Clinicopathological study of renal tumours in surgically excised specimens

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**ABSTRACT**
A study on Clinicopathological Study Of Renal Tumours In Surgically Excised Specimens was conducted for two years from June 2016 to May 2018. The study was on twenty-eight surgically excised specimens of renal tumours in the Department of Pathology of Krishna Institute of Medical Sciences at Karad District in Satara, Maharastra, India. The observed results stood as 75% of Radical Nephrectomy, 17.85% of renal biopsies and partial Nephrectomy in 7.14% cases. The reading revealed 28.5% of cases, that is, a maximum number were found in their 6th decade of life. The rest of the cases, 21.42% were either septuagenarian or quadragenarian. The male preponderance was noted with Male: Female ratio 2.5:1. Out of 28 cases of renal tumours, 50% of cases had flank pain, 28.57% cases with flank pain associated with hematuria in a maximum number of instances had issues that were involving the left-sided kidney. The most common site for tumour involvement was upper pole comprising of 35.71% followed by the lower pole in 28.57% of cases. In a maximum number of instances, grossly the size of tumour ranged from 0-4 cm. Out of all malignant tumours, Renal Cell Carcinoma-RCC was the most common tumour comprising (75%). The majority (42.10%) of renal cell carcinomas were of Fuhrman nuclear grade II. Majority of cases (56.5%) were at TNM stage I. A detailed histopathology examination and routine H and E staining help to diagnose accurately and to determine the various histological type, subtype. It also helps to evaluate other histopathological determinants. The clinical results shifts as per the histologic subtypes.

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**INTRODUCTION**
Historically, Isak Denison defined kidneys as “An ingenious machine designed to turn with infinite artfulness, the red wine of Shiraz into urine”. Human kidneys serve to convert more than 1700 litres of blood per day into more than one litre of urine (Alpers *et al.*, 2010). The kidney can be involved in various pathological processes. Some such may require surgical removal. Neoplastic injuries are as healthy as different sores of the kidney (Yasir *et al.*, 2013). Renal tumours contain a diverse range of neoplastic sores with designs that are generally unmistakable for kids and grown-ups. A wide assortment of both considerate and threatening tumours emerge from various parts of the renal parenchyma, quite cylindrical epithelium (Alpers *et al.*, 2010; Eble *et al.*, 2004).

Worldwide, the renal tumour is the 13th most common malignancy and accounts for approximately 2-3% of adult malignancies and 80-85 % of malignant kidney tumours which are having 2% of overall can-
cer mortality (Ferlay et al., 2010; Bilal et al., 2017). Thus the surgical removal of these tumours is the mainstay of treatment of localised renal tumours, and it also provides survival benefit in the setting of metastatic disease (Pradhan et al., 2009). Despite new imaging techniques like CT/MRI, a detailed and meticulous histopathological examination of surgically excised renal specimens is essential to establish the following

1. Histologic type, subtype and to record accepted histopathological prognostic determinants, i.e. tumour size,
2. Nuclear grade and stage in case of malignant renal neoplasms (Algaba et al., 2004; Juan, 1942).

The present study was undertaken to become familiar with the morphological features of renal tumours and to correlate them with clinical presentation.

Aim
To study various clinical presentations of renal tumours and their histopathological spectrum.

Objectives
1. To study the clinical presentation of various renal tumours.
2. To study in detail about morphological features of renal tumours.
3. To evaluate histopathological types.

MATERIALS AND METHODS

The present study entitled “Clinico-pathological study of renal tumours in surgically excised specimens” was undertaken in Histopathology section of Department of Pathology, Krishna Institute of Medical Sciences, Deemed To Be University, Karad for two years, i.e. from June 2016 to May 2018. The data was collected from 28 cases of surgically resected renal tumour specimens and biopsies sent in 10% formalin solution. From the requisition forms sent along with the specimen, purposive information was collected. The information included age, sex, chief complaints, laboratory investigations, pre-operative imaging (USG/CT Scan) and intraoperative findings.

Inclusion Criteria
All the surgically excised renal specimens of renal tumours.

Exclusion Criteria
Renal lesions other than renal tumours.

Grossing
The detailed gross examination was done as per CAP guidelines, and findings were noted. The specimen was measured for weight and dimensions of tumour. The tumour extent, size, location, gross appearance, necrosis, haemorrhage, invasion into the capsule, perirenal tissue, calyces, pelvis and renal vessels were studied.

The kidney was cut sagitally, and pelvis, calyces and ureter were opened. The specimens were also examined for perirenal lymph nodes and surgically resected margins of the ureter. The entire specimen was embedded and sectioned at multiple levels. After the complete fixation of the specimen, it was sectioned at 3-5 mm intervals. After gross examination of fixed specimen was done, the sections were taken from representative sites as follows:

1. Tumour including interface with surrounding kidney, Gerota's fascia, perinephric fat.
2. All of the grossly different appearing areas of the tumour
3. Renal pelvis
4. Uninvolved kidney
5. Ureter
6. Renal artery and renal vein
7. Other lesions if present
8. Lymph nodes
9. Other tissues submitted with specimens

These sections were further processed into an automated tissue processor (Tissue Tek RX11A). After processing, parts were embedded in paraffin to make paraffin blocks. These squares were then sliced sequentially in three to five-micron thickness utilising Leica microtome to get ready slides. Slides were then recoloured utilising routine Hematoxyl in& Eosin stain and afterwards mounted with DPX. Special stains and immune histochemistry were used as and when required.

Also, clinical, laboratory data and slides were retrieved from the archives for the study. Cases in which the slides were not available, paraffin blocks of the sections of the specimens were retrieved. Additional sections were made from the retrieved paraffin blocks. All the details were entered, and according to histopathological diagnosis, classification was done, and analysis of the data was carried out.

Equipment

1. Fixatives: Buffered formalin solution 10% - For fixation of the specimen.
2. For section preparation: Routine paraffin processing.
3. For Staining: Hematoxylin and Eosin stain, special stains if required.

OBSERVATION AND RESULTS

During the period of 2 years from June 2016 to May 2018, total 28 surgically excised renal tumour specimens, including nephrectomies and renal biopsies, were studied. We analysed these surgically excised renal tumour specimens received in the Histopathology section of Department of Pathology according to nature of surgical excision as follows. Out of 28 samples, 21 (75%) were radical nephrectomy specimens, 2 (7.14%) were partial nephrectomies, and 5 (17.85%) were excisional renal biopsies. The Nephrectomy (partial and radical) specimens were 82.14% among the renal samples received in the histopathology section.

The above Table 1 reveals that most common age group for renal tumours was seen in between 51 and 60 years of age while least was seen in 2nd and 3rd decade of life. Following graph is showing the same. Out of 28 cases of renal tumour, most of the patients, i.e. 14 (50%), were diagnosed as Clear cell RCC. Maximum cases of Clear cell RCC were seen in the age group of 51-60 years.

Only the case of Nephroblastoma seen in the age of group 0-10 years. The above Figure 1 reflects that the male predominance was noted in the study. 20 (71.42%) cases of renal tumours out of 28 were constituted by males and remaining 8 (28.57%) cases were females. Male: Female ratio in our study was 2.5:1.

Clinical representation of renal tumours

Out of 28 cases, 14 (50%) patients presented with flank pain, whereas 8 (28.57%) patients presented with flank pain associated with hematuria. Only 2 cases (7.14%) presented with the clinical triad, i.e. flank pain, abdominal mass and hematuria. Out of 28, one example was an incidental finding.

Laterality of renal tumours

All the cases of renal tumours were unilateral. In these cases, left-sided involvement was found in 15 (53.57%) cases while right-sided renal involvement was seen 13 (46.42%) cases.

Site of renal tumours

In the current study, the upper pole of the kidney was the most common site for the tumour comprising 10 (35.71%) cases followed by a lower pole which was seen in 8 (28.57%) cases. Involvement of mid pole was found in 7 (25%) cases. The case of Angiomyolipoma showed entire kidney involvement while the upper pole and mid pole of the kidney was seen to be involved in 2 (7.14%) cases.

Size wise distribution of renal tumours

Out of 28 specimens, the size of the tumour in received specimens was noted, and it was found that in 18 cases the size of the tumour was less than 4 cm comprising 64.28% of total cases. In 5 cases (17.85%), the tumour size was in the range 4-7 cm. In 2 cases (7.14%), the size was in between 7-10 cm and size more than 10 cm was seen in 3 cases (10.71%). Following graph is showing the same.

Frequency of type of renal tumours

Out of 28 renal specimens, two were benign tumours, 26 were malignant tumours of the kidney. The frequency of benign tumours was 7.14%, and the rate of malignant tumours was 92.86%.

Histological classification

Out of 28 cases of renal tumours, malignant tumours were more common. Among the malignant tumours, renal cell carcinomas were the commonest, and the most prevalent subtype of RCC was found to be Clear cell RCC which was seen in 16 (57.14%) cases. Papillary RCC and Unclassified RCC was seen in 2 (7.14%) cases each, and one case of carcinoma of collecting duct was noted.

Benign renal tumours in study

Angiomyolipoma

In the present study, we found one case of Angiomyolipoma of the kidney. The patient was a 65-year-old male who came with the complaint of left-sided flank pain for a month.

USG findings revealed a mass in the left-sided kidney was almost replacing it entirely. The radical Nephrectomy was done for the same. Gross examination showed a well-circumscribed, non-encapsulated, soft mass replacing the entire kidney.

The cut surface was greyish-white with grey-yellow areas at places. Microscopic examination, in this case, showed a tumour composed of smooth muscle cells, islands of mature adipose tissue and thick-
walled blood vessels. Smooth muscle component arising from vessel walls showed hypercellularity. There was no nuclear atypical or mitosis.

**Oncocytoa**

In the present study, we found a single case of Oncocytoa of the kidney. Fifty years old male patient presented with left-sided flank pain associated with hematuria. USG examination revealed a benign renal mass in the lower pole of the kidney. Partial nephrectomy was done. Gross examination revealed a well-circumscribed, solid homogeneous brown-yellow coloured tumour measuring 3 x 2.8 x 2.7 cm.

Microscopic examination showed a tumour consisting of round to polygonal cells with abundant, intensely eosinophilic and granular cytoplasm arranged in sheets, nests and alveolar pattern. Tumour cells were with evenly dispersed chromatin. Nuclear membrane was with a smooth contour, and no atypical was noted. The invasion was not seen in surrounding renal parenchyma.

**Metastatic adenocarcinoma of the kidney**

In the current study, we noted a case of metastatic renal adenocarcinoma in 66 years old male patient. He was operated for adenocarcinoma of ascending colon two years back from the day he diagnosed for the metastasis of the same. Hematuria was the presenting complaint.

On USG examination, 3x2x2 cm mass was noted in the mid pole of the left kidney. Excisional biopsy was done. Grossly, the excised renal mass was in multiple, grey-brown, firm pieces. Microscopy revealed tumour cells arranged in a glandular pattern. Tumour cells were round to oval with hyperchromatic nuclei and high N:C ratio. Mitotic figures were noted.

**Low-grade Papillary Urothelial Carcinoma in Kidney**

In the present study, we analysed a case of Low-Grade Papillary Urothelial Carcinoma in the kidney in 70 years old male patient. The patient was known case of Urothelial Carcinoma of the urinary bladder and presented with flank pain and hematuria. USG examination showed hydronephrotic changes in left-sided kidney and the left ureter was filled with the tumour growth. Radical Nephrectomy, along with left ureterectomy, was done.

Grossly, the ureter was filled with grey-white friable tumour growth throughout the length, and the growth was extending from the ureter to renal pelvis obstructing the urinary outflow leading to hydronephrotic changes in the kidney. Microscopically, tumour cells were arranged compactly in papillary structure with fibrovascular cores with a variation of cytologic and architectural features. Loss of cellular polarity was noted. Rare to numerous mitotic figures were noted.

**Gross features of renal tumours in received specimens**

In the present study, well-circumscribed borders and variegated appearance was noted in the 9/28 cases of clear cell RCC. Exophytic, friable growth with the well-circumscribed border was noted in papillary RCC, and Fleshy appearance was observed in tumour with sarcomatoid differentiation. A new entity of WHO 2016 renal tumour classification i.e. Multilocular cystic renal cell neoplasm of low malignant potential showed multiple cystic areas filled with haemorrhages.

**Histomorphological features of renal tumours**

The histomorphology study using H and E stained sections was done. The cases of renal tumours were classified into different histological variants. The architectural patterns, cytological features, stromal features were the criteria used for classifying these tumours. The valid option in the current study was clear cell RCC 16 (57.14%) cases, and Papillary RCC was noted in 2 cases (7.14%). Many tumours demonstrated a predominant alveo-
lar pattern of clear cells in 10 cases (35.71%) followed by clear cells in solid sheets pattern in 7 cases (25%) of Clear cell RCC. Most of the Clear cell RCC cases were containing thin-walled blood vessels and numerous capillaries in supporting stroma which was a helpful diagnostic feature. The tumour cells had a clear appearance as the content of lipid and glycogen in the cytoplasm of tumour cells was more, and it got dissolved during routine processing. Also noted few of the cells near necrosis were having granular eosinophilic cytoplasm. Tumour cells had round and centrally placed nuclei. Variable nuclear pleomorphism depending on tumour grade was noted. One of the cases of Clear cell RCC underwent rhabdoid differentiation.

The case of Multilocular cystic renal neoplasm of low malignant potential (a new entity as per 2016 WHO classification of renal tumours) was studied. As showed up by 2004 WHO plan it was a course of action of Clear cell Renal cell carcinoma and was named as Multilocular cystic Renal cell Carcinoma (MCRCC). As no metastasis was encountered and its low-grade cellular features it is now considered as a separate entity and named as Multicystic renal cell neoplasm of low malignant potential. In this case, we could see the multicystic tumour. Cysts were separated by thin fibro collagenous septae lined by aggregated clear cells. The clear cells had mild hyperchromatic nuclei with mild anisonucleosis and inconspicuous nucleoli.

Papillary RCC was seen in 2 (7.14%) patients. The papillae were composed of a fibrovascular core with a round to cuboidal tumour cells over it. Complex branching was noted at places. The size of tumour cells varied from small cells with large nuclei and scanty cytoplasm, resulting in higher nuclear-cytoplasmic ratio too large tumour cells with granular and eosinophilic cytoplasm. The tumour cell nuclei were uniform and round without nucleoli. Tumour cell nuclei showed prominent nucleoli. One of the cases of papillary renal cell carcinoma showed sarcomatoid differentiation and presented with high-grade nuclear features, and the patient was presented at a higher stage.

The Primary Renal Primitive Neuroectodermal Tumour was seen in one of the patients studied. It comprised of small round cells arranged in cohesive sheets, nests, rosettes separated by thin fibrous bands. Perivascular arrangement of tumour cells was also noted. Extensive areas of haemorrhage, necrosis and cyst formation were observed. High mitotic activity was recorded.

Tumour infiltration into the renal capsule, and perinephric fat was noted. In this case, morphological confirmation was done by Immunohistochemistry which showed diffuse membrane positivity for CD 99 (mic-2 gene product) & immuno-negativity for CK, NSE, LCA and Desmin.

**Associated clinical conditions with renal tumours**

Out of 28 cases, 15 patients were suffering from medical illnesses like Diabetes, Ischemic heart disease. Paraneoplastic syndromes were reported in few cases in the form of Hypertension, Polycythemia and Hypercalcemia etc. Hypertension was seen to be the most prevalent medical illness in renal tumour patients. It was found in 6 cases (40%) out of 15, followed by Diabetes seen in 4 cases (26.66%). Hypercalcemia and Polycythemia were noted in 2 cases (13.33%) each. One patient of Clear cell RCC was suffering from Ischemic heart disease.

**DISCUSSION**

Renal tumours involve a varied range of neoplastic sores with designs that are generally particular for youngsters and grown-ups. A wide assortment of both amiable and harmful tumours emerge from various parts of renal parenchyma, eminently cylindrical epithelium (Alpers et al., 2010; Eble et al., 2004). As per literature, Nephrectomy is the mainstay of treatment of localised Renal Cell Carcinoma, which is most common amongst all renal tumours, and it also provides survival benefit in the setting of metastatic disease (Pradhan et al., 2009).

In India, Renal Cell Carcinoma influences the patients two decades earlier (Hashmi et al., 2014). In general, it is the twelfth most basic site of harm in men and seventeenth in ladies. The latest systemic analyses of time in all monitored regions say that there is a general increase in both genders, up until the mid-80s.

Overall, approximately 12 new cases are diagnosed per 1, 00,000 population per year, with a male to female ratio of 3:2. Worldwide, the mortality from renal cell carcinoma is estimated to exceed 1,00,000 per year (Landis et al., 1999).

The urologists, radiologists and chemotherapist are in the end subordinate upon a histological finding of the tumour as histopathological highlights have a significant stake in deciding the anticipation and remedial alternative. Ultrasonographically also it is difficult to differentiate between different renal tumours, so histopathology remains a gold standard for the diagnosis.

Despite new techniques in imaging, renal tumours are primarily diagnosed on histopathology. There
are several separate studies done on clinical presentation and histopathological features. This study had taken into consideration age, gender, clinical performance, histopathological type and characteristics of the tumour and their outcome.

The present study was a two years study within the study period of June 2016 to May 2018, in this study duration, a total of 28 surgically excised renal specimens were studied.

**Age distribution**

According to the literature, the behaviour of the tumour and its histological pattern differs with each age group. In adults, Clear cell RCC and papillary RCC were common but Clear cell RCC was more common in the 6th decade. Only one case pediatric renal tumour, i.e. Nephroblastoma, was noted in a five years old female patient.

In the present study maximum numbers of tumours were found in 51-60 years of age group comprising of 28.5% followed by 61-70 years and 31-40 years of age group consisting of 21.42% each. A study was done by Padmanabhan et al. (2016) showed mean age of renal tumours was 46.2 years with most of the patients in the age group of 41-60 years followed by 20-40 years. The majority of cases were in their sixth decade. Our study correlated with the findings of (Padmanabhan et al., 2016). Most common renal tumour in the present study was Clear cell RCC. In Clear cell RCC, the most common age group was found to be 50-60 years of age group. Similar observations were noted in the study done by (Pradhan et al., 2009). We have studied a single case of Nephroblastoma in 5 yrs—old female patient. (Salma et al., 2016) encountered two patients of Nephroblastoma presented in the first decade of their life.

PNET is a rare tumour of the kidney and seen in young age. The present study showed one PNMT case of in 35 years old patient. In research done by Padmanabhan et al. (2016) showed a renal PNMT case in a 25-year-old patient.

The rate of renal cell carcinoma increments as the age progresses (Eble et al., 2004). It is a general belief that about 5% of all kidney cancers occur in patients younger than 40 years. In contrast, there is limited information about the management of RCC in older people it would be reasonable that renal tumours influencing the youthful grown-ups are symptomatic and possibly forceful the more significant part of the occasions, hence requiring vigorous radical treatment (Bashir et al., 2015).

**Gender distribution**

In this study, 20/28 cases were noted in males, and the remaining 8 cases were recorded in females with M: F ratio of 2.5:1. Male preponderance was observed in our study. The similar findings were noted in the studies done by Latif et al. (2011); Padmanabhan et al. (2016).

**Clinical presentation by patients of renal tumours**

In the present series, the patient presented predominantly with flank pain in 14 cases (50 %) followed by flank pain associated with hematuria in 8 cases (28.57%). These observations were comparable to studies conducted by Popat et al. (2010); Bashir et al. (2015). The classical triad of symptoms of RCC, i.e. hematuria, flank pain and abdominal mass were present in 2 cases (7.14%), and 1 case was detected incidentally during the evaluation for gastrointestinal complaints in the present study. 25-30 % of renal tumours were symptomatic and found on incidental radiological studies.

RCC may remain occult for most of its course. Thus the diagnosis is frequently not made until the disease is either locally advanced or unresectable or metastatic. There is an increasing incidence of incidentally detected RCC seen in the western world. An estimated 50- 60 % tumours in the USA are incidentally detected RCC seen in the western world. An estimated 50- 60 % tumours in the USA are incidentally detected asymptomatic lesions picked up on diagnostic imaging. As a result, the masses tend to be much smaller and tend to be more localised in the west (Bilal et al., 2017).

**Laterality**

All renal tumours were unilateral in the present study. Maximum cases were showing left-sided kidney involvement constituting 15 cases (53.57%) of all tumours, and right side involvement was seen 13 cases constituting of 46.42%. Laterality was compared with Latif et al. (2011); Bashir et al. (2015). All these studies showed concordance with the present study showing the maximum number of cases affecting the left-sided kidney.

**Tumour site**

In the present study upper pole was involved in 10 cases (35.71%), mid pole in 7 cases (25%), lower pole in 8 cases (28.57%), the upper and mid pole was involved in 2 cases (7.14%) and entire kidney involvement was seen in one case (3.57%). Studies were done by Latif et al. (2011); Bashir et al. (2015) showed the general site for tumour involvement was upper pole followed by the lower pole. In the present study, upper and lower pole involvement was seen at the same frequency as of the studies as mentioned above.

**Tumour Size**
Tumour size predominantly ranged from 0-4 cm in the present series which was invariance with the study conducted by Srivastava et al. (2004). However, there is a steady decrease in tumour size at presentation in the west Kane et al. (2008). This is due to maximum incidental tumours are detected on abdominal imaging. Data from National Cancer Database showed size of stage I tumour decreased from a mean of 4.1cm in 1993 to mean of 3.6cm in 2003 (Kane et al., 2008). A study done by Zhang et al. (2012) demonstrated that there is a significant correlation between tumour size and tumour grade with stage. Bigger tumors were inclined to have higher evaluation with stage and the likelihood of being clear cell carcinoma became higher as the tumor size increased (Zhang et al., 2012). This finding of current study was discordant with the studies done in Asian scenario like Hashmi et al. (2014); Bhatarchana (2016). Effective preventive measures were taken to diagnose the renal tumours in early stage explained this discordance.

**Type of renal tumours**

Amongst 28 cases studied we had 26 malignant tumours comprising 92.85% and 2 were benign tumours comprising 7.14%. Other studies done in past are shown in theTable 1 suggesting that malignant tumours were more common than benign tumours in surgically excised renal specimens. In the current study, maximum tumours were malignant showing concordance with the studies done by, Amin et al. (2015); Vinay and Sujatha (2018).

**Distribution of renal tumours according to histopathological diagnosis**

In the present study, 21/28 cases(75%) were Renal cell Carcinomas. Remaining cases (25%) cases were comprised of one case of Multilocular Cystic Neoplasm of Low Malignant Potential (3.57%), one case of Oncocytoma (3.57%) one case of Nephroblastoma (3.57%), one case of mesenchymal tumour i.e. Angiomyolipoma(3.57%), one instance of Primary Renal Primitive neuroectodermal (3.57%) and 2 cases (7.14%) of metastatic renal tumors.

**Tumour staging**

Currently, the most extensively used prognostic tool for RCC is the Primary tumour, localized lymph nodes, distant metastasis (TNM) staging system and the number of studies have shown the accuracy of this system in reflecting RCC prognosis. However number of studies have debated the prognostic accuracy of using the TNM system for RCC staging, particularly in relation to prognosis of locally advanced renal cell carcinoma (pT3-T4 RCC). Various studies reported a relative risk of death over 10 times higher in pT3-T4 stage than pT. Four excisional biopsies for RCCs were studied. As patients were suffering from significant comorbidities, excisional biopsy was performed (Ha and Kwak, 2014). Hence these cases were excluded from TNM staging. In the present study, most of the cases of RCCs were at TNM stage I and similar findings were noted in studies done by Li et al. (2016); Padmanabhan et al. (2016). An investigation by Abel et al. (2014) found that degree of vena caval attack was a significant factor in forecast and that dominant part of cases with positive vascular divider edges have expanded repeat rate. In one case, renal vessel invasion was noted and it was classified as pT3a (Abel et al., 2014).

In the present study, excluding renal biopsies and case of Angiomyolipoma (where renal parenchyma could not be identified) out of 22 cases, most of the cases(40.90%) showed normal renal parenchyma. The same finding was noted in study done by Henriksen et al. (2007) correlating with our study. In our study, the most common finding in adjacent renal parenchyma was chronic pyelonephritis seen in 6 (27.27%) cases. An absence of pathologic findings in non-neoplastic renal parenchyma occurred significantly more often in Papillary RCC in the study by Bijol et al. (2006) and was similar to our study which showed normal non-neoplastic renal parenchyma in both the cases of Papillary RCC. In the present study, 4 patients were having diabetes but none of them showed glomerulosclerosis in adjacent renal parenchyma, similar finding was noted in the study done by Bijol et al. (2006). It proved the well-known observation in the literature that only a subset of diabetic patients develops diffuse diabetic glomerulosclerosis.

**CONCLUSION**

A detailed histopathologic examination and routine H and E staining is helpful in accurately diagnosing and determining the various histological type, subtype and to evaluate other histopathological determinants. The clinical outcomes varies according to the histologic subtypes.

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**Conflicts of interest**

The authors declare that they have no conflict of

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