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HISTOPATHOLOGICAL EVALUATION OF STAGING, GRADING AND PROGNOSTIC FACTORS OF RENAL CELL CARCINOMA

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Introduction: Renal cell carcinoma (RCC) is a malignancy with an adverse prognosis for the majority of the patients. Renal cell carcinoma accounts for 80% to 85% of malignant kidney tumors. Despite that an increasing number of patients incidentally are diagnosed, still around 25–30% of patients with new diagnosed disease already have metastatic disease. Of the remaining patients with nonmetastatic disease, about 30–40% will progress with distant metastases or local recurrent RCC. **Objective:** To assess the prognosis of age, sex, race, tumor size, pathological staging, grading and prognostic factors of Renal Cell Carcinoma. **Material and Methods:** In the retrospective study was done in Department of Urology, Sir Salimullah Medical College, Mitford, Dhaka, Bangladesh from June 2021 to July 2022. A total number of 101 nephrectomy specimens were analyzed and 22 diagnosed cases of renal cell carcinoma were included in the study. The age and sex distribution of renal cell carcinomas diagnosed were study. Histopathological evaluation of renal cell carcinomas was carried out correlating with old records, histopathology slides, special stains and immunohistochemistry. **Results:** Total 101 nephrectomy specimens were analyzed and 22 diagnosed cases of renal cell carcinoma were included in the study. Maximum numbers of cases were seen in 40-49 years' age group (31.8%) and also in 60-69 years' age group (31.8%). Histological subtypes of renal cell carcinoma diagnosed were Clear cell type, papillary type, Chromophobe type and Collecting duct type.

Maximum numbers of cases diagnosed were of Clear cell type renal cell carcinoma (59.09%). Least common subtype diagnosed was Collecting duct type renal cell carcinoma (4.5%). Least common subtype diagnosed was Collecting duct renal cell carcinoma (4.5%). Tumor size was >4cm in maximum number of cases i.e. 20 (72.8%). Most of the subtypes of renal cell carcinoma had Fuhrman nuclear grades 2 and 3. Out of 22 cases of renal cell carcinoma, sarcomatoid differentiation was observed histologically in 3 cases (13.6%) within the tumor tissue. 2 cases of Clear cell type and 1 case of papillary type of renal cell carcinoma had sarcomatoid differentiation. **Conclusion:** In concluded, the underscores the importance of nuclear grading in predicting survival of renal cell carcinoma patients. There is strong correlation between grade, tumor size, and stage. Nuclear grading is important in predicting survival of patients with renal cell carcinoma. Nuclear grading is strongly related to both tumor size and stage. Nuclear grading and staging of the histological subtypes strongly influences the survival of patients, as thus proven in this study.

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INTRODUCTION

Renal cell carcinoma (RCC) is a malignancy with an adverse prognosis for the majority of the patients. Renal cell carcinoma accounts for 80% to 85% of malignant kidney tumors [1]. Despite that an increasing number of patients incidentally are diagnosed, still around 25–30% of patients with new diagnosed disease already have metastatic disease. Of the remaining patients with nonmetastatic disease, about 30–40% will progress with distant metastases or local recurrent RCC. The 5-year survival rate for all stages of renal cell carcinoma improved in recent years because of an important stage migration, whereby the majority of patients are diagnosed with localized disease [2]. Many prognostic factors for survival have been identified in renal cell carcinoma, tumor stage, age, and functional status being the most significant ones [3]. Nuclear grade has also been shown to be an independent predictive factor of survival in many studies [4], higher grades correlating with the biological aggressiveness of the tumor and increased metastatic potential. Surgical resection of localized RCC can be curative, but up to one-third of patients eventually recur. In addition, approximately 15 percent of patients with RCC present with locally advanced or metastatic RCC, for which surgery is noncurative. The natural history of disease for patients with advanced or metastatic RCC can vary widely from a few months to many years depending on the clinical, pathologic, laboratory, and radiographic features of the disease. Recently, studies using current histological subtyping of renal cell carcinoma based on the American Joint Committee on Cancer and Heidelberg recommendations from 1997 or the similar WHO histological classification from 2004 have identified histology as an important prognostic factor of survival [5,6,7]. These classifications include the following distinct malignant histological subtypes: clear cell renal cell carcinoma, papillary renal cell carcinoma, chromophobe renal cell carcinoma, collecting duct renal cell carcinoma, and unclassified renal cell carcinoma. The distinct histological subtypes have been found to have different biological and clinical behavior affecting both the metastatic potential of the tumors and survival of the patients. Using multivariate analysis,

histological subtype has been identified as an independent prognostic factor of survival in many of the studies [8]. The TNM-derived American Joint Committee on Cancer (AJCC) classification represents the gold standard staging scheme after nephrectomy for renal cell carcinoma [9]. Therefore, methods to predict which patients are likely to develop (recurrent) metastases are needed, and it is also important to identify those that respond to various treatments. Nuclear grade is the most important prognostic feature of a renal cell carcinoma, [10] its prognostic value has been validated in numerous studies over the past eight decades. Since its definition in 1982, the Fuhrman grade represents one of the key determinants of renal cell carcinoma-specific survival. This nuclear grading system is based on nuclear size, shape, and prominence of nucleoli [11].

MATERIAL AND METHODS

In the retrospective study was done in Department of Urology, Sir Salimullah Medical College, Mitford, Dhaka, Bangladesh from June 2021 to July 2022. A total number of 101 nephrectomy specimens were analyzed and 22 diagnosed cases of renal cell carcinoma were included in the study. The age and sex distribution of renal cell carcinomas diagnosed were study. Diagnosis of all cases of renal cell carcinoma was made on histopathological examination, on routine H&E stained tissue sections. In addition to H&E staining, special stains and Immunohistochemistry were done wherever necessary.

Inclusion criteria:

- All nephrectomy specimens with histological confirmation of renal cell carcinoma were included in the present study.

Exclusion criteria:

- Non-neoplastic lesions of kidney, Benign and malignant tumours of the kidney other than renal cell carcinoma were excluded in the present study.

Patient's history such as age, sex, laterality of nephrectomy specimens and other relevant clinical details were noted, as provided by the urologist. The relationships of tumor size with pathological diagnosis and nuclear grade were evaluated using logistic regression models.

Statistical Analysis: Data for continuous variables were expressed as mean ± standard deviation and compared using the Student's t-test. Data for categorical variables were expressed as the number of times (percentage) and compared using Pearson's chi-square test. The comparison between tumor size and volume was performed using the paired t-test. Statistical significance was defined as $p < 0.05$. Correlation analyses were performed using the Pearson's correlation coefficient. All data analysis was performed with SPSS statistical software (Statistical Product and Services Solutions, version 20.0, Chicago, IL, USA).

RESULTS

Total 101 nephrectomy specimens were analyzed and 22 diagnosed cases of renal cell carcinoma were included in the study. The age and sex distribution of renal cell carcinomas diagnosed in the present study were tabulated in respectively **(Table1-2)**. Maximum numbers of cases were seen in 40-49 years' age group (31.8%) and also in 60-69 years' age group (31.8%). Histological subtypes of renal cell carcinoma diagnosed were Clear cell type, papillary type, Chromophobe type and Collecting duct type. Maximum numbers of cases diagnosed were of Clear cell type renal cell carcinoma (59.09%). Least common subtype diagnosed was Collecting duct type renal cell carcinoma (4.5%). Histological subtypes and the total number of cases diagnosed are tabulated in **(Table-3).** Based on the tumor size, cases were categorized into three groups i.e. ≤4cm, >4cm - ≤7cm and >7cm **(Table-4).** Tumor size was >4cm in maximum number of cases i.e. 16 (72.8%). In the present study, tumor size ranged from 2.5 cm to 14 cm, mean tumor size

being 6.5 cm. In the present study, nuclear grading of all cases of renal cell carcinoma was interpreted using Fuhrman nuclear grading system. Grade 1 was seen in 3 cases (13.6%), Grade 2 in 8 cases (36.4%), Grade 3 in 10 cases (45.5%), and Grade 4 in one case (4.5%). Most of the renal cell carcinomas had grades 2 and 3. Subtypes of Renal cell carcinoma and their corresponding nuclear grades were tabulated in (**Table-5).** Out of 22 cases of renal cell carcinoma, sarcomatoid differentiation was observed histologically in 3 cases (13.6%) within the tumor tissue. 2 cases of Clear cell type and 1 case of papillary type of renal cell carcinoma had sarcomatoid differentiation **(Table-6).** AJCC-TNM staging scheme (2002) was applied to all the cases of renal cell carcinoma. Number of cases and their corresponding Primary tumor stage (pT), status of Regional lymph node metastasis (N), and assessment of distant metastasis was done and the observations were tabulated in respectively **(Table7-9)**.

Table-1: Age distribution (N=22)

Age Group	**Clear Cell**	**Papillary**	**Chromophobe**	**Collecting Duct**	**Total**	**Percentage (%)**
<40	0	0	1	0	1	4.54
40-49	5	2	0	0	7	31.8
50-59	4	1	1	0	6	27.3
60-69	4	1	1	1	7	31.8
70-79	1	0	0	0	1	4.54
≥ 80	0	0	0	0	0	0.00
Total	14	4	3	1	22	100

Table-2: Sex distribution (N=22)

Sex	**Clear Cell**	**Papillary**	**Chromophobe**	**Collecting Duct**	**Total**	**Percentage (%)**
Male	10	3	1	1	15	68.2
Female	5	1	1	0	7	31.8
Total	15	4	2	1	22	100
M.F	2.2:1	2:1	2:1		2.2:1	

Table-3: Histological subtypes of Renal cell carcinoma (N=22)

Histological Subtype	**No. of Cases**	**Tumor Size Range**
Clear cell renal cell carcinoma	13	2.5-12 cm
Papillary renal cell carcinoma	5	5-8 cm
Chromophobe renal cell carcinoma	3	3.5-14 cm
Collecting duct renal cell carcinoma	1	9 cm
Total	22	

Table-4: Tumor size (N=22)

Tumor size	**No. of cases**	**%**
≤ 4 cm	06	27.8
> 4 cm- ≤ 7 cm	8	36.4
> 7 cm	8	36.4
Total	22	100

Table-5: Fuhrman nuclear grading (N=22)

Subtype Of Renal Cell Carcinoma	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Clear cell	2	5	5	1	13
Papillary	0	1	4	0	5
Chromophobe	1	1	1	0	3
Collecting duct	0	1	0	0	1
Total	3	8	10	1	22
Percentage (%)	13.6	36.4	45.5	4.5	100

Table-6: Sarcomatoid differentiation (N=22)

Sarcomatoid differentiation	**Clear cell**	**Papillary**	**Chromophobe**	**Collecting duct**	**Total**	**Percentage (%)**
PRESENT	2	1	0	0	3	13.6
ABSENT	12	4	2	1	19	86.4
Total	14	5	2	1	22	100

Table-7: Primary tumor stage (pT) (N=22)

Tumor Size	**No. Of Cases**	**%**
T1	12	54.5
T2	5	22.7
T3	5	22.7
T4	0	0.00
Total	22	100

Table-8: Regional Lymph node metastasis (N=22)

Tumor Size	**No. Of Cases**	**%**
T1	12	54.5
T2	5	22.7
T3	5	22.7
T4	0	0.00
Total	22	100

Table-9: Distant metastasis (N=22)

Distant Metastasis (M)	No. Of Cases	%
MX	22	100
M0	0	0
M1	0	0
Total	22	100

DISCUSSION

An increased detection rate of small incidental renal tumors has led to difficult decision making for clinicians [12]. With observations that these smaller tumors tend to be more indolent5 various treatment options may be offered to this patient population. In the past radical nephrectomy was the standard of care in all patients with a renal mass. Recently there has been much success in treating small renal tumors with partial nephrectomy and other investigative ablative techniques [2,3,13-14,15]. A role for active surveillance has also been proposed in elderly and comorbidly ill patients [4,5]. Determining the likelihood of malignancy of a renal mass is important when deciding on a management strategy. In this study we externally validated the findings of Frank et al [16] confirming that the risk of malignancy is directly associated with the size of the renal mass. A total number of 101 nephrectomy specimens were analyzed and 22 diagnosed cases of renal cell carcinoma were included in the present study. The retrospective and prospective study with regards to renal cell carcinoma was done in a detailed manner. Renal cell carcinoma is by far the most common malignant tumor of the kidney, accounting for 4% of adult malignancies. The incidence of renal cell carcinoma increases with age, with a peak in the sixth decade of life and a median patient age of 55 years. Renal cell carcinoma in our study occurred in a wide age range from 30 years to 70 years. Renal cell carcinoma was not seen among children in our study. Right kidney was most commonly involved than the left one. In present study the highest number of cases with renal cell carcinoma was observed in the 4th and 6th decades of life which was similar to the studies done by Leclercq et al [17] and T. Gudbjartsson et al [19], majority of the cases were in the 6th decade. According to the literature men are more often affected than women in a ratio approximately 1.5 to 1. In the present study, males were most commonly affected than females with incidence of 68.2%, and male to female ratio of 2:1 which was similar to studies done by Leclercq et al [17] and Karakiewicz et al [19]. To date, several prognostic indicators including tumor stage, tumor size, Furhman nuclear grade, and symptom classification have been shown to predict renal cell carcinoma-specific survival after nephrectomy [20]. The maximum size of a renal cell carcinoma that correlates with behavior and should determine stage has been surprisingly controversial over the years. A greatest dimension of 4 cm seems to provide the most acceptable cut-off point [21]. In the present study the mean tumor size was 6.5 cm which was strongly correlating with the study done by Leclercq et al [17] and was similar to the study done by Karakiewicz et al [19]. Recently, studies using current histological subtyping of renal cell carcinoma based on the similar WHO histological classification from 2004[23] have identified histology as an important prognostic factor of survival [5]. Histological subtypes of renal cell carcinoma diagnosed were Clear cell type, papillary type, Chromophobe type and Collecting duct type. Maximum numbers of cases diagnosed were of Clear cell type renal cell carcinoma (59.09%). Least common subtype diagnosed was Collecting duct type renal cell carcinoma (4.5%). The study was comparable with the

study done by Rainwater et al and R. Houston et al [24] in their study they also documented clear cell renal cell carcinoma as a predominant variant followed by papillary renal cell carcinoma. The distinct histological subtypes have been found to have different biological and clinical behavior affecting both the metastatic potential of the tumors and survival of the patients. Histological subtype has been identified as an independent prognostic factor of survival in many of the studies. With the exception of stage, nuclear grade is the most important prognostic factor of a renal cell carcinoma [10]; its prognostic value has been validated in numerous studies over the past eight decades. The Fuhrman nuclear grading system is an established predictor of survival in patients with renal cell carcinoma. Grade is also strongly related to both tumor size and the pathologic staging, higher grades implying increased metastatic potential of the primary tumor and biological aggressiveness with reduced survival as a result. This nuclear grading system is based on nuclear size, shape, and prominence of nucleoli [11]. In the present study, nuclear grading of all cases of renal cell carcinoma was interpreted using Fuhrman nuclear grading system. Grade 1 was seen in 3 cases (13.6%), Grade 2 in 8 cases (36.4%), Grade 3 in 10 cases (45.5%), and Grade 4 in one case (4.5%). Most of the renal cell carcinomas had grades 2 and 3. Subtypes of Renal cell carcinoma and their corresponding nuclear grades**.** The present study was similar to studies done by T. Gudbjartsson et al [18] and Leclercq et al [17]. Sarcomatoid renal cell carcinoma is not a distinct histologic entity and represents high-grade transformation in different subtypes of renal cell carcinoma. The presence of a sarcomatoid component in a renal cell carcinoma is widely considered to be a poor prognostic sign and has sufficient patient care implications to warrant inclusion in the diagnosis. The amount of sarcomatoid histology required for diagnosis has not been defined but the suggestion that the sarcomatoid area comprise at least one low-power (4X) field seems reasonable [20]. There is controversy as to whether the amount of sarcomatoid tumor is relevant when analyzing the diseases potential for recurrence. Out of 22 cases of renal cell carcinoma, sarcomatoid differentiation was observed histologically in 3 cases (13.6%) within the tumor tissue. 2 cases of Clear cell type and 1 case of papillary type of renal cell carcinoma had sarcomatoid differentiation. Tumors which showed sarcomatoid differentiation in our study had higher nuclear grades i.e. Grade 2 and Grade 3 and this observation was correlating with the study done by de Peralta – Venturina et al [24]. Sarcomatoid change in renal cell carcinoma protends a worse prognosis. The prognosis of patients with renal cell carcinoma is influenced by multiple factors, including nuclear grade, tumor size, infiltrative margin, tumor stage, and histologic type, but tumor stage is the most important determinant of outcome [25]. The TNM staging system of the AJCC is recommended. In the present study the most common primary tumor staging was T1 accounting for 54.5% (12 cases). This correlates with the studies conducted by Leclercq et al [17] and Karakiewicz et al [19]. It is well known that nodal involvement is one of the major factors influencing the prognosis of cancer patients, including patients with renal cell carcinoma. In our study, 13.6% (3) of the cases had regional nodal metastasis which was a little bit higher when compared to other studies conducted by Leclercq et al [17] and T. Gudbjartsson et al [18]. This slight variation in the present study may be due to a small study group. Several limitations of this study merit discussion. Our data represent a retrospective review of findings at a single center. As such, our findings are subject to the inherent biases of this type of analysis. More importantly our data represent a group of patients who were treated surgically. While the standard of care at our institution during the

study period was to manage a renal mass surgically, patients who were not treated surgically, perhaps due to widespread metastases or inoperable tumors, were not captured in our surgical database. Furthermore, histological diagnosis and grading was not obtained from a single pathologist, which may be associated with different grading parameters. However, diagnoses and grading at our institution were determined by pathologists accustomed to assessing neoplastic disease.

CONCLUSION

In concluded, the underscores the importance of nuclear grading in predicting survival of renal cell carcinoma patients. There is strong correlation between grade, tumor size, and stage. Sarcomatoid change in renal cell carcinoma protends a worse prognosis. Because tumors with even a small component of sarcomatoid change may have an adverse outcome, this finding when present, should be noted in the surgical pathology report. Tumor size is not an independent predictor for the histological subtype of renal cell carcinoma. However, it is closely correlated to histopathological features, with the indications that the greater the tumor size, the more aggressive potential the renal cell carcinoma. Stage and grade, together with age and calendar year of diagnosis, are therefore the most important prognostic factors of survival for patients with renal cell carcinoma.

Conflict of Interest: None.

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