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Study of Prognostic Factors in Renal tumors in nephrectomy specimen: Experience of a tertiary care hospital

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Abstract
Tumours of the kidney are one of the common genitourinary malignancies.A detailed and meticulous histopathological examination of nephrectomy specimens is essential to record accepted Pathological prognostic factors. This study was undertaken to study prognostic value of histological subtypes and pTNM stage and grade of the malignant renal tumor. Nephrectomy specimen from 36 patients were studied. Patient's clinical details, preoperative imaging and surgical details were reviewed. Each specimen was staged according to the 2017 AJCC TNM staging. Nuclear grade was assigned according to the revised WHO/ISUP grade.
Statistical Methods: *Statistical analysis was performed using statistical software and descriptive statistics and survival functions were obtained by Kaplan- Meier product limit method. Univariate and multivariate analysis of factors affecting outcome of the patient were performed. Factors that were found to be significant on Univariate analysis were then subjected to multivariate analysis by Cox proportional hazards regression model*
Results: *Mean follow up period was 26.3 months (range 3 to 63 months). Univariate analysis revealed that histologic types stage and grade were statistically significant (P=0.009,0.007 and 0.003 respectively). Multivariate analysis model revealed that ISUP nuclear grade and stage were statistically significant (P=0.007 and 0.002 respectively).*
Conclusion: *This study emphasizes the pathological pTNM (AJCC) 2017 staging as having significant survival impact in the patients of Renal Cancer in the Indian subpopulation. In these patients Histologic subtype and nuclear WHO/ISUP grade are important independent predictors of survival.Organ confined tumours with high nuclear grades need to be followed up more rigorously.*
Keywords: *Renal Cell carcinoma, Radical Nephrectomy, pTNM staging, ISUP grading, prognostic factors.*

Introduction

Tumours of the kidney are one of the common malignancies accounts for 2 to 3 % of total genitourinary malignancies in adult population[1]. They are one of the ten common cancers in human. Different modalities for the treatment for the renal tumor are available but surgery remains as one of the most commonly used if the disease is limited to the organ. As these tumours are relatively having

low sensitivity to radiotherapy and chemotherapy. so surgery in the form of partial or radical nephrectomy remains the primary modality of treatment in patients with renal tumours. Radical nephrectomy is the gold standard for the treatment of renal tumor significantly increasing survival in patients withorgan confined disease[1]. A detailed and meticulous histopathological examination of nephrectomy specimens is essential to record accepted Pathological prognostic factors like Tumor size, Invasion in perinephric fat or renal sinus tissue, Venous involvement, Histologic subtype, WHO/ISUP grade, Sarcomatoid /Rhabdoid differentiation, Histologic tumor necrosis[2,3,4]. Accurate diagnosis, grading and staging are crucial in the management of these patients, both to improve outcome as well as to allow for accurate prognostication which can be recorded by gross and microscopic examination. So study was undertaken to study prognostic significance of Histological subtypes, Histological grade, pTNM staging in malignant renal tumors in adult nephrectomy specimen [5, 6].There have been significant changes in the staging, classification and grading of renal cell tumor in recent times[7]. Histologic subtyping was done according to recent WHO CLASSIFICATION OF TUMORS OF THE KIDNEY, 4TH Edition, 2016.pTNM Staging of the renal tumors was done according to AJCC CANCER STAGING MANUAL, 8th edition-2017 [8, 9].

Material and Methods

The study was conducted at Histopathology Department, Tertiary care hospital from Jan. 2016 to Dec. 2018.A total 36 tumor nephrectomy specimens from 36 adult patients were included in the study. Inclusion criteria was Nephrectomies either radical or partial, done for malignant tumors in adult patients. Nephrectomies performed for non-neoplastic conditions and also in children were excluded from the study. Nephrectomy specimens received from urology department from this institute were fixed in 10% buffered formalin. Appropriate handling is clearly the first step toward accurate diagnosis and staging of RCC. Gross handling of nephrectomy specimens was done according to the standard protocol (CAP /ISUP practical guidelines for examining nephrectomy specimens.) The specimen processed in a standardized fashion to allow for full pathological assessment. Sections stained with Haematoxylin and eosin (H and E) and examined.

There have been significant changes in the staging, classification and grading of renal cell tumor in recent times. Major changes have occurred in our understanding of extra-renal extension by renal cell cancer and how gross specimens must be handled to optimally display extra-renal spread. Care is taken in grossing to include the sections from the renal sinus tissue, perinephric fat, Gerota's fascia, ipsilateral adrenal gland, cut end of the vein artery and ureter etc. to examine the spread of tumor optimally.

Tumor size is an important determinant of the AJCC TNM pathologic stage and correlates with perinephric fat extension, renal sinus invasion, prognosis and metastatic potential[10,11,12,13].

According to 8th edition of AJCC tumor size (T) was given the category of TI Tumor < 7 cm in greatest dimension, limited to the kidney.T2 Tumor > 7 cm in greatest dimension, limited to the kidney.T3 Tumor extends into major veins or perinephric tissues. But not into the ipsilateral adrenal gland and not beyond Gerota's fascia.T4 Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland).

According to 8th edition of AJCC N category was given N x when Regional lymph nodes cannot be assessed, N O No regional lymph node metastasis, N I Metastasis in regional lymph node(s)M category was given MO No distant metastasis, M 1 Distant metastasis, AJCC Prognostic stage groupsWhen T is... And N is... And M is... Then the stage group is...TI NO MO as I ,TI NI MO as III,T2 NO MO as II,T2 NI MO as III,T3 NO MO as III,T3 NI MO as III,T4 Any N MO as IVAny T Any N MI as IV [12,13].

Recent studies have shown that nucleolar grade alone is sufficient to define grades 1 to 3 for RCC and this provides outcome prediction superior to that of Fuhrman grading[7,14]. So grading was done

according to WHO ISUP grading system. Histological grade was given as GX when Grade cannot be assessed, GI as Nucleoli absent or inconspicuous and basophilic at 400x magnification.G2 when Nucleoli conspicuous and eosinophilic at 400x magnification. Visible but not prominent at 100 x magnification. G3 when Nucleoli conspicuous and eosinophilic at 100x magnification. G4 when marked nuclear pleomorphism and/or multinucleate giant cells and/or Rhabdoid and/or Sarcomatoid differentiation. Histologic subtypes of different tumors of kidney was done following the recent WHO CLASSIFICATION OF TUMORS OF THE KIDNEY, 4TH Edition ,2016.More than 50 subtypes given in the book with few changes in the from the previous classification. Many new morphological types HAVING PROGNOSTIC SIGNIFICANCE have been described in the 2016 WHO classification. Statistical analysis done using SPSS 16.0 software. Survival time was calculated from the date of nephrectomy to the last known date of clinical evaluation or death. Survival functions were calculated using Kaplan- Meier product limit method. Difference between individual prognostic factors was evaluated by performing Univariate analysis using the Log Rank test. Minimum value for statistical significance was taken as P=<0.05. Factors that were found to be significant on Univariate analysis were then subjected to multivariate analysis by Cox proportional hazards regression model.

Results and Observations

A total of 36 renal tumors from adult patients who underwent radical or partial nephrectomy were analyzed who met our inclusion criteria. Mean age of patients was 47.9±15.1 years (Range: 21 - 80 years) of these, 24 (66%) were males and 12 (34%) females ratio was 1.9:1.20 (54%) involved the left kidney and 16 (46%) the right kidney. The mean tumor size was 9.4 cm (range 4 -17 cm) as CT scan and 9.2 cm (range 3.4 -20 cm) on histopathology. Mean follow up period was 26.3 months (range 3 to 63 months).Gross capsular invasion with involvement of perinephric fat in 12 cases (34.1%) [Figure 12]. Renal vein invasion was found on gross examination in 2 (5.55%) cases [Figure 9]. Of these patients 61.11%, 22.22%, 11.1% and 5.5% found to have conventional clear cell carcinoma figure[1]., papillary figure[2]., Chromophobe Figure[3], and mucinous and tubular spindle cell carcinoma figure [4]. Respectively. Table [1] Median survival of the patients with Chromophobe carcinoma was more as compared to clear cell and papillary carcinoma.

WHO/ISUP grading of the tumors revealed 6 cases as grade I figure [5].,14 cases as grade II figure [6]. , 4 cases of grade III figure [7].,12 cases of grade IV figure [8].Table [2]

pTNM Tumor stage according to AJCC cancer staging manual 2017 was associated with histopathological grading of the tumor given by ISUP/WHO. Maximum number of cases were of grade II amounting to 38.2 % of total cases. Out of the total 14 cases of grade II 6 cases having stage II and 6 cases having grade III.

Maximum number of cases were of stage I with 14 cases (38.8%).Out of the total 14 cases of stage I most of the cases were of grade II. Tumor size is an important determinant of the UICC/AJCC TNM pathologic stage and correlates with perinephric fat extension, renal sinus invasion, prognosis and metastatic potential. We found total 14 cases with tumor size T 1 with tumor size <7 cms.8 cases with T2 with tumor size more than 7 cms. 8 cases showing T3 with perirenal fat invasion not beyond the Gerotas fascia 2 cases with T4 category with tumor invading the renal vein as an emboli.4 cases with invasion beyond the Gerotas fascia were assigned the category T4.we also found renal sinus fat invasion and perinephric fat invasion in 4 cases each. Figure [11],[12].

Univariate analysis of the impact of tumor stage tumor grade and histological types on the oncological outcome revealed that stage grade an histological type are the factors having statistically significant impact with p value 0.03,0.030.0.003 respectively. Multivariate analysis of comparing of the effect of the tumor stage grade and histological subtype using cox proportional hazard model

revealed that stage grade and histological subtype has statistically significant impact on survival. Table [6]

Tumor stages (stage 1,2 over stage 3,4) ,WHO ISUP grade (Grade I,II over Grade III,IV), Histological subtypes (Chromophobe over clear cell over papillary) was found to be statistically significant impact on survival with p value having 0.040,0.002 and 0.024 respectively by multivariate analysis using Cox proportional hazard regression model. Table [7]

Table 1 Histological subtype of the tumor

Type	Total no (36)	Percentage
Conventional clear cell	22	61.11
Papillary Carcinoma	8	22.22
Chromophobe Carcinoma	4	11.11
Mucinous tubular spindle cell carcinoma	2	5.5

Table 2 WHO /ISUP Grade wise Distribution of Cases

Grading	No. of cases	Percentage
G 1	6	14.6%
G 2	14	38.2%
G 3	4	11.8%
G 4	12	35.4%

Table 3 Grade wise distribution of cases in different stages

WHO/ISUP Grade	N (36)	STAGE 1	STAGE 2	STAGE 3	STAGE 4	Percentage
G1	6	4	2	0	0	14.6
G2	14	6	2	6	0	38.2
G3	4	0	0	4	0	11.8
G4	12	4	4	0	4	35.4

Table 4 Stage wise distribution of cases

TNM stage	NO	Percentage
Stage 1	14	38.8
Stage 2	8	22.2
Stage 3	10	27.7
Stage 4	4	11.1

Table 5 Stage wise distribution of cases in different ISUP grades

pTNM Stage	N (36)	G1	G2	G3	G4	Percentage
Stage I	14	4	6	0	4	38.8
Stage II	8	2	2	0	4	22.2
Stage III	10	0	6	4	0	27.7
Stage IV	4	0	0	0	4	11.1

Table 6 Univariate analysis of prognostic variables for Cancer Free Survival

Characteristics	Hazard ratio	95% CI (SE%)	P value
Age	0.72	0.25 – 1.43 (3)	0.48
Male gender	0.66	0.18 – 2.12 (4)	0.542
Tumor size (<7cm and >7 cm)	0.47	0.73 - 2.56 (3)	0.32
Systemic symptoms	0.74	0.32 - 1.12 (6)	0.238
Tumor Stage	4.29	1.14 – 15.94 (2)	0.030
WHO/ISUP grade	3.46	1.11 – 10.80 (2)	0.033
Histological type	0.92	0.30 – 2.81 (4)	0.003

Table 7 Multivariate Analysis of the Prognostic Variables for Cancer Specific Survival

VARIABLE	CATEGORY	RR(95%CI)	P-VALUE
Tumor Stage	***Stage 1-2,3-4***	***1.91 (0.78-4.69)***	***0.040***
WHO/ISUP grade	***G1-2, G3-4***	***4 (1.21-13.28)***	***0.002***
Histological subtypes	***Chromophobe, papillary-Clear cell***	***2 (1.14-3.52)***	***0.024***

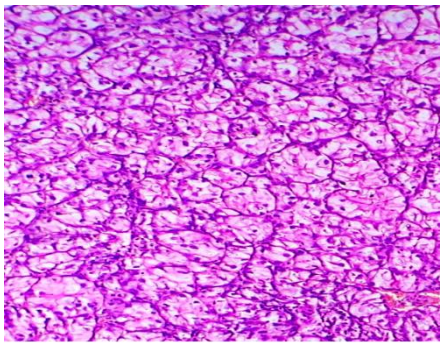

Fig. 1 showing clear cell renal cell carcinoma [H&E X40]

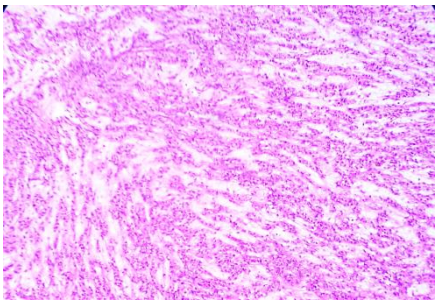

Fig 4 Mucinous tubular and spindle cell carcinoma [H&E X20]

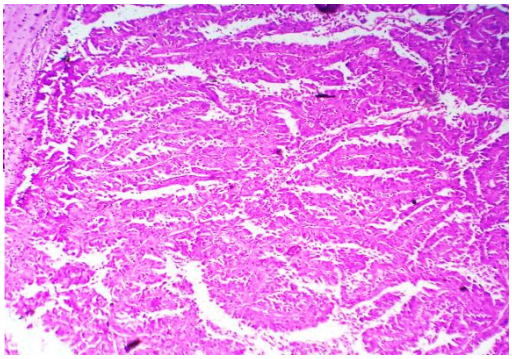

Fig. 2 Showing papillary carcinoma of Kidney [H&E X40]

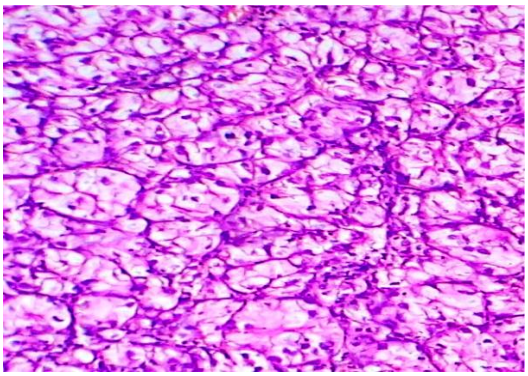

Fig.5 ISUP Grade I RCC with inconspicuous nucleoli [H&E X40]

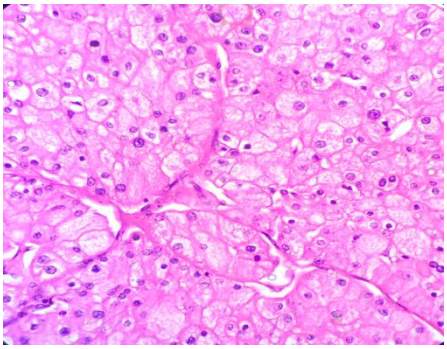

Fig.3 Showing Chromophobe carcinoma [H&E X40]

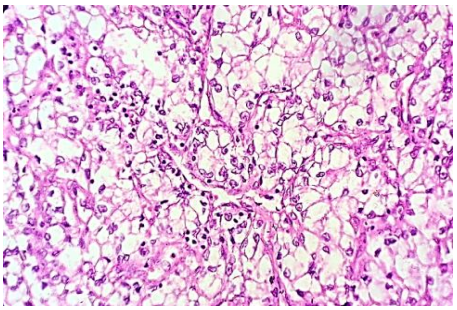

Fig. 6 ISUP Grade Ii RCC with conspicuous nucleoli [H&E X40]

Discussion

In this study, we analyzed the morphologic spectrum and proportion of renal tumors in adults in our set up. We also study histopathologic prognostic characteristics of renal tumors. We found Clear cell RCC and Papillary RCC as the common Histological subtypes as consistent with previous studies. All renal cell carcinomas show a male predominance. Patients with Chromophobe and papillary renal cell carcinoma having better prognosis over the clear cell carcinoma.

The spectrum of adult renal tumors in this study consistent with that of previously reported literature[15,16,17]. Univariate analysis of the earlier studies show histopathological type of the renal cell tumor is important prognostic indicator. Study done by Ljungberg et al and Moch et al reported significantly different outcomes among histologic subtypes for 186 and 423 patients.Motzer et al and Beck et al found that patients with Chromophobe tumors had a longer survival compared with clear cell histology in 64 and 1,057patients respectively.In both Univariate and multivariate analysis we found, the ISUP grade, TNM stage and morphotype, exerted a significant effect. Although significant in Univariate analysis, the histologic subtype was not retained in multivariate analysis in a study done by Patard et al [15].Amin et al [20] does not demonstrate such an independent prognostic value for the histologic type.

In the present study, multivariate analysis for the prognostic value of histologic subtype was done by forming two groups. In first group formed by Chromophobe and papillary carcinoma .As we know Chromophobe carcinoma is regarded as the low grade tumor with little tendency to metastasize [16]. Regarding the papillary carcinoma we found they are limited to kidney and are low grade tumors.

In the second group comprising of the clear cell carcinoma of the kidney. We found most of the cases were of in the higher grades of ISUP and most of the tumors were extending outside of the kidney. so on multivariate analysis we found the significant prognostic difference in two groups with Chromophobe carcinoma and papillary carcinoma having better prognosis over clear cell carcinoma of kidney.

Our data show that grading of the tumor by ISUP grade having significant prognostic value both on Univariate and multivariate analysis. Other studies of ISUP grade and other grading systems found nuclear grade as an independent variable for determining patient's outcome[7,22]. On multivariate analysis of the tumors low ISUP grade tumors comprising of grade I and II have increased cancer specific survival over the high grade tumor comprising of grade III and Grade IV tumors regardless of the histologic types and stage of the tumor. Our results are consistent with the study of Delahunt et al[7] determining the ISUP grade of the large series patients.

Tumor size is a key component of the pTNM staging system and remains one of the most important prognostic factors for RCC [23, 24]. It has been observed that as the tumor size increases, the likelihood of malignant and aggressive behavior of the tumor. The mean tumor size is more in our study as compared to the western literature Regarding pathologic staging of RCC according to 2017 TNM staging system, it is observed that most of cases (68.2%) presented at an advanced stage (pT2 or above) as compared with studies from the other authors, where majority of these tumors were detected as incidental findings and presented at a lower stage. The renal sinus fat invasion, renal vessel invasion as well as the perinephric fat invasion changes the stage of the patient to the higher stage other than the tumor size. So while examining the specimen of renal tumor it is prudent to give attention to these findings both microscopically as well as grossly

Conclusion

This study emphasizes the pathological pTNM (AJCC) staging as having significant survival impact in the patients of Renal Cancer. In these patients HISTOLOGIC subtype and nuclear WHO/ISUP grade are important independent predictors of survival [25]. A meticulous and detailed histopathologic examination of tumor nephrectomy

specimen while gross examination is essential. We recognize that it is a small scale and short duration study. However, we believe it is an important contribution in that it sheds light on the spectrum of renal tumors in adults in our set up and Characterizes in detail the pathologic prognostic factors of renal tumors guiding the management of these patients.

References

1. Robson CJ, Churchill BM, Anderson W. Results of radical nephrectomy for renal cell carcinoma. J Urol;101:297-301,1969.
2. Van Brussel JP, Mickisch GH. Prognostic factors in renal cell and bladder cancer. Br J Urol Int;83:902-9.1999
3. Bonsib SM. Risk and prognosis in renal neoplasms. A pathologist's prospective. Urol Clin North Am;26:643-60. Review.1999
4. Medeiros LJ, Gelb AB, Weiss LM. Renal cell carcinoma. Prognostic significance of morphologic parameters in 121 cases. Cancer;61:1639-51,1988.
5. Guinan P, Sobin LH, Algaba F, Badellino F, Kameyama S, MacLennan G, et al. TNM staging of renal cell carcinoma: Workgroup No. 3. Union International Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer;80:992-3,1997.
6. Bretheau D, Lechevallier E, de Fromont M, Sault MC, Rampal M, Coulange C. Prognostic value of nuclear grade of renal cell carcinoma Cancer;76:2543,1995.
7. Delahunt B, Cheville JC, Martignoni G et al The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J SurgPathol 37:1490–1504.2013
8. Moch H, Humphrey PA, Ulbright TM, Reuter VE (2016) WHO classification Tumours of the urinary system and male genital organs. International Agency for Research on Cancer, Lyon Moch H, Gasser T, Amin MB, Torhorst J, Sauter G, Mihatsch MJ. Prognostic utility of the recently recommended histologic classification and revised TNM staging system of renal cell carcinoma: A Swiss experience with 588 tumors. Cancer;89:604-14.2000.
9. Nativ O, Sabo E, Raviv G, Madjar S, Halachmi S, Moskovitz B. The impact of tumor size on clinical outcome in patients with localized renal cell carcinoma treated by radical nephrectomy. J Urol;158:729-32,1997.
10. Yoshino S, Kato M, Okada K. Evaluation of the prognostic signifi- Srivastava et al: Prognostic factors in patients with renal cell carcinoma Indian Journal of Cancer | July - September 2004 | Volume 41 | Issue 3 103 cance of microvessel count and tumor size in renal cell carcinoma. Int J Urol:119-23,1985.
11. Hafez KS, Fergany AF, Novick AC. Nephron sparing surgery for localized renal cell carcinoma:impact of tumor size on patient survival, tumor recurrence and TMN staging. J Urol;162:1930-3,1999.
12. Delahunt B, McKenney JK, Lohse CM, Leibovich BC, Thompson RH, Boorjian SA, Cheville JC A novel grading system for clear cell renal cell carcinoma incorporating tumor necrosis. Am J SurgPathol 37:311–322(2013)
13. Zisman A, Pantuck AJ, Chao D, Dorey F, Said JW, Gitlitz BJ, et al. Reevaluation of the 1997 TNM classification for renal cell carcinoma: T1 and T2 cutoff point at 4.5 cm rather than 7 cm better correlates with clinical outcome. J Urol;166:54-8,2001
14. Patard JJ, Leray E, Rioux-Leclercq N, Cindolo L et al Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. J ClinOncol 23:2763–2771,2005.
15. Leibovich BC, Lohse CM, Crispen PL, Boorjian SA, Thompson RH, BluteML, Cheville JC Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. J Urol 183:1309–1315,2010.

16. Capitanio U, Cloutier V, Zini L et al A critical assessment of the prognostic value of clear cell, papillary and chromophobe histological subtypes in renal cell carcinoma: a population-based study. BJUI 103:1496–1500,2009.
17. Volpe A, Novara G, Antonelli A et al Chromophobe renal cell carcinoma (RCC): oncological outcomes and prognostic factors in a large multicentre series. BJU Int 110:76–83,2012.
18. Frees S, Kamal MM, Knoechlein L et al Differences in overall and cancer-specific survival of patients presenting with chromophobe versus clear cell renal cell carcinoma: a propensity score matched analysis. Urology.
Doi 10. 1016/ j .urology.2016.05.048,2016.
19. Amin MB, Paner GP, Alvarado-Cabrero I, Young AN, Stricker HJ, Lyles RH, Moch H Chromophobe renal cell carcinoma: histomorphologic characteristics and evaluation of conventional pathologic prognostic parameters in 145 cases. Am J Surg Pathol32:1822–1834,2008.
20. Becker A, Hickmann D, Hansen J et al Critical analysis of a simplified Fuhrman grading scheme for prediction of cancer specific mortality in patients with clear cell renal cell carcinoma–impact on prognosis. Eur J Surg Oncol 42:419–425,2016.
21. Lang H, Jacqmin D. Prognostic factors in renal cell carcinoma. EAU update series; 1:215-9,2003.
22. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: An analysis of pathological features related to tumor size. J Urol;170:2217-20,2003.
23. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol 168:2395–2400,2002.