



Original Research Article

Renal cell carcinoma with IVC tumour thrombus: A study of clinico-pathological outcomes

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ABSTRACT

Objective: To evaluate the experience of RCC with IVC thrombus in terms of impact of clinical and pathological factors, level of thrombus and complications on outcome of the disease .**Materials and Methods:** Seventeen patients underwent radical nephrectomy and IVC tumour thrombectomy during 2012 to 2015 at our tertiary health care centre, clinico -pathological data from these patients were retrospectively analysed.**Results and Discussion:** Of the 17 patients (male: female: 3:1), the mean age was 57 years. The tumour thrombus extension was level I in 58%, level II in 29%, level III in 11%. In our series, the mean blood loss in levels I – III tumour thrombus were 1863 mL, 3380 mL, 3250 ml respectively.

Clavien dindo complications were -grade I in 1 case, grade II in 7 cases, grade III in 2 cases, grade IV in 3 cases. Pathological examination demonstrated that 13 out of 17 patients had clear cell carcinoma, five patients had higher grade(3, 4)and three had perinephric and IVC wall invasion. There was no perioperative hospital mortality. Two patients were lost to followup, one patient died due to extensive metastatic disease after 4 year, all other are under regular followup.

Conclusion: Radical nephrectomy with IVC thrombectomy remains a challenging procedure. Multiple histopathological variables especially tumour stage and grade have a strong impact on the morbidity and mortality and also help in stratifying the subgroup in which adjuvant therapy is essential. With detailed perioperative planning and multidisciplinary efforts, surgical resection is the definitive treatment of choice for patients of RCC with IVC tumour thrombus.© 2020 Published by Innovative Publication. This is an open access article under the CC BY-NC-ND license (<https://creativecommons.org/licenses/by/4.0/>)

1. Introduction

Renal cell carcinoma (RCC) represents 2–3% of all solid cancer, and it is the third most common cancer of the urinary tract, with an incidence of 6–12 cases per 100 000 people in Western countries.¹ RCC is one of the few solid organ tumors with a predilection for vascular invasion. Approximately 10 percent of patients with RCC have tumors associated with thrombus . It is more frequent in men than in women(1.5:1), with a peak incidence between 60 and 70 yr of age.² Presence of vascular invasion indicates a

more aggressive biological behaviour and poses a greater challenge during surgery as well as treatment . Due to recent advances in diagnostic modalities, improved surgical techniques, perioperative care, surgical removal of the kidney with the tumor thrombus, even for tumors extending into the right atrium, can be performed relatively safely.³ However, the prognosis of patients with RCC involving the venous system, particularly the IVC(inferior vena cava), is generally poor, despite surgical resection of RCC and tumor thrombus.^{4–8} Kim et al. reported that the 2-year recurrence-free survival rate in patients with non-metastatic RCC involving the IVC was less than 50%.⁵ Others have shown that the 5-year overall survival rate was 44%.^{7,8}

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2. Materials and Methods

Here we present seventeen patients diagnosed with RCC and venous tumour thrombus who underwent radical nephrectomy and venous tumour thrombectomy during the study period from January 2012 to January 2015.

These patients were retrospectively analysed for clinical parameters such as signs and symptoms, duration of surgery, blood loss, units of blood transfused, hospital stay, 5 year survival and complications which were graded according to Clavien dindo. (Tables 1 and 2)

Laboratory correlates studied were serum calcium, serum LDH, Histopathological diagnosis, size and location of tumour, level of tumor thrombus, IVC wall invasion, perinephric fat invasion and grade of tumour. (Table 1)

All patients underwent routine preoperative blood tests, chest, and abdominal computed tomography (CT), gross extension of tumor thrombus into the venous system was detected by preoperative radiological examinations, including contrast-enhanced CT, magnetic resonance imaging (Figure 1). The level of tumor thrombus was determined according to the Mayo classification.⁹

Pathological diagnoses were determined according to the 2018 American Joint Committee on Cancer 8th edition TNM system. Histological subtype, determined according to the 1997 World Health Organization (WHO) Heidelberg classification, was split into clear cell renal cell carcinomas (ccRCC) versus non-ccRCCs . Tumor nuclear grade was determined according to the Fuhrman system. Perinephric fat and adrenal invasions were specifically recorded.

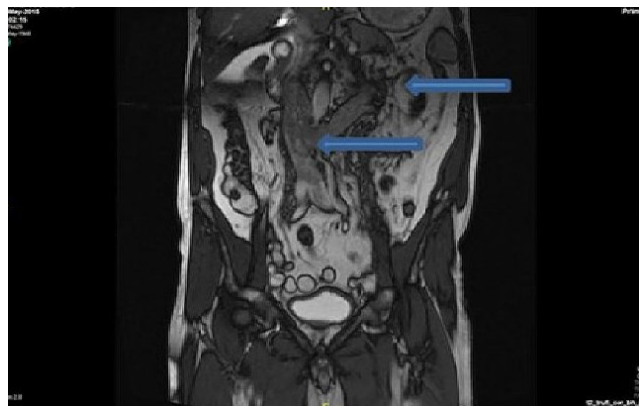


Fig. 1: MRI of the abdomen and pelvis showing left renal mass, renal vein and IVC thrombus.

3. Results and Discussion

Mean age of patients in our study was 57 years and male to female ratio was 3:1. Patients with age >55 yrs and females required more blood transfusion, had more wound infections and higher grade of Clavien complications (III & IV) than patients with age <55 yrs but interestingly 5 yr

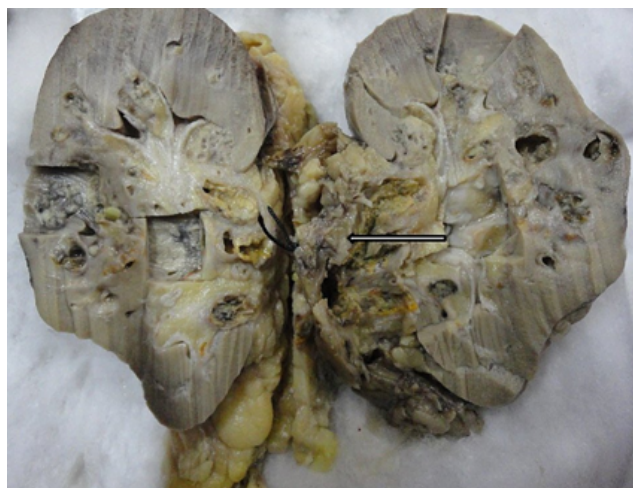


Fig. 2: Gross specimen of a kidney showing tumour extension from medulla into the pelvi calycealsystem (arrow).

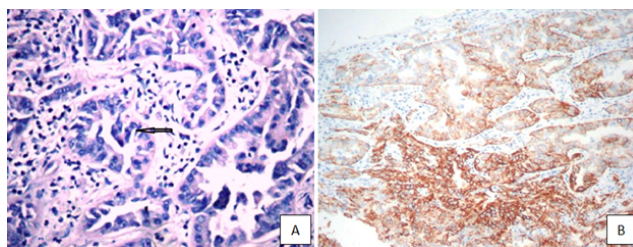


Fig. 3: (a)One of our cases of collecting duct carcinoma showing tubulo papillary arrangement of tumourcells with marked stromal desmoplasia (arrow). Haematoxylin & Eosin. 10x magnification; Figure 3(b)Immunohistochemistry of collecting duct carcinoma showing positivity with High molecular weight cytokeratin.

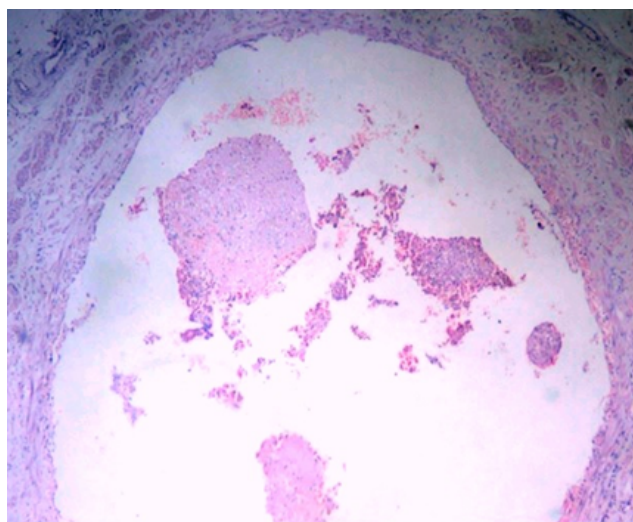


Fig. 4: Tumour thrombus in caval lumen. Haematoxylin & Eosin. 10X magnification.

Table 1: Clinical and pathological variables

S. No.	Age (yrs)	Sex	C/F	Sr. calcium	Sr.LDH	Level of thrombus	Size (cm)	Histology, Grade	IVC wall invasion	Perinephric fat invasion
1	45	m	+nt	n	< 1.5x n	I	7x4x8	clear cell,grade 1	absent	absent
2	50	m	+nt	n	< 1.5x n	I	9x7x8	clear cell,grade2	absent	absent
3	59	f	+ nt	n	< 1.5x n	I	5x6x4	clear cell,grade 2	absent	absent
4	57	m	+nt	high	> 1.5x n	III	10x8x6	clear cell,grade3	absent	present
5	63	f	+nt	n	<1.5x n	III	10x10x8	clear cell,grade 4	absent	present
6	68	m	+nt	n	<1.5x n	I	5x4x6	clear cell,grade 1	absent	absent
7	55	m	+nt	n	<1.5x n	II	6x7x6	clear cell, grade 2	absent	absent
8	56	f	+ nt	n	< 1.5x n	I	7x7x5	clear cell, grade 2	absent	absent
9	67	m	+nt	high	>1.5x n	II	10x5x10	bellini duct,grade 3	present	absent
10	61	m	-nt	n	<1.5x n	I	6x3x4	papillary,grade 1	absent	absent
11	62	f	+nt	high	<1.5x n	II	8x4x3	clear cell,grade 2	present	absent
12	54	m	+nt	n	>1.5x n	II	11x7x8	chromophobe,grade 3	present	present
13	59	m	-nt	n	<1.5x n	I	6x5x6	clear cell,grade 1	absent	absent
14	50	m	+nt	n	<1.5x n	II	7x5x4	clear cell, grade 2	absent	absent
15	65	m	+nt	high	<1.5x n	I	5x4x3	clear cell,grade 3	absent	absent
16	55	m	-nt	n	<1.5x n	I	9x4x5	clear cell,grade 1	absent	absent
17	53	m	-nt	n	<1.5x n	I	10x 5x3	chromophobe,grade1	absent	absent

c/f – Clinical features, Sr. – Serum, LDH –Lactate dehydrogenase, IVC –Inferior vena cava

survival was more (90%) in older age group and females. Similar to other studies in our study also age and gender did not significantly affect overall survival.

Symptomatic patients (flank pain, abdominal mass and hematuria) had longer duration of surgery, more blood loss, more blood transfusion, higher rate of wound infections, higher Clavien Dindo grade and more hospital stay than asymptomatic patients, but 5 yr survival was more in symptomatic group.

Hypercalcemia has been reported as the most common paraneoplastic syndrome, affecting between 13% and 20% of patients.¹⁰ It has been reported to be associated with high-stage lesions in about 75% of cases, but found to have no significant correlation with tumor grade and survival.¹¹ But in our study both hypercalcemia and higher LDH level were associated with higher rate of

blood transfusion, wound infection and higher Clavien grade complications and longer stay. A meta-analysis demonstrated that an elevated serum LDH level was connected to a poor prognosis for patients with RCC and as a prognostic indicator could be utilized to divide risk stratification and formulate individualized treatments for patients with RCC.¹²

Pathological examination (Figure 2) demonstrated that 13 out of 17 patients had clear cell carcinoma, 1 patient had bellini duct carcinoma, 2 had chromophobe, and another 1 had papillary variant.¹³

Consistent with other series¹⁴, in our study tumor size was an important prognostic factor, patients with tumour size > 7 cm had more blood loss, more wound infection, other complications, greater Clavien grade (III,IV), longer hospital stay than patients with tumour size <7 cm. Our

Table 2: Outcome variables

S. No.	Duration Of Surgery (min)	Blood Loss (ml)	No. of Blood Transfusion (units)	Wound Infection	Other complications	Clavien - Dindo Grade	Hospital stay (Days)	Follow up (FUP)
1	210	1500	2	No	Nil	II	6	On Regular FUP
2	250	2000	2	No	Nil	II	7	On Regular FUP
3	240	2200	3	No	Nil	II	7	On Regular FUP
4	220	3500	6	Yes	Sepsis	IV	12	liver & nodal mets,lost to FUP after 3 yrs
5	240	3000	8	Yes	Thromboembolism	IV	10	Lost to FUP after 2 yr
6	240	1500	2	No	Nil	Nil	6	On Regular FUP
7	180	3500	4	No	Nil	II	5	On Regular FUP
8	145	1500	1	No	Nil	Nil	4	On Regular FUP
9	185	3500	5	No	Post op ileus + Seroma	III	10	Nodes,liver & lung mets, mortality at 4 yr
10	180	1800	0	No	Nil	Nil	3	On Regular FUP
11	210	3000	4	Yes	Bleeding	III	8	On Regular FUP
12	200	2900	3	No	Nil	II	4	Bony mets,on FUP
13	145	2000	1	No	Nil	I	3	On Regular FUP
14	220	4000	5	Yes	Nil	II	6	Nodal mets , On Regular FUP
15	160	1700	1	No	Nil	Nil	3	On Regular FUP
16	200	2450	2	Yes	Nil	II	5	On Regular FUP
17	240	1980	1	No	Sepsis	II	8	On Regular FUP

Mets - metastasis

findings support the role of tumor size as a very important predictor of outcome.

In our study there were 6 patients with Fuhrman grade 1 and 2, 4 patients with grade 3 and one patient with grade 4 respectively. Terakawa et al concluded that in patients with RCC involving the IVC, biological aggressiveness is characterized by tumor grade rather than tumor extension and grade has more potential prognostic importance; therefore, more intensive multimodal therapy should be considered in patients with high grade RCC with tumor thrombus extending into the IVC.¹⁵ The importance of tumor invasion in the perinephric fat and its negative impact on prognosis for patients with RCC invading the RV and IVC had been described by Leibovich in 2005 and more also by Ficarra.^{7,16,17} Although some RCC with vein wall invasion can be cured surgically, recurrence developed in a significant proportion of patients, as reported in the review paper by Kirakali and van Poppel.⁹ In three of our patients IVC wall and peri nephric fat invasion was present. Similar to other studies, our study showed that patients with higher grade (3,4), peri nephric fat invasion and ivc wall invasion had greater blood loss, more wound infection and other complications, higher clavien dindo grade, more hospital stay and lesser 5 year survival, as compared to cases in which these histopathological findings were absent.

A case to be brought to notice was that of a rare histopathological entity of collecting duct carcinoma (Figure 3 a,b), which was associated with tumour thrombus extending all the way into the inferior vena cava (IVC) and extensive retroperitoneal lymphadenopathy. (Figure 4)

The tumour thrombus extension was level I in ten (58 %), level II in five cases(29%), level III in two cases (11 %). In our study, the mean blood loss in levels I – III tumour thrombus were 1863 mL, 3380 mL, 32 50 ml respectively and there was more wound infection, other complications of higher clavien dindo grade ,more hospital stay and mortality in patients with level II and III thrombus than those with Level I thrombus. Similar to our study, other authors have also reported decreased survival in patients with tumor thrombus involving the IVC.^{7,18–20}

Clavien dindo complications were grade I in 1 case, grade II in 7 cases, grade III in 2 cases, grade IV in 3 cases, After surgery, the majority of patients with level III thrombus had to stay in ICU for > 24 h with a median time of 3 days One of the patient developed prolonged paralytic ileus prompting insertion of percutaneous drain for retroperitoneal collection which was removed after 2 weeks, two patients had sepsis, 1 patient had bleeding and 1 had thromboembolism, all of which were managed with medical treatment and minor interventions.²¹

Table 3: Correlation of major clinical and pathological variables with outcome variables.

S. No.	Variables		Blood Transfusion (units)	Wound infection (%)	Other complications(%)	Clavien Dindo Grade	Hospital stay (Days)	5 year survival %
1	Age	<55	2.6	1/5 (20)	1/5(20)	II ONLY	6.2	3/5(60)
		≥55	3.5	4/12(33.3)	4/12(33.3)	II,III,IV(morbidity)	6.3	11/12 (91)
2	Sex	M	3	3/13 (23)	3/13 (23)	3/13 (23)	6	10/13 (76)
		F	4	2/4 (50)	1/4 (25)	2/4 (50)	7.2	4/4 (100)
3	Clinical Features	present	3.5	4/13(31)	4/13(31)	II,III,III,IV (morbidity)	6.7	11/13 (84)
		absent	2.2	1/4(25)	1/4(25)	II ONLY	4.7	3/4 (75)
4	Sr. Calcium	normal	3	3/13(23)	2/13(15)	I & II ONLY	5.69	11/13 (84)
		Increased	4	2/4(50)	3/4(75)	III & IV (morbidity)	8.25	3/4 (75)
		<1.5 XN	3	4/14(28)	3/14(21)	II,III	5.7	13/14 (93)
5	Sr. LDH	>1.5 XN	4.6	1/3(33)	2/3(66)	II,III,IV(morbidity)	8.6	2/3 (66)
		1	2	1/10(10)	1/10(10)	I,II,NO	5.2	9/10 (90)
		2	4.2	2/5(40)	2/5(40)	II,III,NO	6.6	4/5(80)
6	Level of Thrombus	3	7	2/2(100)	2/2(100)	IV,IV(morbidity)	11	1/2 (50)
		≤ 7cm	2.5	0	1/7 (14)	1/7 (14)	4.7	6/7 (86)
		> 7 cm	3.7	5/10(50)	4/10(40)	4/10 (40)	7.4	8/10 (80)
7	Tumour size	1 & 2	2.6	3/12(25)	2/12(16)	II,III	5.6	11/12 (91)
		3 & 4	4.6	2/5(40)	3/5(60)	II,III,IV(morbidity)	7.8	3/5(60)
8	Grade	present	4	1/3(33)	2/3(66)	II,III,IV(morbidity)	7.3	2/3 (66)
		absent	3	4/14(28)	3/14(21)	II,III,II	6	12/14 (85)
9	IVC Wall Invasion	present	5.6	2/3(66)	2/3(66)	I,II,IV(morbidity)	8.6	1/3 (33)
		absent	2.7	3/14(21)	3/14(21)	II,III,NO	5.7	13/14 (93)
10	Perinephric Fat Invasion	present	5.6	2/3(66)	2/3(66)	I,II,IV(morbidity)	8.6	1/3 (33)
		absent	2.7	3/14(21)	3/14(21)	II,III,NO	5.7	13/14 (93)

During follow up period, three patients developed metastasis out of two patients with nodal and liver metastases one was lost to follow up and another died, one patient with bony metastasis was referred to oncologist for further treatment and is still on follow up, except one more patient all others are on regular followup.

3.1. Follow-up schedule

Patients were evaluated for postoperative recurrence and general condition by blood count, biochemistry analysis, chest x-ray and abdominal CT every 3 months for the first year, and every 6 months thereafter.

4. Conclusion

Radical nephrectomy and venous tumour thrombectomy still remains a challenging procedure testing surgical acumen & skill of the surgeon involved.

The presence of a Venous tumour thrombus, with its associated risks of venous congestion and distal embolism,

adds urgency to the management of these patients. In addition, the often associated parasitic vasculature and collaterals developing as a result of vena caval occlusion increase the technical difficulty of nephrectomy and achieving a tumour free resection.

Although this is a retrospective descriptive study including a relatively small number of patients with a short follow-up period, the present findings suggest that with detailed perioperative planning and multidisciplinary efforts, the procedure could be performed with an acceptable morbidity and mortality.

Furthermore, various multivariate analysis have demonstrated that multiple histopathological variables such as clinical stage, tumor type-clear cell versus nonclear cell, perinephric invasion, IVC wall invasion and more importantly tumour grade have a strong impact on the morbidity and mortality of these patients and also stratify the subgroup in which adjuvant therapy is essential.

5. Source of funding

None.

6. Conflict of interest

None.

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