



Correlation of Tumour Size with Nuclear Grade, Stage and Extracapsular Extension in Renal Cell Carcinoma

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ABSTRACT

Introduction: Renal cell carcinoma is malignancy of renal tubular epithelium with poor prognosis. We evaluated the association between size of tumor with nuclear grade, stage and extra capsular extension in Renal cell carcinoma as these are the most important parameters in the prognosis

Materials and Method: 30 nephrectomy specimens with a histopathological diagnosis of Renal cell carcinoma were included in the study. The size, stage, integrity of capsule and nuclear grade were assessed and correlated. Study was approved by the institutional ethical committee. Pearson correlation coefficient was done using SPSS program for data analysis.

Result: Large tumors showed extra capsular extension and higher nuclear grade with statistically significant correlation ($p = 0.04$) No significant correlation observed between size of tumor and stage.

Conclusion: Renal cell carcinoma with a large tumor size has higher grade disease and poor prognosis.

Keywords: Nephrectomy, Renal cell carcinoma, Fuhrman nuclear grade.

Introduction

Renal cell carcinoma is a malignancy of renal tubular epithelium. Most common type of renal malignancy in adults is renal cell carcinoma which accounts for 90 - 95% of primary malignancies of kidney. Average age at presentation and diagnosis is between 50-70 years with male to female ratio of 2:1⁽¹⁾ Renal cell carcinoma rarely can occur in children and young adults and the clinical behavior and morphological features are similar to adult Renal cell carcinoma⁽²⁾ Usual clinical presentation

is with a triad of haematuria, flank pain, and renal mass. Other mode of presentations include weight loss, anaemia, fever, and symptoms caused by metastasis. The important risk factors identified are cigarette smoking, high blood pressure, obesity, and exposure to industrial chemicals.⁽³⁾ An association with Von Hippel - Lindau disease is seen in occasional patients with Renal cell carcinoma⁽⁴⁾ Clinically these neoplasms have bad prognosis due to relative resistance to radiotherapy and chemotherapy and associated high chances of

metastases⁽⁵⁾ 5 year survival rate is only 8% for stage 4, 53% for stage 3, 74% for stage 2 and 81% for stage 1 disease (source - The American Cancer Society)

The prognosis of Renal cell carcinoma is related to several clinicopathological factors like size of tumor, stage, extra capsular extension, presence of metastases, invasion into renal veins or renal pelvis and nuclear grade of the tumour. For nuclear grading Fuhrman system⁽⁶⁾ and for staging 2002 American joint committee on Cancer version of the TNM system is commonly used. Fuhrman grading system has good correlation with survival in a large group of patients with good survival in grade 1 tumors and decreased survival in grade 4 tumors. Nuclear grading also has good correlation with surgical TNM staging. Size of primary tumor is very important in assessing the survival, small tumors (<3cm) have good prognosis and large tumors more than 7cm have bad prognosis^(7,6) Significant correlation between the size of RCC, stage, grade and morphological subtypes were observed in various studies in literature.⁽⁸⁾ Extra capsular extension was not seen smaller tumors measuring <4 cm while larger tumors more than 7cm showed increased frequency of extra capsular extension.⁽⁹⁾ In the TNM system of staging tumors are categorized according to size and many studies investigated different cut off sizes for the tumor and greatest diameter has shown maximum prognostic significance. In this study we correlated the size of tumor with the stage, extra capsular extension and nuclear grade of RCC as these are the important tumor related prognostic factors.

Materials and Methods

This cross sectional study was conducted in a tertiary patient care center in South India under the guidance of institutional research committee. 30 cases of radical nephrectomy specimens with a histopathological diagnosis of Renal cell carcinoma were included in the study. Nephrectomy done for other malignancies like transitional cell carcinoma, pediatric neoplasms and non-neoplastic conditions were excluded from the study. Clinical data of the

patient were collected by proforma given to the patient, chart review and from surgical records. Nephrectomy Specimens were fixed in 10% formalin for about 18-24 hours and gross morphological features and size of tumor were noted. Specimens were examined for other abnormalities including invasion of perirenal fat, capsule, ureter, renal vessels. Sampling was done from tumor, capsule, renal pelvis, adjacent parenchyma, ureter, renal vessels and lymph nodes. The size of the tumor was defined as the longest diameter in centimeters. In case of multi focal tumors the size of the larger one was recorded. Tissue was processed, sectioned and histological subtyping and nuclear grading was done in hematoxylin and eosin stained sections. Fuhrman grading system used for nuclear grading and were graded into 4 groups⁶. In lesions having characteristics of two nuclear grades they were assigned the higher nuclear grade. Tumors were stratified into 2 categories according to the size of the tumor; Group A (tumors measuring 0- 7cm) and Group B (tumors measuring more than 7cm) Tumors were pathologically staged according to the 2002 American joint committee on Cancer version of the TNM staging system^(9,10) and graded according to Fuhrman's nuclear grading.⁽⁶⁾ Statistical analysis done (Pearson correlation coefficient) to assess the association between tumor size with stage, extra capsular extension and nuclear grade using SPSS program. A P value less than 0.05 were considered significant.

Observations

83 cases of radical nephrectomies were included in this study. 51 cases (61%) were malignancy and 32 cases (39%) were non neoplastic lesions of kidney. Out of 51 cases of renal malignancies 58% (30 cases) were Renal cell carcinoma, 21% were Transitional cell carcinoma and 16% were paediatric neoplasms. 71% of renal cell carcinoma patients were males and 29% were females with a M:F ratio of 2.4:1

Table 01 Types of Renal malignancy

RENAL TUMOUR	NUMBER	PERCENTAGE
RCC	30	58
TCC	11	21
WILMS	6	11
CSS	2	4
AML	2	4

Age of patients ranged from 24years to 70yrs, four patients were young adults in 20 – 40 years of age. 45% of patients presented with flank pain, haematuria and renal mass, rest of patients with bonepain, infertility fever and urinary tract infection. The classic triad of mass, hematuria and flank pain were seen only in 6% of patients. 69% cases of renal cell carcinoma were on the right side and 31% were on the left side and all the cases of RCC were unilateral.

Table 02 Histologic Variants of RCC

VARIANT	NUMBER	PERCENTAGE
Clearcell	22	70
Papillary	3	10
SarcomatoidRcc	2	7
Unclassified	2	7
Chromophobe	1	3
Total	30	100

All nephrectomy specimens were grouped into 2 groups according to the size of the tumor ie GROUP A tumors measuring 0 - 7cm and GROUP B tumors measuring more than 7cm.

43% Of RCC were Small tumors less than 7cm in diameter and majority of them were lower stage tumors.

Table 03 RCC 0 – 7cm (Group A)

	SIZE	TNM STAGE	GRADE
1	4X4	3	2
2	4X4	1	2
3	4X4	1	2
4	4X3	1	3
5	3X3	1	2
6	1X1	1	3
7	6X4	1	1
8	5X4	1	2
9	5X4	1	3
10	7X5	2	2
11	7X6	2	2
12	6X5	3	3
13	6X4	3	3

57% of Rcc were large tumors measuring more than 7cm in diameter and they showed higher nuclear grade and predominantly were stage 2 tumors.

Table 04 RCC more than 7cm (Group B)

	SIZE	STAGE	NUCLEAR GRADE
1	8X7	3	2
2	8X6	2	2
3	8X5	2	3
4	8X7	2	2
5	8X6	2	1
6	8X5	2	2
7	8X4	2	2
8	9x4	3	2
9	9X7	3	3
10	10X7	2	3
11	10X8	2	3
12	11X8	2	3
13	10X 5	3	3
14	10X6	2	3
15	12X5	2	2
16	17X12	2	3
17	20X17	2	4

Predominant nuclear grade was Fuhrman grade 2 (48%). Table 05 shows as the size increases nuclear grade also increases

Table 05 : Grade and size of Renal cell carcinoma

GRADE	TUMOR SIZE		TOTAL & PERCENTAGE
	0-7cm	>7cm	
1	1	1	2(6%)
2	7	7	14(48%)
3	5	8	13(43%)
4	0	1	1(3%)

77% of Renal cell carcinomas were low stage tumors with a predominance of TNM stage2 and 23% belongs to stage 3.

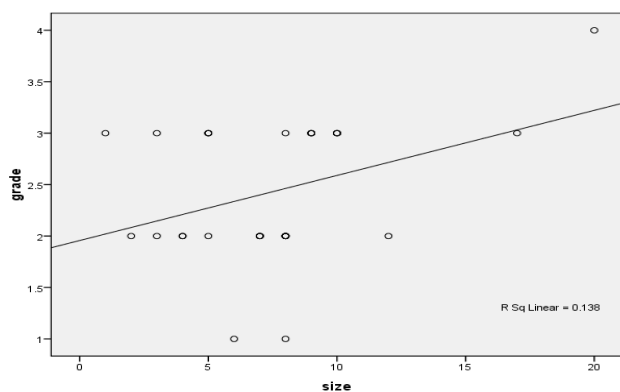
Table 06

STAGE	TUMOR SIZE		TOTAL
	0-7cm	>7cm	
1	8	0	8
2	2	13	15
3	3	4	7

Pearson correlation

Size of RCC and nuclear grade showed statistically significant correlation (pearson correlation coefficient = 0.37) and P (< 0.04).

Pearson Correlation: size and grade



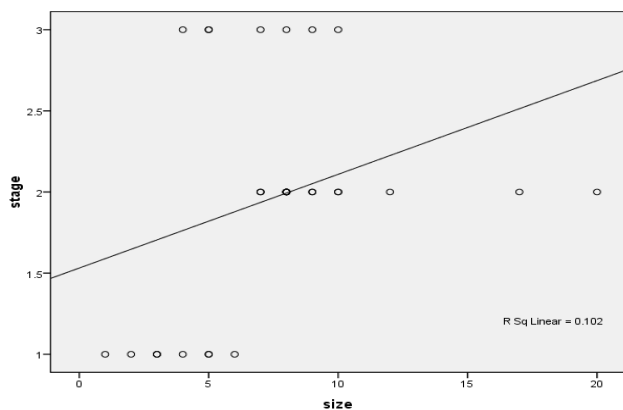
Pearson Correlation: size and grade

		size new	Grade
Size new	Pearson Correlation	1	.371*
	Sig. (2-tailed)		.044
	N	30	30
Grade	Pearson Correlation	.371*	1
	Sig. (2-tailed)	.044	
	N	30	30

* Correlation is significant at the 0.05 level (2-tailed).

The correlation between size of tumor and stage were not statistically significant (pearson correlation coefficient <0.32 and p value =0.085)

Correlation between size and stage of RCC



Pearson Correlation: size and stage

		size new	Stage
Size new	Pearson Correlation	1	.320
	Sig. (2-tailed)		.085
	N	30	30
Stage	Pearson Correlation	.320	1
	Sig. (2-tailed)	.085	
	N	30	30

Table 07 Tumors with extra capsular extension

STAGE	NUCLEAR GRADE	SIZE	HISTOLOGY
T3a	2	8.5X4	Clear cell RCC
T3a	2	8X6	Clear cell RCC
T3a	2	7.5X6.5	Clear cell RCC
T3a	2	4X4	Clear cell RCC
T3b	2	10X5	Clear cell RCC
T3a N1	3	5.5	Clear cell RCC
T3a N2	3	9X7	Clear cell RCC

Out of 30 cases of RCC 7 were stage3 tumors with a distribution of T3a 4 cases,T3b 1case,T3a N1andT3b N2 one case each. Extra capsular extension was seen in large sized tumors.

Discussion

Renal cell carcinoma is a tumor of tubular epithelium with a poor prognosis. The overall survival of these patients depends on the extent of tumor involvement at the time of diagnosis with an overall 5-year survival rate of about 70%. From the pathological and oncological point of view identification of patients with high tumor burden and high risk of disease progression is very important. There are several gross and microscopic tumor related prognostic factors including size, nuclear grade, stage of tumour, presence of metastasis and renal vein invasion. Several investigators documented that nuclear grade and size are the most important prognostic factors in RCC. Some other studies pointed out that TNM stage is more important in determining the outcome especially in intracapsular tumors.⁽¹¹⁾

In this study we correlated the size of RCC with nuclear grade, stage of disease and extra capsular extension. We observed higher nuclear grade, and extra capsular extension in large sized tumors. As the size of tumour increased nuclear grade increased with a statistically significant correlation coefficient of 0.37 (Pearson correlation) and a significant p value (P= 0.04) In a population based study conducted by Tomas Gudbjartssona, Sverrir Hardarsonb et al a strong correlation was found between grade and size with an increase of 0.06 in grade for every 1 cm increase in size of tumor (p <

0.001).⁽¹²⁾ Hsu RM, Chandy et al observed in their study that larger lesions more than 5cm showed higher TNM stage ($p<0.001$) and nuclear grade ($p<0.001$) similar to present study.⁽¹³⁾ Similar to observations made by Sohaib Tariq et al extra capsular extension were seen in large tumors measuring more than 7cm (T3 stage tumours) This observation is important in making decision whether to do a partial nephrectomy or radical nephrectomy. In contrast study conducted by Ljunberg B, Alandari FI et al observed that small renal cell carcinomas up to 3 cm, including asymptomatic lesions, showed a significant incidence of high nuclear grade and tumor extension beyond the renal capsule. These findings support aggressive management of the small lesions. In our study 78% were low stage tumors (T1&T2) with predominance of T2 tumors. There was no significant correlation between size of tumor with the stage probably due to the predominance of T2 tumors and low sample size.

According to Tsui KH et al tumor stage did not demonstrate an independent impact on renal cell carcinoma prognosis under multivariate analysis. Instead other factors such as ECOG status and grade of disease appeared to affect the survival.⁽¹⁴⁾ But independent of tumor grade the prognostic importance of TNM staging for RCC is well known. Gettman M T et al documented the close correlation of stage of RCC and the prognosis.⁽¹⁵⁾ When considering the therapeutical implications histological subtype is another valuable prognostic indicator for RCC. Among the morphological subtypes classical clear cell variant has got the worst prognosis. In our study most of RCCs (70%) were with clear cell morphology and were large sized tumors with high nuclear grade at presentation compared to other morphological variants of Renal cell carcinoma like papillary RCC and chromophobe RCC.

Conclusion

In renal cell carcinoma size of tumor is directly related to the nuclear grade and extra capsular extension. Large tumors show higher nuclear grade

and involvement of capsule. TNM Stage 2 and nuclear grade 2 tumors were the predominant type of Renal cell carcinoma in this study. The correlation between size of tumor with stage was not statistically significant and it may be due to low sample size and predominance of low stage tumors included in this study. In this era of advanced technology apart from grade and stage of the disease demonstration of molecular markers also play a pivotal role in the prognostication of renal cell carcinoma.

Acknowledgment

This research work could not be completed without the help of Dr. Sajna M.V, Assistant Professor of Community Medicine, Govt Medical College Thrissur whose timely guidance and explanation of statistics were contributory.

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