Pathological Features of Renal Cell Carcinoma, A 10- Year Tertiary Centre Experience

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ABSTRACT

Background: Malignant kidney tumors are not uncommon worldwide. They are heterogeneous but have unified pathological prognostic features.

Objectives: we focused on studying renal tumor in our centre, a large tertiary centre in the western region of Saudi Arabia, addressing gross and microscopic features of prognostic significance.

Methodology: Nephrectomies due to renal parenchymal neoplasm from July 2010 to June 2020 in King Abdulaziz University Hospital were studied. Patients' demographic and radiology data were extracted from the Hospital data system. Pathological features were reviewed by combining the radiology, gross and microscopic features and applying the recent diagnostic, grading, and staging guidelines.

Results: 146 out of 154 renal neoplasms were malignant. The patient's average age was 53 years. 62% of the patients were male. Clear cell renal cell carcinoma is the most common subtype (66%), followed by papillary and chromophobe renal cell carcinoma. 59% of the tumors have low nuclear ISUP grade. 55% of tumors were pT1 stage. Two cases were up-staged according to the updated guidelines for renal vein invasion. A shift toward partial nephrectomy is observed in the second five years.

Conclusion: The patients' demographics and pathological tumor features are similar to the results of regional studies in our country and the Middle East. The updated staging guidelines modified the stage of two tumors. Lacking information such as tumor laterality may impact the patients' follow-up. A shift toward partial nephrectomy reflects early-stage tumor detection and advanced radiology modalities and will improve the patient's outcome and save the residual kidney function.

Key words: Clear cell renal cell carcinoma, Chromophobe RCC, ISUP grading, Papillary RCC, Renal cell carcinoma, RCC staging, RCC prognosis, Translocation RCC

INTRODUCTION

According to the recent united states global cancer statistics, kidney cancer is the 7th and the 9th most common cancer among males and females, respectively. The incidence and mortality rate for renal cell carcinoma (RCC) between 2015 to 2020 is 17.3 and 3.5 for both sexes, respectively. A decline in mortality rate by approximately 2% from 2016 through 2020 in renal cell carcinoma is described, which is explained by the significant advance in treatment modalities[1]. In the Saudi population, the incidence of kidney cancer is 3.4%, estimated to be 24.485 cases in 2020[2]. The mortality rate for kidney cancer is 2.9%, lower than other more prevalent tumors such as breast and colon cancer[3]. Despite increasing incidence in addition to tumor heterogenicity, this decrease in mortality rate derived our attention to describing the anatomical and microscopic renal cell carcinoma features in our center. We focused on prognostic significance parameters and traced the recent advances and current suggestions to grading and staging that would impact the patients' outcomes and applied them as much as possible.

METHOD

The total number of nephrectomies performed King Abdulaziz University Hospital between the first of July 2010 & first of June 2020 exceeded 250 cases. The resections among pediatrics and those performed due to mesenchymal tumors and other non-neoplastic causes were excluded. A few cases with no available slides or block for review were also excluded from the study. The patients' demographics, clinical information, and related radiological information were extracted from the hospital data system. Gross features of tumors were extracted by carefully reviewing the pathology reports available in the Hospital data system. Glass slides of the cases were pulled from the Histopathology store and scrutinized by the author, and the microscopic findings were precisely described. The related immunohistochemistry slides of the cases were also reviewed when needed. Information in the radiology reports, gross description, and the findings on the glass slide examination were combined, and all the prognostic significance parameters were measured as precisely as possible. The tumors were

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classified according to the new WHO classification. This update was issued by the Genitourinary Pathology Society (GUPS) and released in 2021. It reviewed the existing 2016 tumor classification regarding diagnostic criteria, molecular subtypes, and nomenclature. Therefore, the cases of unequivocal diagnosis of papillary renal cell carcinoma typed I and II were lumped into one category according to this update. Also, the recommended immunohistochemistry and molecular tests were performed for certain tumor subtypes[4].

RESULTS

The total number of cases involved in the study is 154 cases. The patients' age ranges from 18 years to 89 years. The average age is ~ 53 years. The male patients represented 62% (96/154) of the patients, while the female represented 38% (58/154). The average age for the male patients was 53 years, while the female age range was three years younger.

The type of surgical resection was radical nephrectomy in 70% (107/154) of the patients and partial nephrectomy in 30% (47/154). The surgical approach has changed between the period 2010-2015 and 2016-2020 since the number of partial nephrectomy procedures has increased, and this approach managed 49% of the cases during the second period compared to 12% only in the first period.

Regarding the anatomical characteristics of the tumor, the number of left-side tumors is slightly more than the right-side ones. 53% (81/154) was left kidney tumors while 46% (71/154) was right kidney tumors.

The laterality could not be decided in two cases since it was not mentioned in the pathology report, radiology records or operative note. Tumor arises from the upper pole of the kidney in 34% (53/154) of the cases, from the lower pole in ~ 29% (44/154) of the cases, and from the middle pole in ~14% (21/154) of the cases. Most of the kidney parenchyma was involved by the tumor in four cases. The tumor site was not specified in the pathology report, radiology record or operative note in ~21% (32/154) of the cases.

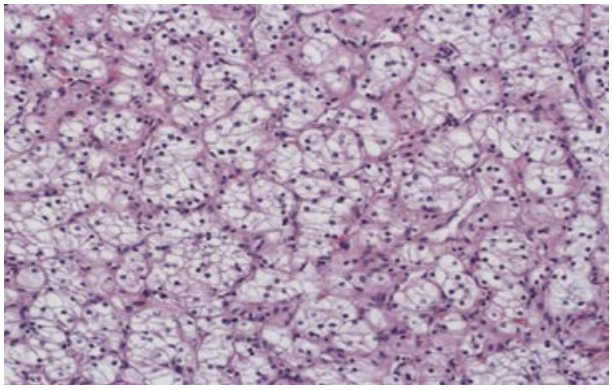
The tumor size ranges from as small as 1 cm to as large as 20 cm. The average size is 6 cm. In most cases, the histopathological diagnosis is clear cell carcinoma (CCRCC), followed by papillary renal cell carcinoma and chromophobe renal cell carcinoma. The details are listed in Table 1.

Table 1: The tumor diagnosis of all the 154 neoplastic cases

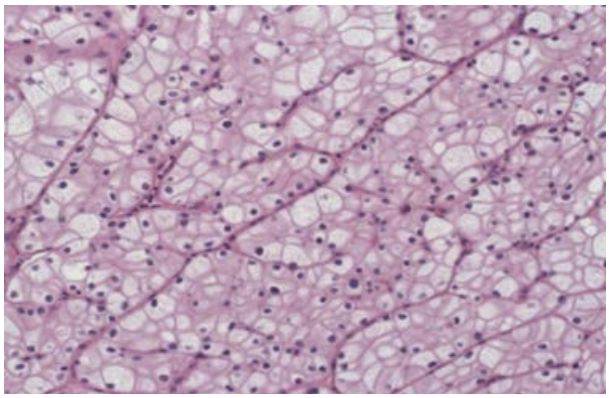
Diagnosis	Number of cases
Clear cell renal cell carcinoma	97
Chromophobe renal cell carcinoma	19
Papillary renal cell carcinoma	18
Oncocytoma	7
Clear cell papillary renal cell carcinoma	2
Mucinous tubular & spindle renal cell carcinoma	2
SMARB1-deficient renal cell carcinoma: Renal Medullary carcinoma	1
Hereditary renal carcinoma syndrome/ Fumarate Hydratase deficient/ hereditary leiomyomatosis and renal cell carcinoma.	2
Hereditary renal carcinoma syndromes/ SDH deficient RCC	1
TFE3 rearranged renal cell carcinoma.	2
Two primaries in the same patient (Clear cell and papillary renal cell carcinoma)	1
Extensive sacromatoid differentiation	1
Unclassified renal cell carcinoma	1

The microscopic appearance of the tumors diagnosed is demonstrated in Figure 1.

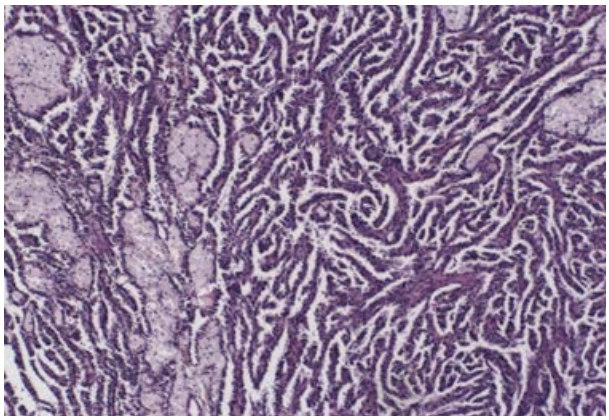
Figure 1: The microscopic pictures of the most common and some of the recently described renal cell carcinoma studied in this project



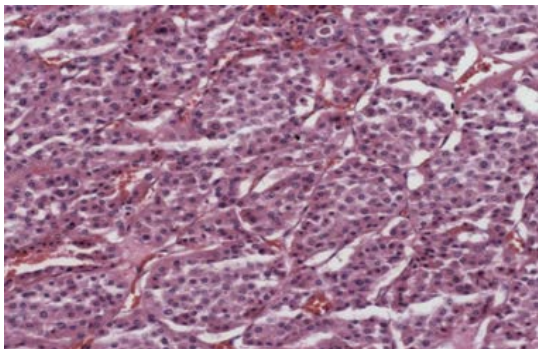
A- Clear cell renal cell carcinoma; nest of cells with clear cytoplasm.



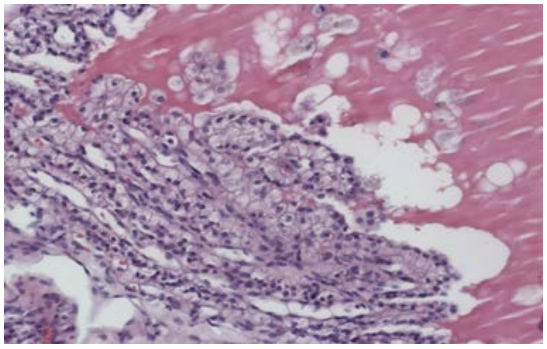
B- Chromophobe renal cell carcinoma; tumor cells with prominent cell borders, dark raisionoied nuclei.



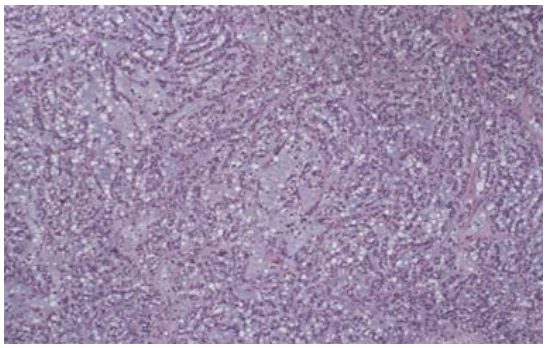
C- Papillary renal cell carcinoma: papillary architecture with foamy macrophages within the fibrovascular stalk.

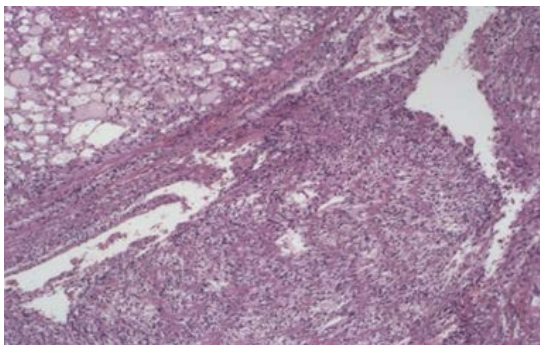


D- Oncocytoma: nests of cuboidal cells with round eosinophilic cells (oncocytes) with dense granular cytoplasm, round nuclei with regular with even chromatin, and small but conspicuous nucleoli.

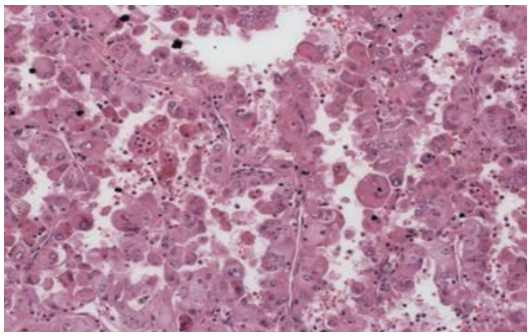


E. Clear cell papillary renal cell carcinoma: Focally branched papillary architecture with hypocellular fibrovascular projecting into cystic spaces. Cores are lined by cuboidal to flat cells with clear cytoplasm with characteristic luminal polarization of nuclei.

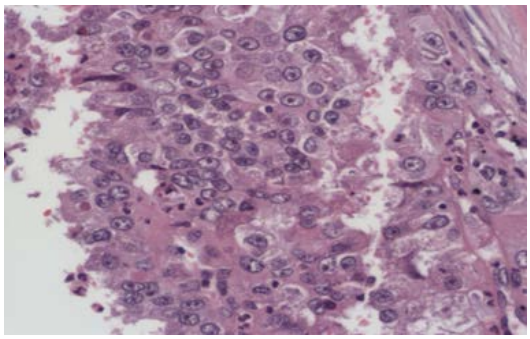




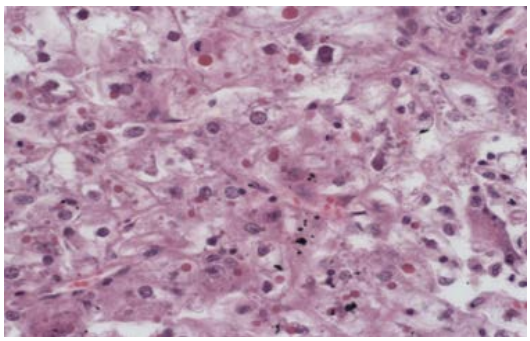
F. Mucinous tubular and spindle cell renal cell carcinoma: a) cord-like growth formed of uniform, bland, low cuboidal cells epithelial cells with eosinophilic, focally vacuolated cytoplasm myxoid matrix. b) Anastomosing spindle cells beside tubulo- reticular growth pattern.



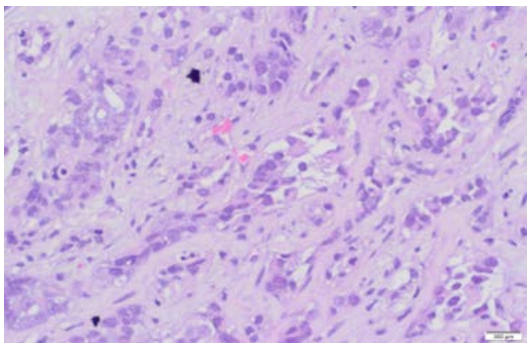
G. TFE3 rearranged renal cell carcinoma: Papillary growth formed of discohesive pseudostratified epithelial cells with voluminous dense eosinophilic cytoplasm, and high grade nuclei.



H. Hereditary renal carcinoma syndromes/ Fumarate Hydratase deficient/ hereditary leiomyomatosis and renal cell carcinoma: Tumor cells with characteristic prominent nucleoli, occasionally surrounded by clear halo.



I. Hereditary renal carcinoma syndromes/ Succinate dehydrogenase deficient tumor: The epithelial cells are of variable growth pattern, but show the characteristic flocculent cytoplasmic vacuoles. The nuclei are round with smooth contours and fine chromatic pattern.



J. Medullary carcinoma: Cords and poorly formed glands of pleomorphic cells, in a desmoplasia.

The International Society of Urological Pathology (ISUP) grading system was used in all the cases[5]. The old cases, initially graded according to the Fuhrman grading system, were regraded upon reviewing the slides. Most tumors fell in ISUP grades I & II. Further details are shown in Table 2.

Table 2: The tumors ISUP nuclear grade distribution

ISUP Grade	Number of Cases
Grade I	29
Grade II	47
Grade III	17
Grade IV	23

Rhabdoid differentiation and Sarcomatoid differentiation are present in 13% (19/146) and 6% (9/146) of the malignant cases, respectively (Figure 2). The presence of necrosis and its extent is remeasured in each case by combining the gross description and the findings on the glass slide examination. Necrosis is present in 39% (57/146) of the malignant cases. The extent of necrosis varies from 10% to 80% of the tumor mass. Tumors with ISUP grades III & IV represents 57% (30/53) of the tumors with necrosis, while tumor with ISUP grade I & II represents 21% (11/53) of tumors with necrosis. The pathological T tumor stage is shown in Table 3.

Table 3: The tumors pathological stages

pT stage	Number of cases
T1a	50
T1b	31
T2a	7
T2b	3
T3a	37
T3b	2

Details about renal vein invasion, including retrograde one, perinephric fat, and renal sinus invasion, are shown in Table 4. Only six tumors (4%) showed regional lymph node involvement by the tumor, and four cases (~3%) presented with distant metastasis upon tumor detection.

Table 4: The frequency of perinephric fat, renal sinus and renal vein invasion, which categorize the tumors in pT3 stage, some tumors show more than one feature

Tumor extent	Number of cases
Perinephric fat invasion	11
Renal sinus invasion	22
Renal vein invasion	24
Retrograde renal vein invasion (tumor nodule)	2

DISCUSSION

The tumor gender distribution concurs with the percentages described by a previous study performed in a tertiary canter within the central region of our country, which demonstrated that nearly 60% of patients with renal cell carcinoma were male, and nearly 40% of them were female among 371 patients with renal cell carcinoma[6]. Also, a study on a smaller population in the western region demonstrated that 66% of the patients were male and 34% were female among 42 patients[7].

The average patient's age is 52.7 years old, which is relatively younger but not very far from the previously described study on a smaller scale population in the western region of our country[7]. In this study, the average age was 54.5 years old, and the study was performed on a larger scale in the central region of our country, where the average age was 56.3 years old[6]. In our study, the female average age is three years younger than the male patients. This younger female age at diagnosis could be explained by the more frequent female exposure to medical and radiological assessment, especially in childbearing, and perimenstrual age in which other incidental abnormalities could be discovered.

Although the information about the tumor laterality and its anatomical location within the kidney may not be of that prognostic significance, lacking this information in the records drew our attention to the significance of record completion, especially the pathology report in which the tumor laterality is an essential element. In our study, the left kidney is more affected than the right. 53% (81/154) was left kidney tumors while 46% (71/154) was right kidney tumors. This finding contrasts with the previous two studies performed in the Middle East and described this entity. For instance, a study performed in Pakistan showed that two-thirds of the tumor was in the right kidney[8]. Also, another study in Oman found that tumor is slightly more frequent on the right side, with 52.2% of tumor in the right kidney[9]. Renal cell carcinoma arises more frequently from the upper pole of the kidney in our study, which is in concordance with what was described by the study performed in Pakistan[8].

CCRCC is the most common tumor subtype diagnosed in our study. It represents 66% (97/146) of the malignant tumors. Most of the previously published papers described the epidemiology of renal cell carcinoma has shown similar finding. The two studies performed in our country have proved this[6,7]. Also, studies performed in other countries of the Middle East, such as Oman, Pakistan and Lebanon, showed that CCRCC represents 59.1%, 55%, and 59.2% of the total cases of renal cell carcinoma, respectively[6,7,10]. Also, data from Europe in a study performed in France showed that CCRCC represents an even higher percentage (92%) among cases of RCC. Another study from the West performed in the USA showed that the percentage of CCRCC is 75% of the studied RCC cases[12]. The percentage of CCRCC is higher in the West than in the Middle East. Such variation may be explained by factors affecting the incidence of other RCC types, such as demographics, socioeconomics, and geographics. Also, genetic factors can play a significant role, especially in the middle east, where consanguinity is still prevalent.

CCRCC is one of the most aggressive tumors. It develops due to a mutation in the von Hippel-Lindau (VHL) tumor-suppressor gene region (chromosome arm 3p). This mutation accounts for 45% of clear renal cell carcinoma cases. It has high hematogenous metastatic potential[13]. In our study, four of the 147 patients with malignant tumor presented with distant metastasis upon tumor detection; all were CCRCC.

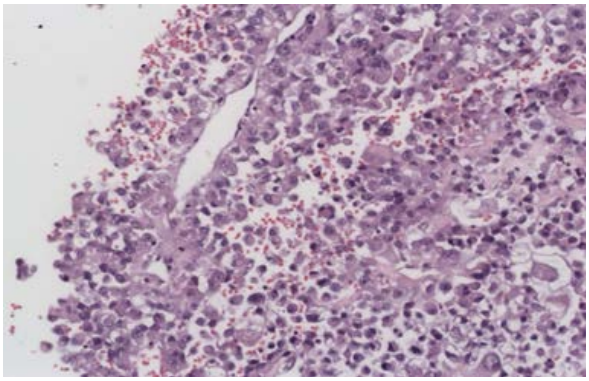
Interestingly one patient presented with two different tumors; the larger one is CCRCC measuring 5.5 cm in maximum dimension, while the smaller one is papillary renal cell carcinoma, measuring 1 cm in maximum dimension. These tumors are of unrelated genetic pathogenesis, as previously stated for CCRCC is initiated by VHL gene mutation. Papillary renal cell carcinoma is associated with gain in chromosomes 7, 17, 12, 16 and 20. Other chromosomal gains are also described for chromosomes 2 and 3[14,15,16].

However, it has been recently discovered that the genetic make- up of papillary renal cell carcinoma is further complicated, and there is an association with mutations in protooncogenes such as MET and CDKN2A genes[17]. None of those genetic disorders has been described in CCRCC, indicating that this patient has two tumors of different natures.

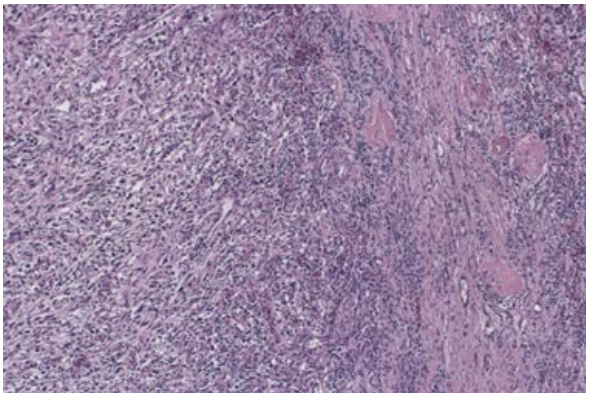
A single case of medullary renal cell carcinoma was diagnosed in a patient with sickle cell trait. The rest of the tumors are much less common than CCRCC, papillary, and chromophobe renal cell carcinoma and are under the umbrella of the less common renal cell carcinoma. Challenges in tumor classification were faced in two cases. The first case showed an overlapping feature between clear cell and papillary renal cell carcinoma. This case could not be classified despite extensive sampling, histochemistry and molecular work-up. The second case showed only extensive Sacromatoid differentiation with extensive necrosis. No epithelial elements could be identified despite extensive sampling. However, immunohistochemistry could prove its epithelial nature by positive staining for pan-cytokeratin and variable positive staining for low molecular weight cytokeratin. Molecular tests for clear cell and papillary renal cell carcinoma were equivocal. Unfortunately, next generation sequencing is unavailable in our centre, so the definitive diagnosis of both cases cannot be attained with certainty. However, both showed aggressive gross and microscopic features with large tumor size, 40% necrosis in the first case and 80% in the second and pT3 stages.

Sacromatoid and rhabdoid differentiation is associated with aggressive tumor behavior and poor patient outcomes, Figure 2. This fact was proved in more than one study[18-20]. Due to its prognostic significance, the percentage of cases with such differentiation in our study is carefully measured. It is present in less than 20% of the malignant tumors. According to ISUP nuclear grade, the tumors that showed this differentiation are classified as ISUP grade IV[21].

Figure 2: The microscopic appearance of Rhabdoid and Sarcomatoid differentiation



A- Rhabdoid differentiation: defined by cells with abundant eosinophilic cytoplasm, eccentric nuclei and prominent nucleoli.



B- Sacromatoid differentiation: Fascicles of spindle cells with elongated hyperchromatic dark nuclei.

Tumor necrosis is also an independent prognostic factor, and its presence in a renal tumor, regardless of its extent, is associated with poor outcomes. This fact is well-studied for clear cell and chromophobe renal carcinoma[22]. However, another study measured the impact of necrosis extent on the overall patient outcome. This study suggested using 20% as a cutoff percentage for the necrosis extent to be significant and impacts the outcome[23]. Moreover, based on that, attention was paid to necrosis presence and its extent. We measured it as accurately as possible by combining the gross and microscopic findings. Necrosis is present in 39% of malignant tumors, and its extent varies from 10-80%. Of those tumors with necrosis, 61% (35/57) showed at least 20% necrosis, potentially impacting the outcome than those with less necrosis extent[23]. Another study addressed the prognostic significance of the ISUP grade and necrosis and proposed the classification of the tumors by combining these two factors. Our study's findings concurred with this proposed grading as most of the tumors with necrosis (57%) clustered in the ISUP nuclear grade of III and IV, and 21% showed ISUP nuclear grade of I and II[24].

The tumor stage is decided by tumor size and extent. These two elements are well-studied in our cases. As stated in Table 3, 55% (81/146) of the tumors are stage pT1. Data from the regional studies showed that most of the tumors have fallen in stage pT1. For example, the study performed in the central region of our country showed that 40% of the tumors are stage pT1[6]. Data from Oman also showed an even higher percentage for stage pT1, and 88% were in this early stage[9]. This dominant early-stage tumor could be due to early tumor detection, especially in the era of advanced radiological modalities. Also, it may reflect younger age population in our country and its neighbors. In our centre, most tumors are evaluated by at least two radiological methods, mainly ultrasound and computed tomography. In some cases, MRI was also used. This early tumor detection has a dramatic impact on patient management. For instance, the surgical approach has shifted from radical nephrectomy to partial nephrectomy, which saves the kidney, and the adrenal function. Not only that but some cases of partial nephrectomy are done via a conservative approach, such as laparoscopy with the aid of a robot in some cases. This approach has less morbidity, mortality, and hospitalization period, with high applicability for enhanced recovery after surgery[25]. From 2010 to 2015, partial nephrectomy was the surgical approach in 18% of the tumor cases, while in the next five years, the percentage of partial nephrectomy jumped by 33%, and this conservative approach treated 51% of the tumors.

Tumor extension to perinephric fat, renal vein, and renal sinus was described well in Table 4. As any of these findings will qualify for tumor stage pT3, which dramatically impacts the patient's outcome, this value was carefully evaluated and measured in all cases[26]. The hypothesis of multiple tumor nodules or tumor nodules that bulge within the tumor capsule or the perinephric fat may represent a retrograde renal vein invasion rather than two tumor foci, as suggested by Sean Williamson is considered in our study[27]. Also, the updated criteria of renal vein invasion, which no longer requires the presence of a muscle wall nor the gross identification of renal vein branch involvement by the tumor, was followed in evaluating the cases for renal vein invasion[28]. By careful evaluation of the gross features of the tumors and correlation with microscopic findings, retrograde renal vein invasion could be identified in two cases. These two cases were initially described as multiple tumor nodules; however, the fact that these are retrograde renal invasions rather than multiple tumor nodules has changed the tumor stage, subsequently correlating with the patient's outcome. The tumor nodule within the renal vein branch lacking continuous muscle coat is illustrated in Figure 3.

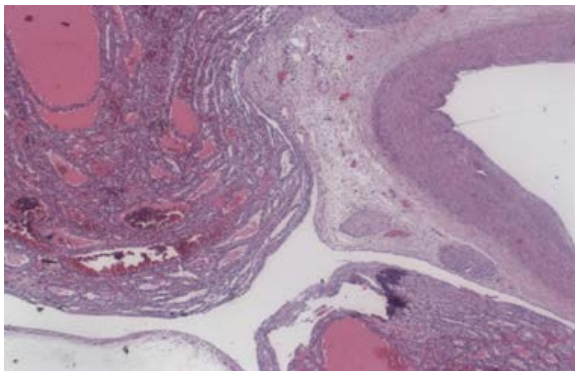


Figure 3: Tumor nodule within renal vein branch beside the renal artery. The renal vein branch is lined by endothelial cells and has discontinuous smooth muscle coat

CONCLUSION

The prognosis of renal cell carcinoma has improved recently, and the survival rate is excellent compared to other more prevalent tumors. In this study, we described the cases of renal cell carcinoma in our centre by addressing the gross and microscopic features of prognostic significance. Also, we applied the most recently proposed grading and staging guidelines. The recent updates regarding renal vein invasion criteria and the suggestion of measuring the necrosis extent were applied. Tumor stages were updated in two cases accordingly. Our study's findings concurred with this proposed grading system that suggests combining necrosis in the grading system as most of the tumors with necrosis (57%) clustered in the ISUP nuclear grade III and IV, and 21% of them showed ISUP nuclear grade of I and II.

We found that in our population, the affected female is relatively younger than the male, and the average patient's age is relatively younger than that described in regional and international studies. This may reflect dominant young population in our country, in addition to early tumor detection. Tumor subtypes and stages concur with regional data performed in our country and other countries in the Middle East. Molecular studies are needed in some instances for accurate classification. Report completion is essential for patient care since some information is missing from the record. However, they are not necessarily prognostic significant, such as tumor laterality and the affected kidney pole. Nevertheless, they are still essential for the record regarding the potential of future procedure-related complications such as tumor laterality and the affected renal pole.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

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Competing Interest: None

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