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Research Article

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Association of Ki-67 Immunoexpression with Histological Grades and Pathological Stage in Renal Cell Carcinoma

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ABSTRACT

Introduction: Renal cell carcinoma (RCC), being the14th most common cancer worldwide is an aggressive tumor causing lots of death worldwide.

Objective: Aim of this study is to observe the association of ki-67 immunoexpression with histological grades and pathological stage in renal cell carcinoma.

Methodology: This cross-sectional observational study was conducted in the Department of Pathology, Shaheed Suhrawardy Medical College, Dhaka, Bangladesh from March 2021 to February 2023. In this study 50 diagnosed cases of renal cell carcinoma were included. Purposive sampling was done. Paraffin blocks of all the cases were collected and sections were taken from each paraffin block for routine haematoxyline and eosin (H&E) stain and for immunohistochemical stain for Ki-67 antibody. Relevant clinical and microscopic data including age, sex, tumor size, histomorphologic type and tumor grade were collected and recorded in a predesigned data collection sheet. The statistical analysis was carried out using the SPSS version 22 for Windows (SPSS Inc., Chicago, Illinois, USA) Fisher Exact test was used to analyze the association between different categorical variables.

Results: In this study, among 50 selected cases, the age of the patients varied from 20-75 years. Most cases were in the age 40-59 years (76%) and the mean age of the study cases was 50.86 ± 9.55 (SD) years. About 70% (n=35) of the patients were male. Most were clear cell carcinoma 29(58%). 20(40%) patients were at stage pT1. Stage pT2 comprised 24(48%) cases. Stage pT3 were found in 5(10%) cases and stage pT4 in 1(2%) case. 30(60%) patients were grade 2, grade 1 comprised 09(18%) cases, grade 3 were found in 6(12%) cases and grade 4 in 5(10%) cases. High Ki-67 expression was found in 12 (24%) cases. In this study, the association of Ki-67 with the pathological stage (pT), histological grades, and Ki-67 expression was statistically significant. The association of Ki-67 expression in morphological variants with stages of tumour was not significant. But at the pT1 stage of CC-RCC 9 (90.0%) cases showed low Ki-67 expression but 1 (10.0%) case showed high Ki-67 expression. This 1 case with high Ki-67 expression showed aggressive behavior in the early stage (pT1) of CC-RCC and could be treated with chemotherapy as well as anti-Ki67 targeted therapy. The association of Ki-67 expression in morphological variants with grades of tumour was highly significant. In grade 3 and grade 4 tumours Ki-67 expression was high.

Conclusion: Ki-67 expression has been shown to significantly associated with advanced histologic grade and stage of RCC

Keywords: Ki-67, Immunohistochemestry, Renal cell carcinoma

Background

Kidney cancer ranks as the 14th most common cancer globally, with an estimated 431,288 new cases and approximately 179,368 deaths reported in 2020.1 Renal cell carcinoma constitutes 85% of all primary malignant renal tumors in adults. In Bangladesh, the prevalence of renal cell carcinoma is 1.96% [1]. Most renal cell carcinomas are detected as small tumors, are advanced, or present with distant metastases at the time of diagnosis [2].

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Currently, tumor stage and nuclear grade are regarded as the most significant prognostic variables for patients with renal cell carcinoma. No specific serum markers or prognostic factors exist to predict metastasis development, tumor recurrence, or to monitor therapeutic response.

Ki-67 is a nuclear DNA-binding protein that is essential for cellular proliferation [3]. Ki-67 is an excellent marker of the growth fraction of a given cell population; hence it has drawn increasing attention as an attractive prognostic, predictive, and potential therapeutic target in malignant neoplasms of lung, bladder, breast, cervical, urothelial carcinomas, upper urinary tract, lymphoma, and cervical cancer [4]. It represents the proliferation of tumour cells indirectly denoting the aggressiveness of the tumour. As molecular alteration precedes phenotypic change, the immunohistochemical study is used as a valuable tool for identifying aggressive cancers.

Renal cell carcinoma is characterized by a variety of biochemical and functional traits. Based only on histological features, renal cell carcinoma prognosis prediction is challenging. Early on, it typically spreads widely, and patients with the same tumor grade may have quite different clinical outcomes. Immunohistochemical analysis is a useful method for detecting aggressive tumors because molecular change occurs before phenotypic change [5]. Ki-67 expression is correlated to the stage and grade of tumors. More importantly, various studies have indicated that the strategy of inhibiting Ki-67 holds promise for renal cancer therapy. The predictive function of Ki-67 in renal cell carcinoma has not received much attention to date. The purpose of this study is to investigate Ki-67 immunohistochemistry expression in renal cell carcinoma, assess its correlation with histopathological type and grade, and ascertain the utility of Ki-67 immunostains as an auxiliary tool.

Aims and Objectives

To see the expression of Ki-67 in renal cell carcinoma and to determine their association with histological grades and pathological stage.

Materials and Method

Study Design

This study was a cross-sectional observational study.

Place of Study

Department of Pathology, Shaheed Suhrawardy Medical College, Dhaka, Bangladesh.

Study Population

Cases histologically diagnosed as renal cell carcinoma at the department of Pathology, ShSMC, and NIKDU were included in this study. Specimens were collected from all age groups and both sexes.

Period of Study

The study was carried out from March 2021 to February 2023.

Sampling Method

Purposive sampling.

Inclusion Criteria

a) Histologically diagnosed cases of renal cell carcinoma.
b) Patients of any age and either sex.

Exclusion Criteria

a) Patients having a history of receiving radiotherapy or chemotherapy before surgery.
b) Extensive necrosed tissue in the tumor.

Sample Size Determination

A total of 50 cases were taken as a study sample.

Data Collection and Recording

During the collection of specimens, patients' information and demographic data were recorded systematically in a prepared proforma. Informed written consent was obtained from the patient's attendant in each case. All the cases were numbered chronologically and the same number was given to histological as well as immunohistochemical slides.

Samples Collection and Grossing

After getting permission from the Ethical Review Committee (ERC) of ShSMC, specimens of known cases of RCC received at pathology department, ShSMC and NIKDU, Dhaka were collected and grossed according to standard protocol.

Routine Histopathology and Case Selection

In the pathological laboratory, tissue processing, paraffin embedding, sectioning of the paraffin blocks, H&E staining were done according to the standard protocol followed at ShSMC. Afterward, these cases were assigned for histological diagnosis. Then diagnosed cases of RCC were selected for the study by inclusion and exclusion criteria.

Evaluation of Histopathological Parameters

Cases were evaluated elaborately and histological parameters including morphological type, pathological stage, and grade of tumour. Representative sections from each paraffin block were selected for immunohistochemical stain with Ki-67. The data was recorded on a data sheet.

Immunohistochemical Study

Immunohistochemistry was done in Immunohistochemistry laboratory of Anatomic Pathology, Square Hospitals Ltd. Formalin fixed paraffin-embedded tissues sections of 3-4 micrometer thickness were used.

Immunohistochemical Analysis of Ki-67

Primary Antibody: FLEX Monoclonal Mouse Anti-Human Ki67 Clone MIB-1 Ready to use.

Secondary Antibody: DAKO REALTM EnVision TM (HRP RABBIT/MOUSE) (ENV) Positive control: Specimen of tonsils with positive lymphocytes was taken as a positive control.

Scoring system and cut-off value: For Ki-67, at least 1000 tumour cells at x400 magnification from the most immunopositive region of each slide were visually counted and the percentage of positive cells was calculated. Immunoreactivity was considered overexpressed when sections showed more than 15% nuclear reactivity.

Statistical Analysis and Result

The statistical analysis was carried out using the Statistical Package for Social Sciences version 26 for Windows (SPSS Inc.,

Chicago, Illinois, USA). Descriptive statistics (frequencies and percentages) were used to summarize the patients' demographic characteristics and presented in Tables, Figures, and Charts. The frequencies of different entities were expressed as percentages. Fisher Exact test and Chi-square tests were used to analyze the association between different categorical variables. To avoid differential assessment of participants potentially resulting in bias, labeling of the participants' paraffin blocks was coded by unidentifiable numbers; for example- case 1, case 2, etc. Coding was done in every step of data collection, adjudication, and statistical analysis.

Ethical Aspects

- Ethical clearance for the study was taken from the Ethical Review Committee (ERC), ShSMC.
- Every ethical issue was discussed with the patients regarding the study and informed written consent was taken from each of them.
- All data were secured with the confidentiality of the study population.

Observations and Results

Out of the total 50 cases, 20(40.0%) cases belonged to the age group of 50-59 years. 18(36.0%) cases were 40-49 years, 07(14.0%) cases were 60-69 years, 2(4.0%) cases were 20-29 years, 02(4.0%) cases were more than 70 years and 1 (2.0%) was 30-39 years. The mean age was 50.86 ± 9.55 years (Table 1).

Table 1: Distribution of the study subjects by their age (n = 50).

Age (years)	Frequency	(%)
20-29	2	4.0
30-39	1	2.0
40-49	18	36.0
50-59	20	40.0
60-69	7	14.0
≥ 70	2	4.0
Mean ± SD		50.86 ± 9.55
Range (Min-Max)		(20-75)

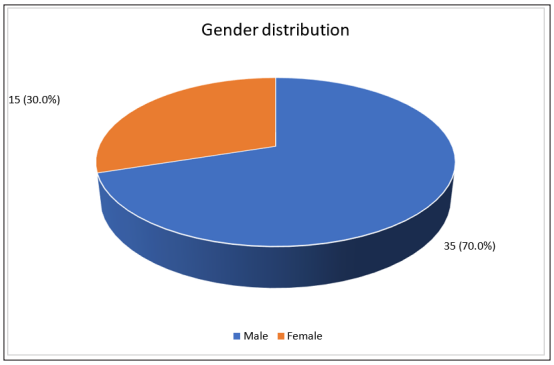

Figure 1: Distribution of patients according to gender (n=50).

It was observed from the present study that among the 50 patients, 70% (n=35) patients were male, and 30% (n=15) patients were female (Figure 1).

Figure 2 shows that among the study cases of renal cell carcinoma, most were clear cell carcinoma 29(58.0%). Papillary renal cell carcinoma was the second most common 13(26.0%) followed by chromophobe variant 7(14.0%) and collecting duct carcinoma 1(2.0%).

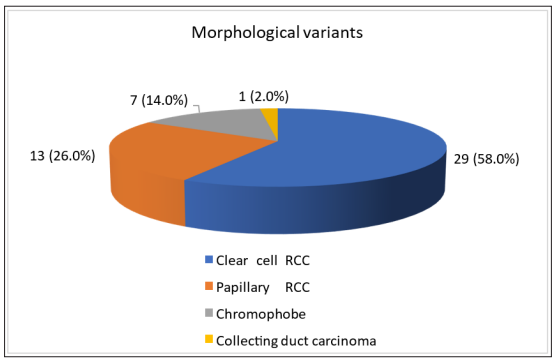

Figure 2: Distribution of patients according to morphological variants (n=50)

Figure 3 depicts the distribution of the study population according to pathological stage of the tumour. It reveals that among the 50 cases, 20(40%) patients were at stage pT1. Stage pT2 comprised 24(48%) cases. Stage pT3 was found in 5(10%) cases and stage pT4 in 1(2%) case.

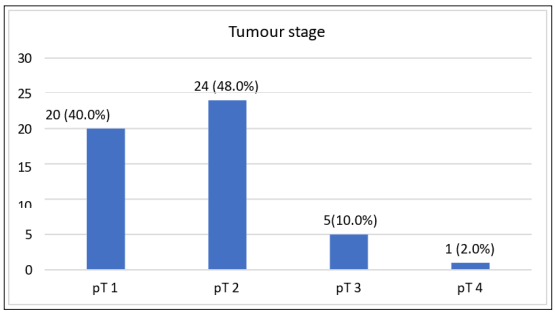

Figure 3: Distribution of patients according to tumor stage (n=50).

Figure 4 depicts the distribution of the study population according to the histological grade of the tumour. It reveals that among the 50 cases, 30(60%) patients were grade 2. Grade 1 comprised 09(18%) cases. Grade 3 was found in 6(12%) cases and grade 4 in 5(10%) cases.

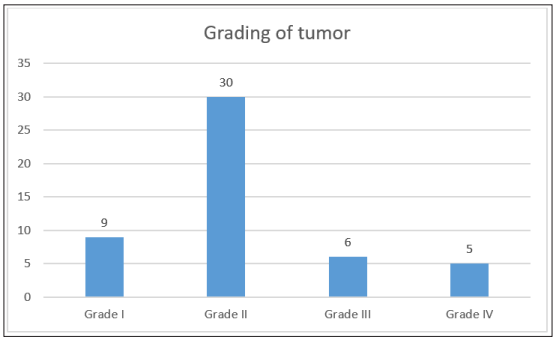

Figure 4: Distribution of patients according to tumor grade (n=50).

Expression of Ki-67 immunostain in study cases (n=50)

Figure 5 reveals that Ki-67 was low (<15%) in most of the cases 38(76%).

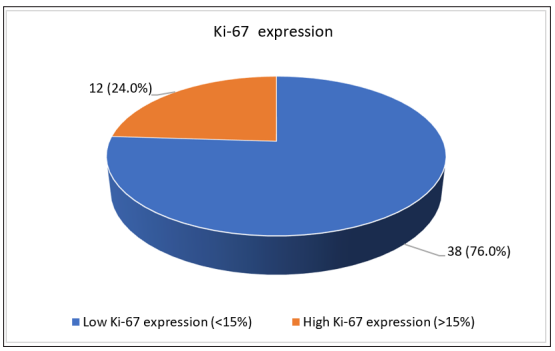

Figure 5: Expression of Ki-67 immunostain in study cases (n=50).

Association between Ki-67 expression and morphological variants of tumour (n=50)

Table 2 shows that there was no significant association between morphology of the tumour and Ki-67 expression (p-value 0.626).

Table 2: Association between Ki-67 expression and morphological variants of tumour (n=50).

Morphological types	Low (<15%)	High (>15%)	p-value
Clear cell RCC	23 (79.3%)	6 (20.7%)	
Papillary RCC	10 (76.9%)	3 (23.1%)	
			0.626[ns]
Chromophobe	4 (57.1%)	3 (42.9%)	
Collecting duct carcinoma	1 (100.0%)	0 (0.0%)	

ns = not significant, *p value was determined by Fisher Exact test Variables were expressed as frequency.

Association between Ki-67 expression and pathological stage of tumour in clear cell carcinoma (n=29)

Fisher exact test showed that there was no significant statistical difference between the stage of the tumour and Ki-67 expression (p=0.239).

Table 3: Association between Ki-67 expression and stage of tumour (n=29).

Ki-67 expression Stage		p-value	
	Low (<15%)	High (>15%)	
pT1	9 (90.0%)	1 (10.0%)	
pT2	12 (80.0%)	3 (20.0%)	0.239[ns]
pT3	2 (50.0%)	2 (50.0%)	

ns = not significant, *p value was determined by Fisher Exact test Variables were expressed as frequency.

Association between Ki-67 expression and grade of tumour in clear cell carcinoma (n=29)

In table 4, grade 1, all 2 (100.0%) patients had low Ki-67 expression and in grade 2, most of the patients 19 (90.5%) had low Ki-67 expression while in grade 3, all 2 (100.0%) showed low Ki-67 expression and in grade 4, none of the patient showed low Ki-67 expression. Fisher exact test showed that there was significant statistical difference between grade of tumour and Ki-67 expression in clear cell carcinoma (p=0.002).

Table 4: Association between Ki-67 expression and grade of tumour (n=29).

Ki-67 expression Grade		p-value
	Low (<15%)	High (>15%)
Grade 1	2 (100.0%)	0 (0.0%)
Grade 2	19 (90.5%)	2 (9.5%)
		0.002
Grade 3	2 (100.0%)	0 (0.0%)
Grade 4	0 (0.0%)	4 (100.0%)

*p value was determined by Fisher Exact test Variables were expressed as frequency.

Association between Ki-67 expression and pathological stage of tumour (n=50)

In table 5, T1 and T2 stages, 18 (90.0%) and another 18 (75.0%) patients had low Ki-67 expression while in T3 2 (40.0%) showed low Ki-67 expression and in T4, none of the patient showed low Ki-67 expression. Fisher exact test showed that there was significant statistical difference between stage of tumour and Ki-67 expression (p=0.030).

Table 5: Association between Ki-67 expression and stage of tumour (n=50).

Ki-67 expression Stage		p-value
	Low (<15%)	High (>15%)
pT1	18 (90.0%)	2 (10.0%)
pT2	18 (75.0%)	6 (25.0%)
		0.030
pT3	2 (40.0%)	3 (60.0%)
pT4	0 (0.0%)	1 (100.0%)

*p value was determined by Fisher Exact test Variables were expressed as frequency.Association between Ki-67 expression and grade of tumour (n=50)

In table 6, grade 1 and 2, 8 (88.9%) and 27 (90.0%) patients had low Ki-67 expression while in grade 3 half 3 (50.0%) showed low Ki-67 expression and in grade 4, none of the patient showed low Ki-67 expression. Fisher exact test showed that there was significant statistical difference between grade of tumour and Ki-67 expression (p<0.001).

Table 6: Association between Ki-67 expression and grade of tumour (n=50).

Ki-67 expression Grade		p-value
	Low (<15%)	High (>15%)
Grade 1	8 (88.9%)	1 (11.1%)
Grade 2	27 (90.0%)	3 (10.0%)
		<0.001
Grade 3	3 (50.0%)	3 (50.0%)

Grade 4	0 (0.0%)	5 (100.0%)

*p value was determined by Fisher Exact test Variables were expressed as frequency.

Discussion

In this study, the total number of cases was 50 nephrectomy specimens histologically diagnosed with renal cell carcinoma. Statistical analysis showed the mean age of the cases was 50.86 ± 9.55 (SD) years (Table 1). A study done by Zheng and his team showed the mean age was 54 years which is consistent with this study [6]. According to this study, 35 (70%) of the cases were male and 15 (30%) were female with a male-to-female ratio of 2.3:1 (Figure 1).

Most of the tumors were clear cell carcinoma 29 (58.0%). Papillary renal cell carcinoma was the second most common 13(26.0%) followed by chromophobe variant 7(14.0%) and collecting duct carcinoma 1(2%). This finding correlated with Alzubaidi and his team's findings, who described that 65% of tumors were clear cell carcinoma [7]. According to Delahunt & Eble, 15% of cases were papillary renal cell carcinoma [8]. A study by Bonsib & Lager showed 9% of the cases were chromophobe Renal cell carcinoma [9].

In the association of the pathological stage (pT), 20(40%) of the cases were at stage pT1, and most of the cases were at stage pT2 comprising 24(48%) cases. Stage pT3 was found in 5(10%) cases and stage pT4 in 1(2%) case. In the association of the histological grades, among 50 cases, 30(60%) were in grade 2. Grade 1 comprised 09(18%) cases. Grade 3 was found in 6(12%) cases and grade 4 in 5(10%) cases. It correlated with the study of C S SD and his colleagues [10].

Regarding the evaluation of Ki-67, among 50 cases, Ki-67 was found overexpressed in 12 (24%) cases and negative or low Ki-67 expressed in 38 (76%) cases. The statistical analysis has no significant association between Ki-67 expression and morphological variants of renal cell carcinoma. The analysis of the association of Ki-67 with pathological stages (pT) of CC-RCC is also not significant. At the pT1 stage of CC-RCC 9 (90.0%) cases showed low Ki-67 expression but 1 (10.0%) case showed high Ki-67 expression. This 1 case with high Ki-67 expression showed aggressive behavior in the early stage (pT1) of CC-RCC and could be treated with anti-Ki67 targeted therapy [11]. An association of Ki-67 with grades (G) of CC-RCC showed strong statistical significance (p=0.002) which was a higher expression of Ki-67 is highly associated with Grade-4 CC- RCC.

It was observed from the study that a significant association (p<0.001) was found between Ki-67 expression and the grade of tumour. It was evident that Ki-67 was progressively overexpressed with the increasing grade of the tumour. A similar study by Riese and his team showed expression of the high Ki-67 was higher in grades 3 or 4 than in grades 1 or 2 [12].

In this study, the association between pathological stage (pT) and Ki-67 expression of all 50 cases was found statistically significant (p=0.03). This could be explained by the increased proliferative capacity of the tumour cells leading to increased aggressiveness. It was clear that Ki-67 was progressively overexpressed with the increasing stage of the tumour. A similar study by Riese et al. (1993) showed expression of the high Ki-67 was 5-fold higher in stages pT4 or pT3 than in stages pT1 or pT2. It also helps regarding the choice of Anti-Ki 67 targeted therapy in an early stage (pT) of tumour [12].

Summary

The aggressiveness and behavior of renal cell carcinoma depend on different histopathological parameters including histological types, stage, grade, etc. This cross-sectional study aimed to observe the immunohistochemical expression of Ki-67 in renal cell carcinoma and to compare with different histopathological parameters. A total of 50 cases of diagnosed renal cell carcinoma were selected for the study. In this study, the age of the patients varied from 20-75 years. Most cases were in the age group 40-59 years (76%) and the mean age of the study cases was 50.86 ± 9.55 (SD) years. About 70% (n=35) of the patients were male. Most were clear cell carcinoma 29(58%). 20(40%) patients were at stage pT1. Stage pT2 comprised 24(48%) cases. Stage pT3 were found in 5(10%) cases and stage pT4 in 1(2%) case. 30(60%) patients were grade 2, grade 1 comprised 09(18%) cases, grade 3 were found in 6(12%) cases and grade 4 in 5(10%) cases. High Ki-67 expression was found in 12 (24%) cases. In this study, the association of Ki-67 with the pathological stage (pT), histological grades, and Ki-67 expression was statistically significant. The association of Ki-67 expression in morphological variants with stages of tumour was not significant. But at the pT1 stage of CC-RCC 9 (90.0%) cases showed low Ki-67 expression but 1 (10.0%) case showed high Ki-67 expression. This 1 case with high Ki-67 expression showed aggressive behavior in the early stage (pT1) of CC-RCC and could be treated with chemotherapy as well as anti-Ki67 targeted therapy. The association of Ki-67 expression in morphological variants with grades of tumour was highly significant. In grade 3 and grade 4 tumours Ki-67 expression was high.

Conclusion

The pathological stage (pT) and histological grades (G) of renal cell carcinoma were statistically significantly correlated with Ki-67 expression. In renal cell carcinoma, routine use of Ki-67 in combination with histopathological grading and staging may offer prognostic information for classifying patients at high risk. Clinicians may use this classification to assess whether surgery, adjuvant chemotherapy, radiation therapy, immunotherapy, or Anti-Ki67 targeted therapy are necessary.

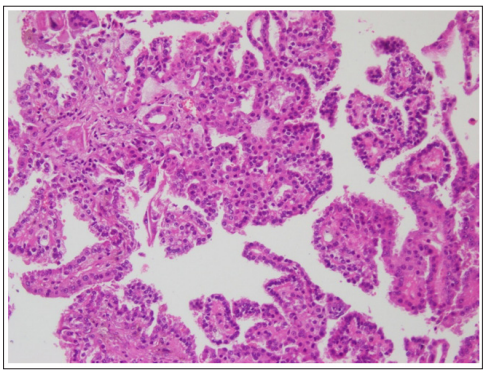

Figure 1: Photomicrograph shows Papillary RCC (G-3) (H&E, 200X).

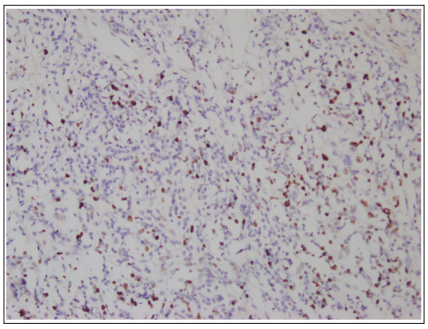

Figure 2: Photomicrograph shows Papillary RCC (G-3) with high ki-67 expression (200x).

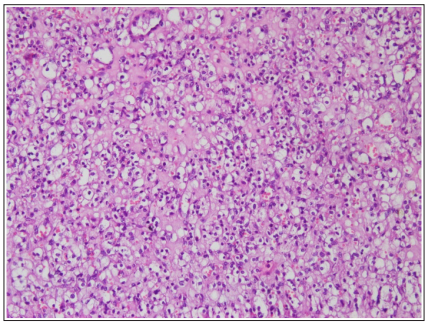

Figure 3: Photomicrograph showing Clear cell RCC (G-2) (200X).

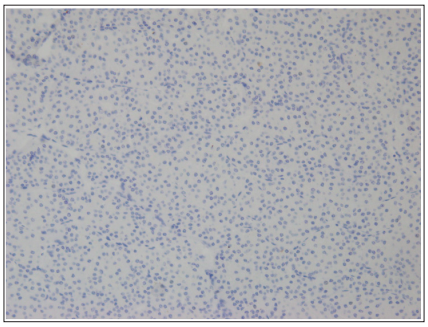

Figure 4: Photomicrograph showing Clear cell RCC (G-2) with negative Ki-67 expression (100X).

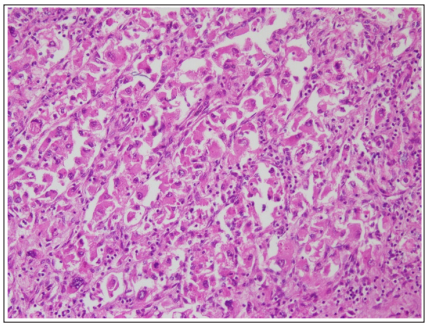

Figure 5: Photomicrograph shows Chromophobe RCC (G-4) (H&E, 400X).

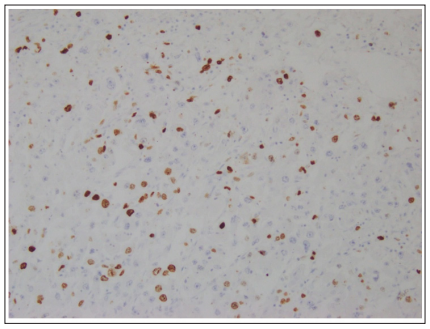

Figure 6: Photomicrograph shows Chromophobe RCC (G-4) with high Ki-67 expression (400X).

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