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A study on sporadic renal cell carcinoma in young adults, our institutional experience

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ABSTRACT

Background: Renal cell carcinoma (RCC) accounts for around 2–3% of all adult malignant neoplasms. Most RCC instances are sporadic, with about 4–6% being familial. Sporadic RCC is uncommon in young patients under 45, accounting for 3–7% of all instances. We report our experience with sporadic RCCs in young adults between the age of 20 and 45 years. **Aims and Objectives:** The aim is to study clinical presentation, evaluation, management, and prognosis of sporadic RCC in young adults. **Materials and Methods:** A retrospective review of 22 patients diagnosed with sporadic RCC between ages 20 and 45 years during a period of 7 years from 2016 to 2022 was performed at Government Stanley Medical College. Demographic details such as age, gender, clinical condition, blood investigations, radiological imaging, and histopathological evaluation were conducted. Patients were assessed for long-term outcomes by comparing metastasis and lymph node involvement with survival outcomes. **Results:** The mean age at diagnosis was 37 years. Most patients belong to lower socioeconomic status (54.5%), Tumors were detected incidentally in 9 patients (41%) and were symptomatic in 13 (59%). Around 87% of patients were not having any associated comorbidities. The average duration of presenting complaints in symptomatic patients was 41 days. About 59% of patients were smokers or chewing tobacco before diagnosis. Renal biopsy was performed in 27% of patients before definitive surgery. The difference in prognosis was found to be insignificant between patients who were asymptomatic at the time of diagnosis compared to patients who were symptomatic. The tumor stage and grade had a significant impact on survival. The mean postoperative follow-up was 38 months. **Conclusion:** The result of our study shows that sporadic RCC does not behave aggressively in young adults. The most important determinants in prognosis are tumor stage and histological grade. The type of surgical procedure does not affect the overall outcome.

Key words: Renal cell carcinoma; Sporadic; Biopsy; Stage; Grade; Prognosis

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INTRODUCTION

Renal cell carcinoma (RCC) is one of the most frequent urologic malignancies, accounting for 2–3% of all adult malignant neoplasms.[1,2] RCC has been found in male patients at a 2:1 ratio compared to females.[2] However, diagnosis of RCC has increased more rapidly in young adults than in any other age group,[3] and the incidence of RCC has increased by an average of 3% per year since the 1970s, owing primarily to the increased use of ultrasound and computed tomography (CT) scan to evaluate various non-specific abdominal complaints. This trend of early detection at a young age was associated with an increase in the number of incidentally detected and more localized tumors, as well as better 5-year survival rates for individuals at this stage of the illness. Most RCC occurrences are sporadic, with only 4.6% being familial.[4] In addition, if a patient diagnosed with multiple renal masses above 46 years of age has a family history of RCC, the patient should be considered for genetic testing.[5]

By definition, all RCCs are adenocarcinomas originating from renal tubular cells.[5] Tobacco exposure is the most widely established environmental risk factor for RCC, with

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an associated relative risk ranging from 1.4 to 2.5 compared to controls. The risk increases as the cumulative dosage of pack years increases. Tobacco usage accounts for 20–30% of RCC cases in males and 10–20% in women. Obesity is also recognized as a key risk factor for RCC, with every extra unit of body mass index carrying a relative risk of 1.07. According to studies, RCC is more prevalent among those with poor socioeconomic status and who live in cities, although the causes are unknown.[4,5]

In most studies, tumor size has ranged from a few millimeters to huge enough to occupy the whole abdomen. Nuclear characteristics are an independent prognostic factor for RCC, clear cell, and papillary types.[6] RCC affects the venous system in around 10% of patients. The majority of occasional RCCs are solitary. Clear cell RCC is the most prevalent variety, accounting for 70–80% of all RCCs, followed by papillary and chromophobe.[7] Many renal tumors remain asymptomatic and non-palpable clinically until they progress locally due to the kidneys' sequestered placement in the retroperitoneum. More than 60% of RCCs are now diagnosed incidentally.[8] Given the prevalence of accidental findings, RCC would be more aptly referred to as a Radiologist's tumor. Local tumor development, paraneoplastic diseases, bleeding, or metastasis cause symptoms. The traditional triad of flank discomfort, hematuria, and palpable abdominal tumor is relatively uncommon. Paraneoplastic syndromes are observed in 10–20% of cases, with hypercalcemia (13%), hypertension (HTN), and polycythemia being the most prevalent. The RCC staging method is based on the 8th edition of the AJCC Tumor, node, metastasis (TNM) classification, published in 2016. A detailed history, physical examination, and the prudent use of laboratory testing are the first steps in the clinical staging of the illness. A high-quality abdomen CT scan, a regular chest radiograph, and the selective use of magnetic resonance imaging (MRI) can be used to accomplish radiographic staging. More than 15–20 HU enhancement is indicative of RCC. However, this does not rule out benign histology.[9]

In all situations, a chest radiograph, a thorough assessment of abdominal and pelvic CT or MRI, a liver function test, and a chest CT scan are required for patients with pulmonary symptoms or an abnormal chest radiograph. The abdominal imaging investigations advised good diagnostic accuracy. As a result, a needle biopsy is not always required before surgery, particularly in individuals whose imaging investigations demonstrate unequivocal findings. A needle biopsy for tiny lesions may be considered in chosen patients to establish the diagnosis of RCC and guide active surveillance, cryosurgery, radiofrequency, and ablation methods. The pathological stage has been identified as RCC's most critical prognostic factor.[10]

Prognosis is also affected by nuclear grade and histologic subtype. Tumor size is also an important prognostic marker highly linked to tumor stage. RCC is a complicated disease with several histologic subtypes and nuclear grading. Some individuals are more aggressive than others. A percutaneous biopsy can detect benign masses as well as the aggressiveness of the tumor in some circumstances. As a result, it may be possible to stratify patient risk before treatment.[11] Our study aimed to investigate the clinical presentation and characteristics at diagnosis, surgical procedures, pathological outcomes, and survival in adult patients presenting with RCC and underwent surgery for the same.

Aims and objectives

Aim of the study is to understand the clinical presentation, complete evaluation, management and prognosis of sporadic renal cell carcinoma in young adults in our institute.

MATERIALS AND METHODS

Study design

The design involves retrospective observational study.

Study period

The study period was 7 years (January 2016–December 2022).

Study place

Department of Urology, Government Stanley Medical College and Hospital, Chennai. Tamil Nadu-600001.

A retrospective assessment of 22 patients diagnosed with sporadic RCC between 20 and 45 years from 2016 to 2022 was conducted at Government Stanley Medical College.

Inclusion criteria

Our research included all patients aged under 45 years who underwent surgical treatment for renal mass and diagnosed to have RCC in previous 7 years (from 2016 to 2022).

Exclusion criteria

Patients aged above 45 years or with familial RCC syndromes, such as von Hippel–Lindau disease, were not eligible.

The study was conducted in a single clinical tertiary centre, namely Department of Urology and Renal Transplantation in Government Stanley Medical College and Hospital in Chennai. Since only recorded data in medical charts were used, our institute's Ethical Committee approved the study with exempt informed consent with EC Reg No.ECR/131/Inst/TN/2013/RR-22.

Symptoms at presentation, as well as radiological and histological features, were retrieved from patient records. Physical examination, laboratory investigations, ultrasound, and radiographic staging, including chest X-ray, contrast-enhanced CT with unenhanced followed by three phases of post-contrast study, or MRI performed to evaluate patients before surgery. Patient age, TNM/pathological stage, tumor size, tumor histology, and nuclear differentiation grade were all evaluated regarding disease-specific survival using univariate and multivariate analyses (cox regression modelling). The Statistical Package for the Social Sciences program version 11.5 was used to analyze the data.

Patients' demographics, TNM classification, tumor complexity R.E.N.A.L. Nephrometry Score, CT data, type of surgery, histological examination findings and grade of tumor, outcome, and follow-up data were all documented.

R.E.N.A.L nephrometry score (NS) was initially introduced to quantify the renal mass characteristics on imaging which allows standardized reporting on renal masses and assist in surgical decision-making. NS suggests the complexity level divided as low, intermediate, and high based on NS 4–6, 7–9 and 10 or more, respectively. NS of 10 or more indicates high complexity and patients usually undergo radical nephrectomy.[12] NS calculated using following parameters: Radius or largest diameter of mass, endophytic or exophytic percentage, nearness to the hilum of kidney, anterior/posterior, location with respect to the polar lines.

During follow-up, patients were clinically examined with blood investigations annually, X-ray chest, contrast-enhanced CT abdomen every 6 months for the first 2 years and then once a year till 5 years. Beyond 5 years as clinically indicated based on individual patient characteristics and tumor risk factors. Based on the follow-up and assessment, patient data were obtained.

RESULTS

Twenty-two patients aged <45 years old and surgically treated for renal masses were included in our study.

The average age at diagnosis is 37, and most patients (54.5%) are from the lower socioeconomic category, followed by the lower middle group (36.5%). Tumors were discovered by chance in 9 patients (41%) and were symptomatic in 13 (59%). Around 87% of patients had no associated comorbidities. In symptomatic patients, the average duration of presenting complaints was 41 days. Before diagnosis, 59% of patients smoked or chewed tobacco. Blood and urine parameters of majority of the patients were within normal range. Around 28% of patients had a disturbed renal function test at diagnosis. R.E.N.A.L NS in 77% patients was in intermediate and high complexity levels. In symptomatic patients, the average duration of presenting complaints was 41 days (Table1). 27% of patients were diagnosed RCC on post-operative histopathology in whom preoperative renal biopsy was performed. Survival was significantly affected by tumor stage and grade of the tumor. The is no significant difference in survival between incidentally presented patients and patients who were symptomatic at the time of diagnosis.

Of the patients, 22.7% were female, and 77.3% were male (Figure 6). Most patients (54.5%) had a lower socioeconomic status. Over half of patients (54.5%) presented with loin pain. 27.3% of patients had haematuria. Most patients (86.4%) had no surgical history or comorbidities in the past. For those with comorbidities, coronary artery disease/HTN was present in 4.5% and diabetes mellitus in 9.1%. Smoking was reported by 54.5% of patients, while 18.2% reported tobacco chewing and 31.8% reported alcohol consumption. Our study found that most of the patients shows renal mass without tumour thrombus on contrast imaging (Figure 1), and post operative gross specimen showing variegated appearance with yellowish areas with hemorrhagic dark red areas (Figure 2).

The R.E.N.A.L NS in 77% patients was in intermediate and high complexity level hence, most of the patients (68%) underwent open radical nephrectomy and rest of the patients underwent open partial nephrectomy. Clear cell RCC was the most common histopathological examination (HPE) finding found in 17 patients (73%), with gross specimen showning variegated appearancewith yellowish areas with haemorrhagic dark red areas (Figure 2) followed by papillary RCC in 4 patients (18%) and chromophobe type in one patient and tubulocystic variant in one patient patient (Figure3). On contrast imaging/angiography evidence of renal mass associated with tumour thrombus seen confined to renal vein without extending into its tributaries or into the IVC and without lymph node involvement, seen in only two patients (9.1%) (Figure 4). Both the patient underwent radical nephrectomy. The post operative gross specimen of both patients shown tumour thrombus in renal vein (Figure 5). Of the patients, 22.7% were female, and 77.3% were male (Figure 6). Most patients had negative margins (95.5%), and lymphovascular invasion was present in 13.6% of cases. Regarding pathological staging, the most common stage was T1bN0M0 (31.8%). Most patients did not have lymph node (LN) involvement (72.7%) or metastasis (86.4%) (Figure 7). The average postoperative follow-up period was 38 months. Most patients had an uneventful follow-up duration (59%). During follow-up, 27% of patients were reported to have expired, and 2 patients (9%) developed chronic kidney disease on long-term follow-up duration and one patient (4.5) reported to have raised

Table 1: Baseline characteristics of the patients

Patient characteristics	Median	Percentile 25	Percentile 75
Age	39.00	33.00	41.00
Duration of presenting complaints	1.00	0.00	4.00
BMI	23.25	21.00	25.00
Hemoglobin	13.00	11.30	14.10
TLC	8750.00	7300.00	10200.00
HCT %	43.50	41.00	46.00
Platelets in lakhs	3.10	2.80	3.30
Urea	21.50	18.00	27.00
SR creatinine	1.00	0.90	1.20
ESR mm/h	14.00	13.00	15.00
Total bilirubin	1.00	0.90	1.20
Direct bilirubin	0.30	0.20	0.30
Indirect bilirubin	0.70	0.60	0.80
AST U/L	39.00	35.00	44.00
ALT U/L	32.00	29.00	36.00
ALP U/L	106.50	90.00	110.00
Albumin g/dL	3.10	3.00	3.40
SR calcium mg/dL	10.00	9.00	11.60
LDH	115.00	110.00	120.00
Pre contrast+HU	38.50	36.00	42.00
Post contrast+HU	91.95	73.40	108.30
R.E.N.A.L score	8.00	7.00	11.00
Follow-up duration	41.50	24.00	52.00

TLC: Total leukocyte count, HCT: Hematocrit, ESR: Erythrocyte sedimentation rate, ALP: Alkaline phosphatase, AST: Aspartate transaminase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase, BMI: Body mass index

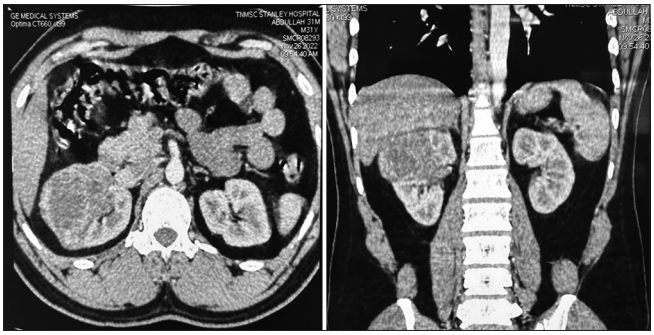

Figure 1: An enhancing right renal mass of size around 7 cm

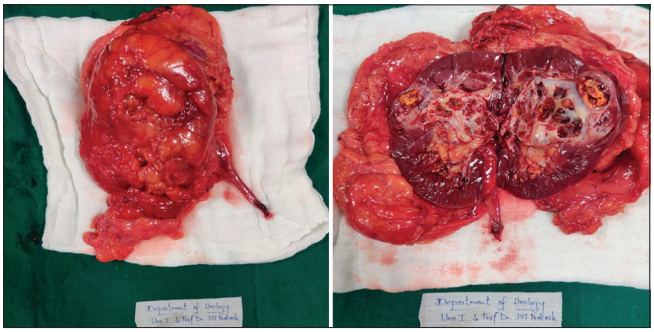

Figure 2: Gross and cut section of post right radical nephrectomy specimen

creatinine (serum creatinine-1.5) after 6 months of surgery and he is under periodic follow-up. Follow-up was ongoing for 73% of patients. Imaging and routine blood tests were performed on patients at regular intervals during follow-up.

Finally, 82% of patients have not received any adjuvant therapy. Systemic therapy with sunitinib 50 mg per oral qDay for 4 weeks then 2 weeks drug free then repeat cycle was given in 18% of cases with histologically proven clear cell RCC (Table 2).

The current study findings did not report survival distribution compared to tumor presentation ($P = 0.567$). The survival analysis was performed for more than 60 months, which did not reveal significant (Figure 8).

The survival distribution for tumor presentation was statistically insignificant ($P = 0.567$).

The study found that there was no significant difference in the rates of metastasis between patients whose cancer was incidentally detected and those whose cancer was not incidentally detected (Table 3).

The study found that patients with T stage 1 cancer had a significantly higher survival rate than patients with T stage 2 or 3 cancer. The study also found that patients with histological grade 1 cancer had a significantly higher survival rate than patients with histological grade 2 or 3 cancer (Table 4).

DISCUSSION

Our study reports the assessment of outcomes in 22 adult patients with a follow-up period of more than 60 months

Table 2: Clinical characteristics and outcomes in 22 patients

Clinical characteristics and outcomes	Count	Column n %
Socio-economic status		
Lower	12	54.5
Lower middle	8	36.4
Upper lower	2	9.1
Fever		
No	16	72.7
Yes	6	27.3
Loin pain		
No	10	45.5
Yes	12	54.5
Hematuria		
No	16	72.7
Yes	6	27.3
Incidental		
No	13	59.1
Yes	9	40.9
Wt loss/reduced appetite		
No	17	77.3
Yes	5	22.7
Surgical history		
External fixation of the femur	1	4.5
Hemorrhoidectomy	1	4.5
Hysterectomy	1	4.5
Nil	19	86.4
Comorbidities		
CAD/HTN	1	4.5
DM	2	9.1
Nil	19	86.4
Smoking		
No	10	45.5
Yes	12	54.5
Tobacco chewing		
No	18	81.8
Yes	4	18.2
Alcohol		
No	15	68.2
Yes	7	31.8
Urine routine		
Alb+	3	13.6
Renal doppler/CT angiogram		
Lt renal vein involvement+	2	9.1
ND	20	90.9
Tumor stage		
T1aN0M0	6	27.3
T1bN0M0	8	36.4
T2aN0M0	1	4.5
T2bN0M0	3	13.6
T2bN1M0	1	4.5
T3aN1M0	2	9.1
T3aN1M1	1	4.5
Surgery performed		
Partial nephrectomy	7	31.8
Radical nephrectomy	15	68.2
HPE		
Chromophobe RCC	1	4.5
Clear cell RCC	16	72.8
Papillary RCC	4	18.2
Tubulocystic RCC	1	4.5
Pathological staging		
pT1a	6	27.3
pT1b	7	31.8
pT2a	2	9.1
pT2b	2	9.1
pT3a	5	22.7
Histological grade		
1	7	31.8
2	14	63.6
3	1	4.5
Margins		
Negative	21	95.5
Positive	1	4.5
LVI		
Positive	3	13.6
Nil	19	86.4
LN status		
Nil	16	72.7
Positive	6	27.3
Chemotherapy		
No adjuvant therapy	18	81.8
Sunitinib	4	18.2
T		
1	14	63.6
2	5	22.7
3	3	13.6
N		
0	18	81.8
1	4	18.2
M		
0	19	86.4
1	3	13.6
Follow up		
CKD	2	9.1
Expired	6	27.3
Raised creatinine	1	4.5
Uneventful	13	59.1
Pts in follow-up		
No	6	27.3
Yes	16	72.7
Expired		
No	16	72.7
Yes	6	27.3

CKD: Chronic kidney disease, LVI: Lymphovascular invasion, LN: Lymph node, HPE: Histopathological examination, RCC: Renal cell carcinoma, CT: Computed tomography, CAD: Coronary artery disease, HTN: Hypertension, DM: Diabetes mellitus

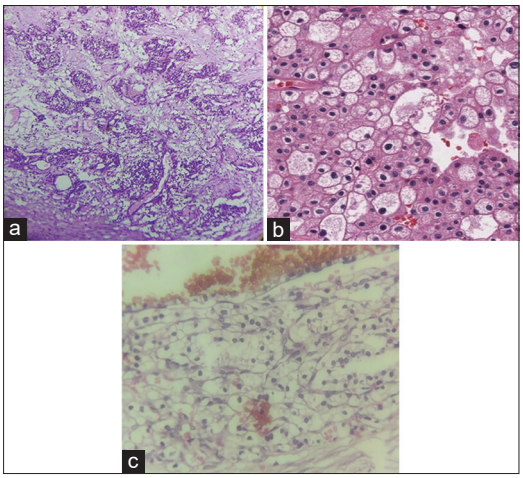

Figure 3: Histopathological slides of (a) Clear cell renal cell carcinoma (RCC), (b) Chromophobe RCC, (c) Plasmacytic variant of RCC

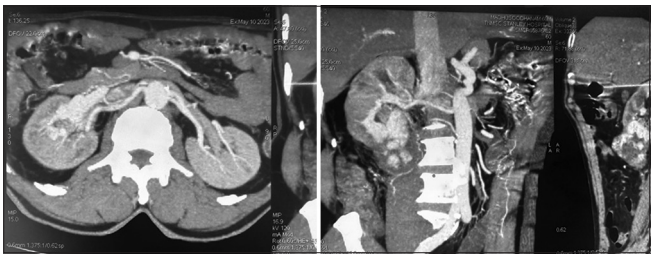

Figure 4: A right renal enhancing mass with right renal vein involvement

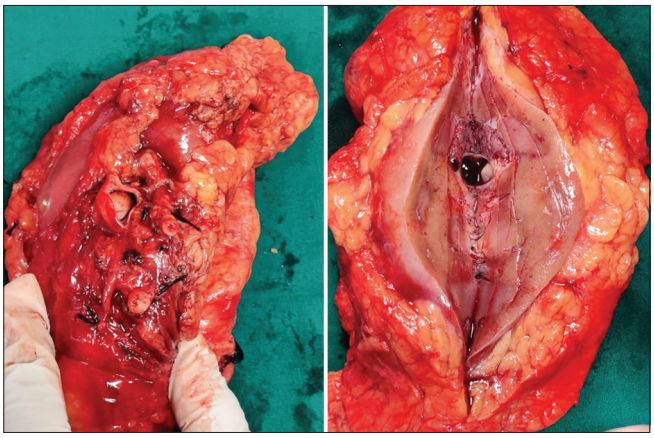

Figure 5: Post right radical nephrectomy specimen with thrombus present at the renal vein hiatus. Pathologic examination revealed clear cell renal cell carcinoma

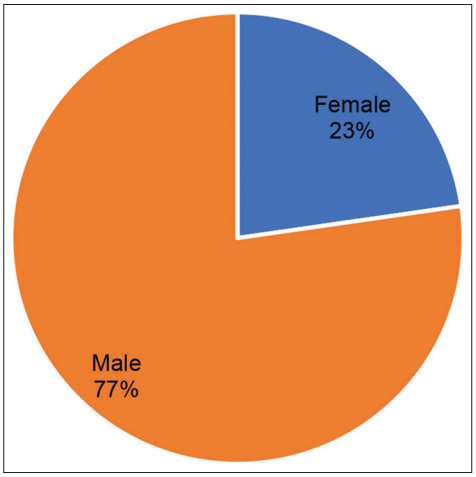

Figure 6: Pie chart of gender distribution

with a comparison of clinical presentation, pathological condition, outcomes, and survival.

We have observed in our study that the mean age of presentation or diagnosis was 37 years, with a male predominance and found more in patients who belongs to lower socioeconomic status. In 13 patients (59%) the diagnosis of RCC was based on clinical symptoms which is in accordance with study carried out by King et al., who reported value of 60%,[13] whereas nine patients were incidentally detected and diagnosed with RCC. Eggener et al., found a rate of 55.9% of patients with symptomatic presentation in young adults with renal tumors.[14]

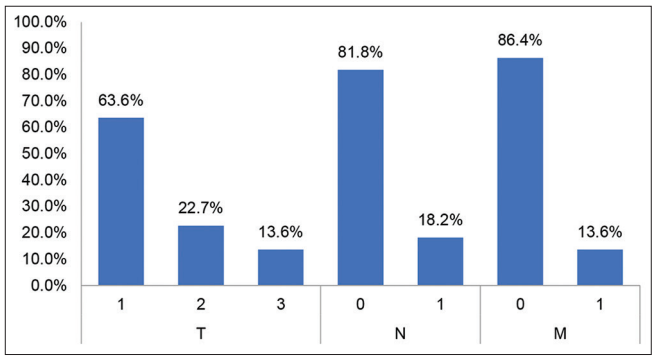

Figure 7: Histogram of tumor, node, metastasis staging

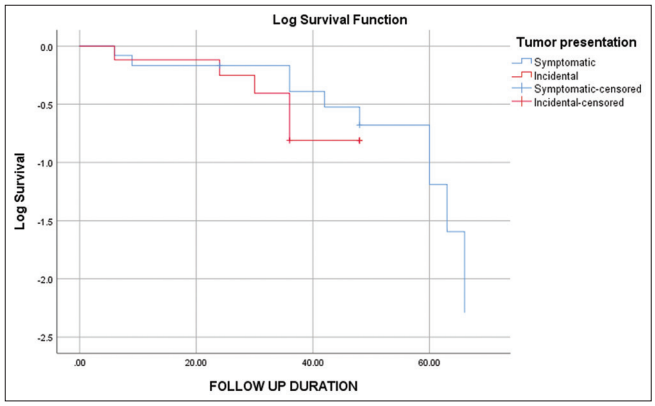

Figure 8: Log survival functioning

Table 3: Incidence of metastasis detected in incidentally diagnosed patients

Metastsis	Incidentally detected				P-value
	No		Yes		
	Count	Column n%	Count	Column n %	
Metastatis					
Yes	2	15.4	2	22.2	0.682
No	11	84.6	7	77.8	

Table 4: Correlation of tumor stage and grade with patient mortality

Tumour stage and grade	Expired				P-value
	No		Yes		
	Count	Row n %	Count	Row n %	
T					
1	13	92.9	1	7.1	0.004
2	3	60.0	2	40.0	
3	0	0.0	3	100.0	
Histological grade					
1	8	100.0	0	0.0	0.042
2	9	64.3	5	35.7	
3	0	0.0	1	100.0	

RCC dominates the histology even in young population, in current study results corresponding to such entity in proportion of 73%. In young age patients, tumors tend to be at lower stage and grade[15] which makes there management less debilitating. We found in our study that higher incidence of favorable pathological stages (pT1, pT2) in young adults (86.3%). Gillett et al., found a significantly high incidence of pT1-2 stages in patients 18–40 years as compared to patients aged 60–70 years (82.7% vs. 69.9%).[16]

The current study reports 5 year cancer-specific survival rate of 72.7%. RCC mortality and morbidity rose with age, as reported by Eggener et al., who found that cancer-specific survival was 84.9% in young people after 5 years.[14] A similar pattern was observed by the Mayo Clinic group, which found a 5-year cancer-specific survival rate of 75.3% in adults compared to older adults (50–60 years of age). In addition, Siemer et al., reported that 17.2% of patients with RCC died with a mean follow-up of 27.5 months.[17] Comparing the studies signifies a favorable trend with better outcomes and survival in adult patients compared to old-age patients.

A recent study found that individuals with RCC with no symptoms were less likely to develop metastases and had a higher chance of survival. Several authors have shown that staging, grading, patient age, tumor size, and symptoms are all prognostic factors in RCC patients.[17,18] In our patient cohort, multivariate cox regression analysis demonstrated significant connection between stage of the disease and tumor grading with survival and outcome. However, Siemer et al., reported a significant difference in LN metastasis and tumor grading, which can be used as a prognostic factor for survival rate and outcome.[17]

Clear cell RCC was the most prevalent histopathological diagnosis in 72.7% of the patients, followed by papillary RCC in 18.2% and tubulocystic RCC in one case. Histopathological data can be used to determine the survival rate as one of several criteria. Cao et al., observed clear cell RCC as the most frequent HPE in younger individuals.[19] The current study found no significant difference in results when comparing the surgical procedure (partial or radical nephrectomy) to the patient's age. This was also consistent with the findings of Siemer et al., who found no correlation between surgical procedures and patient age.[17]

Our study's overall survival rate was 72.7%, with 27.3% (n=6) died owing to cancer specific mortality and concomitant diseases. Siemer et al., observed similar findings, with death occurring in 21 of 120 patients.[17] According to our results, most of the young adult patients presented with symptoms but incidentally diagnosed patients does not show significant difference in rate of distant metastasis as compared to symptomatic patients. Other studies, however, have found that young adults are more likely to develop symptomatic tumors, which can result in a poor prognosis. In accordance to our study Eggener et al., found to have symptomatic presentation in 55.9% patients with RCC in young adults.[14] In the current study, symptoms such as loin discomfort (54.5%), hematuria (27.3%), weight loss/reduced appetite (22.7%), and fever (27.3%) were recorded.

Our research discovered no link between unfavourable histological characteristics and a greater prevalence of LN metastasis compared to survival rates. Sánchez-Ortiz et al., found an association between young age and RCCs with more unfavourable histological features and a higher incidence of LN metastases when comparing the pathological characteristics and survival rates of sporadic RCC in young adults with those in older patients.[20] According to the study, the frequency of LNs and distant metastases varies. Siemer et al., found metastases in 6.9% of the young patients and LN metastases in 12.6%, with no statistically significant difference between the two groups.[17] According to Eggener et al., 4.4% of patients experienced distant LN metastases.[14]

Limitations of the study

Since it is a retrospective, single centre, small sample sized study. The findings may not be applicable to overall general population. Further multi institutional study warranted in future.

CONCLUSION

Our findings suggest that sporadic RCC does not behave more aggressively in young persons under 45. Lower socioeconomic groups are particularly affected. Tumor stage and grade are the most important prognostic factors. When compared to symptomatic tumors, incidentally detected tumors does not found to have a significant difference in metastasis of the disease or in prognosis. The type of surgery (partial or radical) performed has little effect on the final prognosis. Surgery is still the basis of treatment for this condition. While open radical nephrectomy has long been considered the gold standard for any renal tumor surgery, partial nephrectomy is now used for clinically localized renal masses.

When an elevated oncologic risk is suspected, radical nephrectomy should be considered. R.E.N.A.L. and other nephrometry devices enable the assessment of tumor complexity and complication risk and compare evolving surgical approaches. Patients' post-surgery surveillance can be customized to their pathologic tumor stage and grade.

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