic treatment. Mean rise in creatinine was 0.36±0.68. Mean drop in Hb was 1.6 1.03 g/dl. The mean length of stay (LOS) was 4.8±1.9 days (range: 3–30 days). 43 patients needed additional organ removal during RN, they are shown in figure 3.

Forty-six (13.4%) patients died during the study period with 33 (9.5%) disease-related deaths. Forty-nine (14.2%) patients had disease recurrence with 6 local and 43 distant metastases. The distribution of the metastasis is shown in figure-2. Minimum time to recurrence was 1 month and maximum time of recurrence was 108 months while the median time to recurrence was 33 months. The 5-year progression-free survival was 37% (95% CI: 27.6–38.4) and the median overall survival was 103.7 months (95% CI: 95.7–111.7).

Life-tables and Kaplan-Meier survival analysis were conducted to estimate 5 and 10-year survival as well as to compare groups of patients with respect to stage and grade of the disease, presence or absence of disease recurrence.

The mean overall survival was 103.7 months (95% CI: 95.7–111.7), the 5-year overall survival was 76.1% (95% CI: 75.2–77), the 5-year progression-free survival was 61% (95% CI: 49.04–72.76) and

10-year survival was 70.8%. The overall survival curve is shown in figure-4.

On Life table test the overall five-year survival for T1 stage patients was 87%, for T2 it was 67%, for T3 it was 65% and T4 it was 50% as shown in the figure-5. Similarly, on Kaplan Meier analysis the mean survival for T1 stage disease was 118.2 months (95% CI: 110.7–127.2), for stage 2 disease it was 65.7 months (95% CI: 67–74), for T3 it was 79 months (95% CI: 66.7–91.1) and for T4 it was 21 months (95% CI: 17.7–24.3), as shown in the table:5. The log-rank test revealed significant differences for survival distribution ($\chi 2$ =13.3, p<0.01).

For Fuhrman's grade 1 the 5-year survival was 100%, 86% for grade 2, 61% for grade 3 and 26% for grade 4 (Figure-6). The log-rank test for difference of the median survival showed a significant difference ($\chi 2$: 19.73, p<0.0001). The mean survival for Fuhrman grades are shown in the table-6.

For recurrent disease, the 5-year survival rate was only 14% while it was 89% for patients without recurrent disease. Patients who had a recurrence during the study period had a median survival of 33.0 (95% CI, 27.6–38.4) months. This was shorter than the median survival for patients with no recurrent disease who had a median survival of 87.0 (95% CI, 83.9–91.8) months. Log-rank test showed significant differences in survival in patients with or without recurrence ($\chi 2$ = 117.5, p<0.0001) as shown in figure-7. Factors associated with disease recurrence are listed in table-7.

In survival analysis for histopathological tumour types, it was observed that 5-year survival for the multiloculated and unclassified variant of RCC was 100%, 79% for clear cell variant of RCC (Figure-8), 71% for the papillary variant, 92% for the chromophobe variant and 24% for the sarcomatoid variant. The mean survival for each histological variant is shown in table-8. Log-rank test showed significant differences for survival in patients with different histopathological variants ($\chi 2$ =5.01, p<0.025).

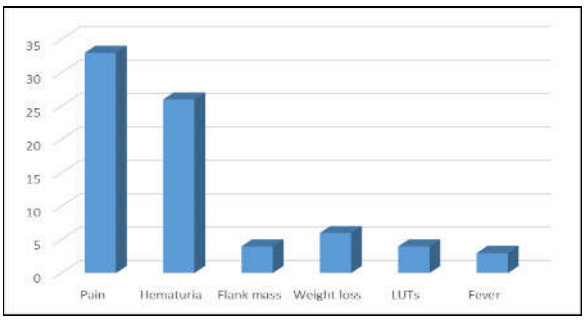

Figure-1: Patron of Symptoms at presentation in percentage.

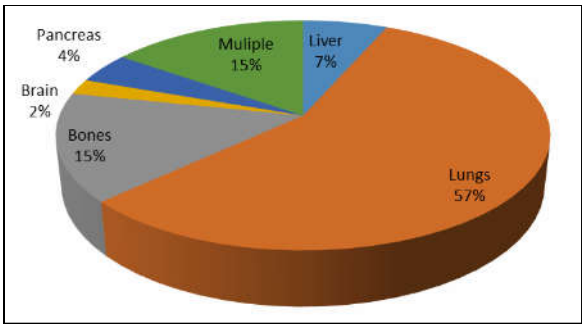

Figure-2: Distribution of Mets

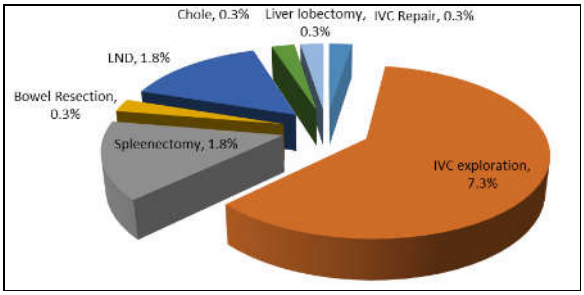

Figure-3: Additional surgery during RN

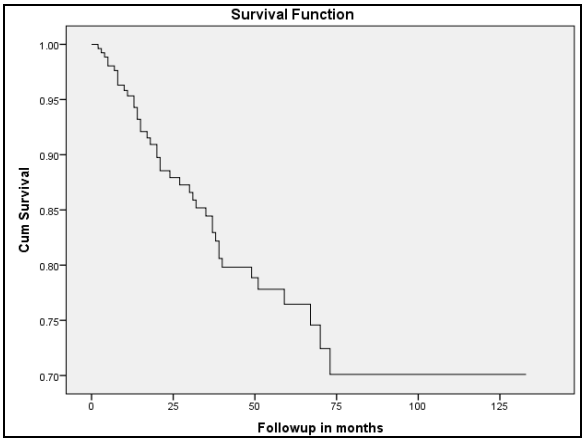

Figure 4: Overall survival curve

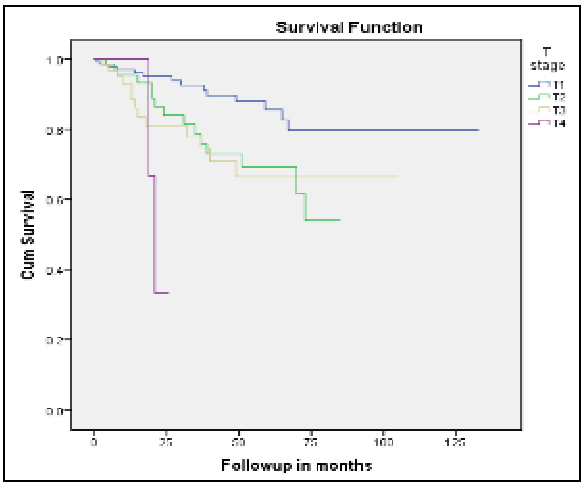

Figure-5: Survival analysis for T-stage

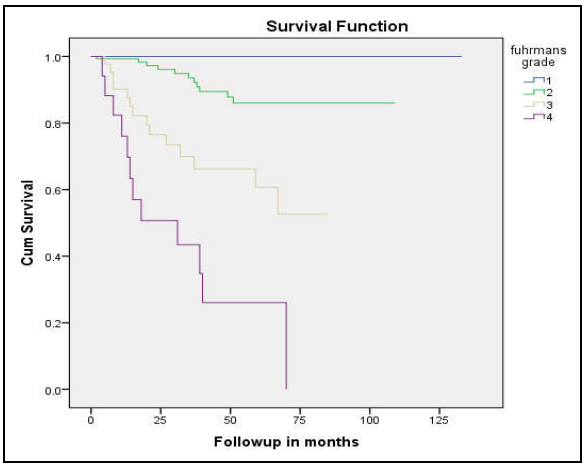

Figure-6: Survival analysis for Fuhrman's grade

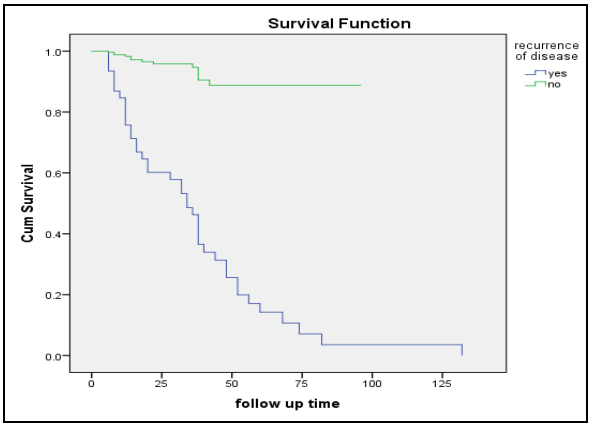

Figure-7: Survival analysis for patients with or without recurrence

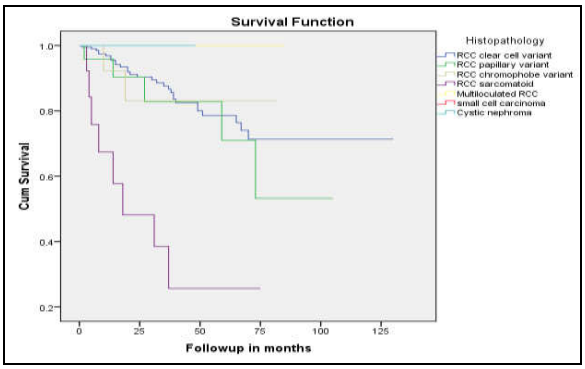

Figure-8: Survival analysis for Histopathological types

Table-1: General characters

General Characteristics	Numbers	Percentage
Males	195	56.7
Females	149	43.3
DM	58	16.9
HN	18	5.2
Right Kidney	191	55.5
Left kidney	149	44.5

Table-2: Stage at presentation

T&N Stage	Numbers	Percentage
T1	166	48.3
T2	82	23.8
T3	83	24.1
T4	9	2.6
N0	328	95.3
N1	15	4.4

Table-3: Histological Characteristics

Histological characteristics		
Furhman grade	**Numbers**	**Percent**
G1	37	10.8
G2	186	54.1
G3	65	18.9
G4	55	16
Variants of RCC	**Numbers**	**Percent**
Clear cell	254	73.8
Papillar	29	8.4
Chromophobe 27		7.8
Sarcomaoid	17	4.9
Mulilocular 6		1.7
Eosinophilic 3		0.9
Unclassified 3		0.9
Others	5	1.45

Table-4: Post RN surgery related complications.

Post op complication	Numbers	Percent
Mortality	2	0.6
Incisional hernia	7	2.0
Wound infection	6	1.7
Chronic incision site pain	9	2.7
Reteroperitoneal hematoma	1	0.3
Hydrocele	1	0.3
Mean drop IN Hb g/dl	1.6	
Mean rise in Cr mg/dl	0.36	

Table-5: Mean survival times (months) for various t stages

T stage	Mean Survival (months)
T1	118.2
T2	65.7
T3	79
T4	21

Table-6: Mean survival times (months) for various Fuhrman's grade

Fuhrman's grade	Mean Survival in months (95% CI)
1	100%
2	99.124 (93.658–104.6)
3	62.8 (53.4–72.2)
4	30.3 (17.64–42.96)

Table-7: Factors associated with disease recurrence.

Factors	*p*-value
Age	0.012
Pain at presentation	0.034
T stage	0.002
Renal sinuses involvement on Histopathology	0.012
Complaints at 1st visit	0.004

Table-8: Mean survival times (months) for various histological variants of RCC

Histopathology	Mean Survival in months (95% CI)
RCC clear cell variant	109.32 (100.36–118.3)
RCC papillary variant	81.8 (63.2–99.17)
RCC chromophobe variant	69.65 (55.24–84.05)
RCC sarcomatoid	33.25 (15.81–50–68)

DISCUSSION

The incidence of RCC is rising worldwide and the gap in mortality among the developed and developing countries is widening.[1,2] Radical nephrectomy remained the gold standard treatment of renal tumours for more than 50 years. The decrease in the size of renal tumours at presentation due to more commonly used cost-effective imaging techniques has introduced the trends of nephron-sparing surgeries in small renal tumours (T1 stage).[7] In spite of that RN remains gold standard treatment for localized T2 tumours or larger and in selected T1 tumours which are not amenable to NSS.[9–11]

Trends toward partial nephrectomy are increasing in developed countries[12] but in Pakistan, due to lack of published research articles on nephron-sparing surgeries, we concluded that radical nephrectomy is still in practice for small and larger renal tumours.

Demographic analysis of our study shows that the RCC is more prevalent in male population as compared to female which is similar to other international studies. In western countries, the age of presentation is in 6th and 7th decades of life, similarly in our study the median age of presentation was 53 years (6th decade). According to some international studies, the incidental finding of renal tumours varies from 38% to 61% while in our study, it was around 54%.[16,17]

In our study, the classical triad of haematuria, palpable mass and the flank pain was present in only 6 (1.74%) patients which is less than some reported studies 6–10%.[13,18] Most common T stage tumours at presentation were T1 and T2, the most common variant of RCC was clear cell followed by papillary and chromophobe variant while the most common Fuhrman grade was 1 followed by grade 2.

Perioperative mortality in (0.6%) cases. Two patients died before discharge from the hospital. One patient had stage T3 disease who died of myocardial infarction post-surgery on 30th post OP day, the 2nd patient had stage T1 disease and died of myocardial infarction 9th post OP day. Both the deaths were of non-operative causes.

RN related complications observed in our study were chronic incision site pain in 2.7%, incisional hernia in 2.0%, wound infection in 1.7%, retroperitoneal hematoma 0.3% and hydrocele in 0.3% of patients. Mean drop in Hb was 1.6 g/dl (0g/dl to 6.5 g/dl) and mean rise in creatinine was 0.36 mg/dl (0mg/dl–10.9mg/dl). The mean length of hospital stay (LOS) was 4.8±1.9 days (range: 3–30 days). These findings are similar to the other reported international studies of the developed countries.[19,20]

Iatrogenic IVC and gall bladder injuries were negligible our study. Splenic injury is not uncommon during oncological surgeries performed in the left upper quadrant of the abdomen but again was rare in our study. Left radical nephrectomy is the 2nd most common cause of iatrogenic splenic injury and incidental splenectomy. Giorgio Carmignani and colleagues conducted a study in Italy in patients with incidental splenectomy during procedures of left RN and they concluded that Cruciate Mercedes incision has very less chances of causing splenic injury (2.6%) as compared to Chevron incision (13.2%) for RN.[21] Incidental splenectomy due to splenic injury was performed in 6 (1.8%) patients in our study which is less than above mentioned article.

In our study the mean follow-up was 31.1±26.77 months (range: 3–132 months) and 46 (13.4%) died during the study time period. Forty-nine (14.2%) cases had a disease recurrence with 33 (9.5%) deaths from disease progression. The 5-year progression-free survival was 37% (95% CI: 49.04–72.76) with a median time to recurrence of 33 months (95% CI: 27.6–38.4) and the median overall survival was 103.7 months (95% CI: 95.7–111.7). The 5-year overall survival was 76.1% (95% CI: 75.2–77) while 10-year survival was 70.8%.

For T1 stage patients the overall five-years survival was 87% which is comparable to 93% in a reported study conducted by Department of Urology, University of Michigan USA.[22] In international studies survival for T2 stage varies, a study conducted by Ganesh and colleagues at University of California the 3 year survival for T2 stage disease was 69%[23] while a study performed in South Korea by Woojub Jeong the 5 year survival for T2 disease was 88%[24], while in our study it was 67%. For stage T3 and T4 disease the 5-year survival was better in our study as compared to international study, i.e., 65% against 42% for T3 disease and 50% against 28% for T4 stage disease respectively.[25]

CONCLUSION

Radical nephrectomy offers the best survival for non-metastatic renal cell carcinoma patients with excellent postoperative survival and progression-free profile. Although renal cell cancer presents in younger age group but the long-term survival after radical nephrectomy in Pakistani population is similar to the rest of the world.

Conflict of interest: None declared

AUTHORS' CONTRIBUTION

NK: Principal author, literature search, data collection, write-up, data interpretation. AI: Literature search, data collection. AA: Data interpretation, write-up. NU: Data collection. SM: Data analysis, data interpretation, SPSS export. KM: Conceptualization of study design, topic selection, overall supervision, proof reading.

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