Association of Various Subtypes of Renal Cell Carcinoma with Smoking, Grading and Staging

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Abstract

Objective: To determine the association of various subtypes of Renal Cell Carcinoma with smoking, grading and staging.

Methods: A descriptive cross-sectional study was conducted in the Pathology and Oncology departments of King Edward medical University, Lahore from April 2019 to June 2020. A total of 226 cases were included in the study using purposive consecutive sampling. Association of tumor subtype with smoking, grade and stage of tumor was studied with the help of cross tabulation of these variables in SPSS 22.

Results: Out of the 226 cases, 57(25.2%) presented with high grade and 169(74.8%) with low grade RCC. Out of these, there were 98(43%) male smokers and 22(9.7%) female smokers.

When subtype was cross-tabulated against smoking (p=0.013) there were 74(32.7%) cases of clear cell carcinoma (including its subtypes sarcomatoid and rhabdosarcomatoid), 43(19.02%) cases of papillary RCC and 3(1.32%) cases of chromophobe RCC.

When subtype was cross-tabulated against stage (p=0.018), 62 (27.43%) cases of clear cell, 25(27.7%) cases of papillary and 3 (3.3%) cases of chromophobe variant presented at the T4 stage.

Conclusion: Chromophobe carcinoma of kidney is associated with smoking, higher grade and higher stage. We found no significant association of any other specific subtype with gender, smoking and grade of RCC.

Key Words: Renal cell carcinoma, grade, smoking, subtype stage.

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Introduction

Renal Cell Carcinoma (RCC) is a prevalent kidney cancer that stands at the 8th place in adult neoplasms.[1] There are different subtypes of RCC based on their histologic, cytogenetic and molecular characteristics. A well-established association is exists between morphology and genetics of RCC[2]. A single subtype of RCC may be an assortment of diverse morphologies. Many a times, a single subtype comprises of 2 to 3 distinctive subtypes. Carbonic Anhydrase IX can serve as a useful marker in determining its differential diagnosis.[3] However for the selection of suitable treatment plan, specific diagnosis of its subtype is quite crucial. Staging is based on the size and pathological features of the tumor. Metastatic disease manifests in about 30% of the patients while tumor recurrence occurs in 40% of the patients.[4] While determining treatment plan and its effectiveness, factors influencing the prognosis portray a major role.[5] Patients with slow growing tumors and lesser metastatic risk can be kept under observation before the initiation of the treatment. On the contrary, cytoreductive nephrectomy will be required for patients with bad prognosis.[6] There is a well-established association between RCC and various environmental factors such as smoking, obesity, hypertension, estrogen and metal exposure.[7] Documented studies have demonstrated fluctuating relationship between smoking and various subtypes of RCC.[8] In this study, we tend to explore the relationship of various subtypes of RCC

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with smoking, grading and staging.

Methods

This was a descriptive cross-sectional study carried out at the Department of Pathology in collaboration with the Department of Oncology, King Edward Medical University, Lahore, from April 2019 to June 2020. The study was approved by Institutional Review Board (710/RC/KEMU)of the university in 2019. A total of 226 cases were selected using the databases of the involved departments. The inclusion criteria included all excisional/incisional, adequate biopsies of renal cell carcinoma after taking telephonic consent. Auto-lyzed / inadequate specimens and those patients who did not give consent or having insufficient clinico-radiological data for staging of tumor were excluded from the study. The subjects were either approached directly or via audio/video telecommunication. Complete history was recorded in 226 cases/patients out of 400 patients. Rest 174 patients did not have complete histological or radiological data to be included in the study.

The histological subtyping for each subject was undertaken according to the WHO classification (The International Society of Urologic Pathologists (ISUP) in 2012 suggested a grading system for clear cell RCC and papillary RCC, as follows:

Grade 1 = Inconspicuous nucleoli at 400x magnification of microscope.

Grade 2= Clearly visible nucleoli at 400x magnification.

Grade 3= Clearly visible nucleoli at 100 x magnification

Grade 4= Extreme pleomorphism or rhabdosarcomatoid and/or sarcomatoid morphology.[9]

Staging was done with the help of TNM staging system 2019 i.e.T1: Tumor of kidney 4-7cm size, T2: tumor size >7cm, T3:Tumor extension into major veins, T4:Tumor reached adrenal gland or beyond.[9]

Quantitative variables like age were expressed as mean and standard deviation. Qualitative variables including gender, smoking, tumor type, stage and grade were analyzed by percentages, descriptive statistics and cross-tabulations.

Results

A total of 226 cases of Renal Cell Carcinoma were included in the study. Age of these patients ranged from 23 to 77 years of age with a mean age of 54.31± 9.185. 187 (82.7%) were males and 39 (17.3%) were females. Out of 226, 57 (25.2%) were low grade tumors and 169 (74.8%) were high grade tumors **(Table II)**. Similarly, 19 (8.4%) presented with T1, 23 (10.1%) with T2, 94 (41.5%) with T3 and 90(39.82%) at T4 stage of RCC **(Table I)**. Clear Cell Subtype (including its subtypes sarcomatoid and rhabdosarcomatoid variants) was found in 151 (66.8%) of the cases, Papillary Carcinoma in 71 (31.4%), and Chromophobe RCC in 4 (1.8%) cases.

Out of the 226 cases, there were 98(43%) male smokers and 22(9.7%) female smokers. When subtype was cross-tabulated against smoking (p = 0.013), there were 74 (32.7%) cases of clear cell carcinoma (including its subtypes sarcomatoid and rhabdosarcomatoid), 43 (19.02%) cases of papillary RCC and 3(1.32%) cases of chromophobe RCC**(Table III)**. Similarly among the non-smokers, there were 77(34.02%) cases of clear cell carcinoma, 28(12.38%) cases of papillary RCC and 1(0.44%) case of Chromophobe RCC. When subtype was cross-tabulated against stage (p=0.018, Table I), there were 10 (4.4%) cases at T1, 15 (6.6%) cases at T2, 64 (28.31%) at T3 and 62 (27.43%) cases at T4 stage for the clear cell variant of RCC. Similarly, 9 (3.9%) cases of papillary RCC presented at T1, 8 (3.5%) at T2, 29 (12.38%) at T3 and 25 (11.06%) at T4. There were null cases of chromophobe variant of RCC presenting at T1 and T2 while there was just one case of chromophobe RCC presenting at T3 and 3 (1.3%)

Table 1: *Cross-tabulation of Subtype and stage of tumor (p value=0.018)*

Tumour Size and Extent	Subtype			Total
	Clear cell	**Papillary**	**Chromophobe**	
Confined to kidney, 1-7 cm, T1	10(4.4%)	9(3.9%)	0	19(8.4%)
Confined to kidney, >7 cm,T2	15(6.6%)	8(3.5%)	0	23(10.1%)
Extension into major veins or perinephric tissues, but not into ipsilateral adrenal gland or beyond Gerota's fascia,T3	64(28.3%)	29(12.38%)	1(0.44%)	94(41.5%)
Involves ipsilateral adrenal gland or invades beyond Gerota's fascia,T4	62(27.4%)	25(11.06%)	3 (1.3%)	90(39.82%)
Total	151(66.8%)	71(31.41%)	4(1.8%)	226(100%)

Table 2: *Association of subtype of tumor with Grade (p=0.261)*

Grade	Subtype			Total
	Clear cell	Papillary	Chromophobe	
Low grade (Grade I,II)	43(19.02%)	13(5.75%)	1(0.44%)	57 (25.2%)
High Grade (Grade III,IV)	108(47.7%)	58(25.6%)	3(1.32%)	169 (74.8%)
Total	151	71	4	226

Table 3: *Association of RCC Subtypes with Smoking (p=0.013)*

Smoking	Subtype			Total
	Clear cell	Papillary	Chromophobe	
Smokers	74(32.7)	43(19.02%)	3(1.32%)	120
Non-Smokers	77(34.02%	28(12.38%)	1(0.44%)	106
Total	151	71	4	226

cases at T4 stage. Similarly when subtype was cross-tabulated with grade (p=0.261,Table II), there were 108(47.7%) cases reported as high grade clear cell and 43(19.02%) cases were low grade clear cell carcinoma. Papillary high grade tumors were 58 (25.6%) and 13(5.75%) were low grade tumors. The cases of chromophobe carcinoma with high grade nuclear features were 3(1.32%) and low grade were 1(0.44%).

Discussion

Tobacco use registers as a high risk, which is still avertable habit in industrialized nations. Tobacco is a well-known fount of aromatic hydrocarbons and nitroso compounds, all of which lead to bulky DNA adduct formation, single- and double-stranded DNA breaks, and base modifications, and hence can cause DNA damage.[10] These events complement an individual's tendency of genetic predisposition to smoking-related cancer like VHL mutations.[11] In US, the average age for diagnosis of RCC is 6412. Clear cell subtype manifests the greatest association with many modifiable and non-modifiable risk factors and is the most common histological subtype, succeeded by papillary and chromophobe.[13] A study conducted in India also demonstated clear cell variety to have association with advanced stage.[14] Another study from India showed 52.79 years to be the mean age of presentation. A study in Pakistan in the year 2011 revealed that the mean age of presentation was 56.3 years which was quite similar to Indian study as compared to the West that showed 64 years as mean age. The most common was Grade II (60%) followed by grade III (36%) and then grade IV (4%). Again in this study, clear cell variant once again appeared

as the most frequent subtype (n=9; 69.2%).[15] The chromophobe type of renal cell carcinoma was very rare in their study, similar to our findings.[16]

Considering the trends of association of various subtypes with the stage of RCC as noticed in the previous studies, the clear cell subtype showed a less favorable outcome compared with papillary and chromophobe subtypes, and is more expected to present at an advanced stage, and shows a greater inclination towards metastasis.[17] A case report demonstrated RCC invading uterus, fallopian tube and bilateral ovaries was of clear cell subtype demonstrating grade 3 and final pathologic stage as pT4N1M1.[18] These studies support our findings of clear cell carcinoma being associated with advanced stages (T3 and T4) with p-value of 0.018(p<0.005) as 64(28.3%) and 62(27.4%) of the cases of RCC are of clear cell carcinoma in the T3 and T4 stages respectively versus only 10(4.42%) and 15(6.63%) cases (clear cell carcinoma) in T1 and T2 stage. Pattern of involvement of other subtypes were also observed in some other studies showing tumor stage was significantly associated with histopathology (p< 0.001).They observed clear cell histology, of whom 28% had T3, T4, N or M disease, while patients with papillary and chromophobe varieties, in comparison, had less odds to present with advanced disease (17.6% and 16.9%, respectively).[19] Our findings oppose the results of the above mentioned previous studies as papillary and chromophobe subtypes are also significantly associated with large tumour size or advanced stage with 29(12.83%) and 25(11.06%) cases of papillary subtype being in T3 and T4 stage versus only 9(3.98%) and 8 (3.54%) in T1 and T2 stages. Similar trends were observed in the chromophobe subtype with 1(0.44%) and 3(1.33%) cases being in T3 and T4 stage and no case in T1 and T2 stage.

Viewing the trends in association of subtype with grade, our studies clearly negate the results of previous studies where they found major link between grade and subtype with 94.7% of clear cell variant were cases that showed grade 3 or 4 tumors compared with only 28.8% and 32.7% of papillary and chromophobe cases, respectively (p <0.001) by finding no significant association between histopathology subtype and grade with p-value of 0.457 (p>0.005) as all the three subtypes showed an equal percentage of high and low grade feature in them and overall both papillary and chromophobe appeared to have shown high grades as 58(25.6%) cases were of high grade papillary (compared to only 13(5.75%) of low grade papillary cases) and 3(1.32%)

cases were high grade chromophobe (vs only 1(0.44%) cases of low garde chromophobe carcinoma.

In an analysis of smoking's association with subtypes in already done studies the USKC (United States Kidney Cancer) investigation denoted that smoking status didn't have any association with any RCC sub-types, although, current smokers were found to be at increased risk for all subtypes but chromophobe RCC which is highly in accordance with our findings of no significant association of smoking with any particular subtype having the p value of 0.351 (p>0.005) and an equal incidence of almost any subtype in patients irres-pective of their smoking status with least incidence of chromophobe subtype in both smokers and non smokers with 1.36% and 0.44% respectively.[20] As claimed by another study, active smoking happens to be more common with clear cell (23%) or papillary (26%) renal cell carcinoma than chromophobe renal cell carcinoma (6 %) (p< 0.05 vs clear cell or papillary). Any coupled history of smoking was comparatively less common with chromophobe (26%) vs clear cell(56% p=0.003) or papillary 58% (p=0.001) histology.[4] Our study distinc-tly opposes the findings of this study by having no association of smoking with any particular subtype with smokers and non-smokers both at equal risk of developing the clear cell (32.7% cases in smokers vs 34.07% in non-smokers), papillary (19.02% cases in smokers vs 12.38% in non-smokers) and chromophobe (32% vs 0.44%). Although all three high grade and high staged chromophobe carcinomas are associated with smoking, the number of cases is too low to infer any definitive conclusion.

In another study, active smoking was found to be more common in patients with clear cell RCC and papillary RCC than those with chromophobe RCC.[4] Our findings revealed that chromophobe carcinoma, all three cases were associated with history of smoking. No other specific subtype had any association with smokers as both smokers and non-smokers with comparable occu-rrence of almost all the subtypes.

Conclusion

Chromophobe carcinoma of kidney is associated with smoking, higher grade and higher stage. We found no significant association of any other specific subtype with gender, smoking and grade of RCC.

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