JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(1)63–68
doi:10.1093/jjco/hys192
Advance Access Publication 15 November 2012

A Preoperative Prognostic Model Predicting Recurrence-free Survival for Patients With Kidney Cancer

Ozgur Yaycioglu[1,*], Saadettin Eskicorapci[2], Erdem Karabulut[3], Bulent Soyupak[4], Cagatay Gogus[5], Taner Divrik[6], Levent Turkeri[7], Sertac Yazici[8], Haluk Ozen[8] and Society of Urooncology Study Group for Kidney Cancer Prognosis[†]

[1]Department of Urology, Baskent University, Adana, [2]Department of Urology, Pamukkale University, Denizli, [3]Department of Biostatistics, Hacettepe University, Ankara, [4]Department of Urology, Cukurova University, Adana, [5]Department of Urology, Ankara University, Ankara, [6]Department of Urology, Tepecik Hospital, Izmir, [7]Department of Urology, Marmara University, Istanbul and [8]Department of Urology, Hacettepe University, Ankara, Turkey

*For reprints and all correspondence: Ozgur Yaycioglu, Baskent University School of Medicine, Department of Urology, Adana Clinic & Research Center, Dadaloglu MH. 39 SOK. NO:6, 01250 Yuregir, Adana, Turkey.
E-mail: yaycioglu@yahoo.com
[†]Members of the Society of Urooncology Study Group for Kidney Cancer Prognosis are listed in the Appendix.

Received June 26, 2012; accepted October 16, 2012

Objective: To develop a preoperative prognostic model in order to predict recurrence-free survival in patients with nonmetastatic kidney cancer.
Methods: A multi-institutional data base of 1889 patients who underwent surgical resection between 1987 and 2007 for kidney cancer was retrospectively analyzed. Preoperative variables were defined as age, gender, presentation, size, presence of radiological lymph nodes and clinical stage. Univariate and multivariate analyses of the variables were performed using the Cox proportional hazards regression model. A model was developed with preoperative variables as predictors of recurrence after nephrectomy. Internal validation was performed by Harrell's concordance index.
Results: The median follow-up was 23.6 months (1–222 months). During the follow-up, 258 patients (13.7%) developed cancer recurrence. The median follow-up for patients who did not develop recurrence was 25 months. The median time from surgery to recurrence was 13 months. The 5-year freedom from recurrence probability was 78.6%. All variables except age were associated with freedom from recurrence in multivariate analyses ($P < 0.05$). Age was marginally significant in the univariate analysis. All variables were included in the predictive model. The calculated c-index was 0.747.
Conclusions: This preoperative model utilizes easy to obtain clinical variables and predicts the likelihood of development of recurrent disease in patients with kidney tumors.

Key words: kidney cancer – survival – nephrectomy – nomograms

INTRODUCTION

Renal cell carcinoma is a heterogeneous disease with a highly variable prognosis. Although numerous prognostic factors have been described, no single factor has been shown as a perfect indicator of prognosis. Outcome prediction models also known as prognostic models combine several prognostic factors in order to better predict the prognosis. These models may be used by practitioners to guide treatment decisions, counsel patients, select follow-up schedules tailored to the risk of cancer progression, determine the need for adjuvant therapy and stratify patients for clinical trials. As far as renal cell carcinoma is considered, various

prognostic models have been developed for both patients with localized and metastatic diseases (1–11). Models for localized disease can further be subcategorized as preoperative and postoperative models. The preoperative models might suffer from lack of accuracy because they do not have the advantage of incorporating powerful prognostic variables such as histological type and grade of tumor. An ideal preoperative model with very high accuracy is yet to be described and externally validated.

The objective of this study was to develop a preoperative prognostic model that can be used to predict recurrence-free survival after nephrectomy in patients with renal cancer and no sign of distant metastasis at the time of surgery. We used data from a multi-institutional database and defined a nomogram utilizing readily available clinical and radiological parameters to achieve a practical but also accurate preoperative prognostic model.

PATIENTS AND METHODS

Twenty-five institutions participated to the study. These centers contributed data retrospectively from all patients who underwent radical or partial nephrectomy between 1987 and 2007 for kidney tumors and had no evidence of distant metastasis at the time of surgery. Patients with von Hippel-Lindau disease and synchronous bilateral tumors were not included in the database. A datasheet was provided to all centers to enter the required data that were then pooled in one single database. The final database consisted of 1889 patients.

Preoperative variables were defined as age at the time of surgery, gender, clinical presentation, radiological size, presence of radiological lymph nodes and clinical stage. Clinical presentation was categorized as incidental, local symptoms or systemic symptoms. Incidental tumors were defined as those that were detected during evaluation of an unrelated medical condition, and the patients had no kidney tumor-related symptoms at the time of diagnosis. Patients with Common Terminology Criteria for Adverse Effects (CTCAE) Grade 1 or greater symptoms (such as Grade 1 pain, urine color change or constitutional symptoms etc.) were regarded as symptomatic. Locally symptomatic patients were defined as those who presented with flank pain, flank or abdominal mass or hematuria. Patients with systemic symptoms were defined as those who presented with fever, weight loss, fatigue or signs and symptoms caused by paraneoplastic disorders. Those with both local and systemic symptoms were considered in the systemic symptoms group. Preoperative work-up for staging varied between the centers but mostly consisted of bone scans, blood biochemistry and computerized tomography (CT) scans of the chest, abdomen and pelvis. Some patients had magnetic resonance imaging (MRI) scans of the abdomen. Cross-sectional imaging (CT and/or MRI scans) were used to measure the radiological size, assign clinical stage and identify the presence of regional lymph nodes. The radiological size was defined as the largest diameter of the tumor. The presence of regional lymph nodes was defined as nodes >10 mm. Clinical T and N stages were assigned according to the 2002 TNM staging system of the American Joint Committee on Cancer (12).

The follow-up protocols varied between centers. Generally, patients were followed up at 3–12 monthly intervals by physical examination, routine laboratory evaluation, chest X-ray, CT or ultrasonography. The time to recurrence was defined as the interval from surgery to the first evidence of disease recurrence.

The end points of the study were time until the detection of kidney cancer recurrence and the time to last follow-up if the patient was alive, or time until death if the patient died without kidney cancer recurrence. Kidney cancer recurrence was defined as local or metastatic cancer recurrence or development of cancer in the opposite kidney. Outcomes were measured in terms of disease recurrence. Patients were either alive without metastases, dead without metastases or had disease recurrence (local or metastatic). Patients were censored at the time of death or last follow-up without metastasis. Progression-free probability was estimated using the Kaplan–Meier method. Univariate analysis of the variables was performed by the Cox proportional hazards regression model. Multivariate analysis was performed with the Cox proportional hazards regression model and 95% confidence intervals (95% CI) were calculated on 1000 bootstrap samples. The results of the analyses were used to model preoperative variables as predictors of recurrence after nephrectomy. Thus, a nomogram was constructed for the probability of recurrence-free survival. Internal validation of the model was performed by calculating Harrell's concordance index. All analyses were performed using S-plus 2000 professional software.

RESULTS

Characteristics of the 1889 patients are presented in Table 1. The types of surgical procedures were as follows: 1655 patients open radical nephrectomy, 194 patients open partial nephrectomy, 36 patients laparoscopic radical nephrectomy and 4 patients laparoscopic partial nephrectomy. The smallest tumor was 9 mm and the largest tumor was 300 mm in size. Pathologic evaluations revealed clear cell carcinoma in 1431 patients (75.8%), papillary in 185 (9.8%) patients, chromophobe in 138 (7.3%) patients. In the remaining 135 (7.1%) patients, the histological subtype was reported as collecting duct carcinoma or unclassified/undetermined. The median follow-up was 23.6 months and ranged from 1 to 222 months. During the follow-up, 258 patients (13.7%) developed recurrent disease. The median follow-up for patients who did not develop recurrent disease was 25 months and ranged from 1 to 222 months. The median time from surgery to disease recurrence was 13 months and ranged from 1 to 153 months. The 5-year freedom from

Table 1. Patient characteristics

Total number of patients	1889
Gender	
Male	1178 (62.4)
Female	711 (37.6)
Mean age ± SD at diagnosis (years)	56.7 ± 12.4
Presentation	
Incidental	821 (43.5)
Local symptoms	821 (43.5)
Systemic symptoms	247 (13.1)
Mean tumor size ± SD (mm)	67.1 ± 33.6
Clinical T stage (TNM 2002)	
T1a	290 (15.4)
T1b	775 (41)
T2	400 (21.2)
T3a	249 (13.2)
T3b	91 (4.8)
T4	84 (4.4)
Presence of radiological lymph nodes	
No	1723 (91.2)
Yes	166 (8.8)
Disease recurrence	
No	1631 (86.3)
Yes	258 (13.7)

SD, standard deviation; numbers in parentheses are percentages.

recurrence probability for the study cohort was 78.6% (95% CI 75.9–81.3%).

On univariate analysis, patient age, gender, mode of presentation, radiological size of the renal mass, clinical tumor stage and evidence of lymph nodes on imaging were significant predictors of recurrence. The results of univariate and multivariate analyses are presented in Table 2. All of the variables except age were associated with freedom from recurrence in multivariate analyses ($P < 0.05$). However, since patient age was marginally significant in the univariate analysis, all variables including age were included in the predictive model. The nomogram constructed from the multivariate Cox regression coefficients is shown in Fig. 1. Harrell's c-index developed across the 1889 patients was 0.747.

COMMENTS

Standard treatment for patients with renal cell carcinoma is radical or partial nephrectomy. Preoperative diagnosis is made with radiological evaluation in most of the cases and tissue diagnosis is seldom indicated. With no pathologic variables available, decision-making and patient counseling before nephrectomy are based mostly on clinical variables. An accurate tool for the prediction of prognosis would serve well for clinical decision-making and patient counseling. Preoperative predictive differentiation of patients is useful to choose patients for neoadjuvant treatment trials and possibly for neoadjuvant treatment protocols in the near future. The prediction of prognosis with preoperative clinical variables is also useful for patients whose pathologic variables are not available such as those treated with needle ablative procedures and morcellation of the specimen during laparoscopy.

Five preoperative prognostic models have been published to date (Table 3) (1–5). Yaycioglu et al. reviewed data from 296 patients who underwent open nephrectomy at Johns Hopkins Hospital and generated a prognostic model to categorize patients in low- and high-risk groups in terms of disease recurrence according to the clinical size and mode of presentation (1). A similar model was also developed with data from three European institutes (2). The main limitation of such models is that they omit individual differences in prognosis and instead categorize patients into limited number of risk groups. This results in clustering of patients with varying prognosis in the same group. Accordingly, these two models, although very easy to use, suffered low predictive accuracies in a multi-institutional external validation study (13). The third published model is developed by a multi-institutional study from Canada and Europe. This model is a nomogram for the prediction of freedom from renal cell carcinoma-specific mortality (3). Nomograms are graphic charts that provide outcome probabilities tailored to the individual's characteristics and provide information for individual patient counseling. This study had a model development cohort and an external validation cohort, and the nomogram prediction at 5 years was 86.8% accurate. The fourth model is a preoperative nomogram that predicts the 12-year probability of metastatic renal cancer after radical or partial nephrectomy in patients with renal masses and no concurrent evidence of metastasis (4). It was based on data from Memorial Sloan-Kettering Cancer Center and Mayo Clinic. This model was internally validated with a bootstrapping technique and the resultant concordance index was 0.8. The fifth preoperative model was reported by authors from Japan. It is a preoperative nomogram based on the TNM classification and predicts cause-specific survival in patients with renal cell carcinoma (5). This study utilizes only variables from TNM classification, and some groups have very limited number of patients. Internal validation of 200 bootstrap samples produced a concordance index of 0.81. The models by Raj et al. and Kanao et al. have not yet been externally validated. Models by Karakiewicz et al. and Kanao et al. include patients with and without metastasis. As metastatic renal cell carcinoma has a much worse prognosis compared with localized disease and the rationale for surgery in patients with and without metastasis is quite different, it is

Table 2. Univariate and multivariate Cox regression model for the prediction of recurrence-free survival after nephrectomy

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value*	HR (95% CI)	*P* value*
Patient age	1.01 (1.002–1.021)	0.017	1.01 (0.998–1.020)	0.155
Gender	0.64 (0.479–0.820)	0.002	0.64 (0.472–0.840)	0.002
Presentation				
Incidental	1.00	0.000	1.00	0.000
Local symptoms	1.98 (1.496–2.643)	0.001	1.51 (1.116–2.069)	0.010
Systemic symptoms	4.10 (2.933–5.689)	0.001	2.35 (1.632–3.364)	0.001
Radiological size	1.02 (1.014–1.020)	0.001	1.01 (1.004–1.012)	0.001
Clinical stage				
T1a	1.00	0.000	1.00	0.000
T1b	1.63 (0.913–3.333)	0.113	1.24 (0.690–2.626)	0.470
T2	3.85 (2.267–7.813)	0.001	1.74 (0.944–3.984)	0.111
T3a	4.33 (2.524–8.997)	0.001	1.88 (0.967–4.199)	0.074
T3b	10.56 (5.583–22.232)	0.001	3.88 (1.982–8.929)	0.001
T4	9.85 (4.912–21.707)	0.001	2.27 (1.084–5.983)	0.046
Radiological lymph nodes	4.99 (3.670–6.749)	0.001	2.47 (1.692–3.617)	0.001

HR, hazard ratio; CI, confidence interval; CS, clinical stage.
**P* value calculated on 1000 bootstrap samples.

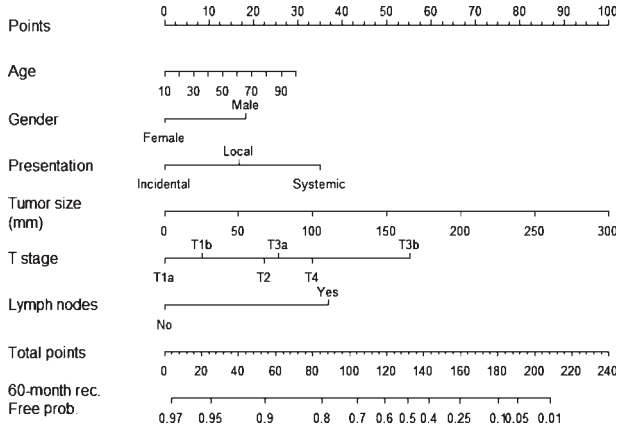

Figure 1. Preoperative nomogram predicting probability of recurrence-free survival at 5 years.

controversial to pool patients with and without metastatic disease in a single cohort. There are already predictive models widely in use for patients with metastasis (11).

There are several postoperative models that predict clinical outcomes based on clinical and pathologic data (6–10). It has been shown that models that incorporate pathological data perform better than preoperative models. The discriminating ability of four prognostic models was compared using an independent dataset containing more than 2404 patients from six European centers (13). As previously mentioned, two of these were preoperative Yaycioglu and Cindolo models, and the other two were postoperative Kattan and UISS models (1,2,6,7). The Kattan nomogram was consistently the most accurate model with a concordance index of 0.807 for recurrence-free survival followed by the UISS model. On the other hand, the same Kattan nomogram showed low predictive accuracy in a sample of 565 French patients with a concordance index of only 0.607 (14). The significance of this variation in different datasets is not very clear because there is no threshold for concordance index to label a model as clinically useful or not (15). Although factors such as differences in the definition of variables in different datasets may result in variations in the accuracy of a certain model (methodologic and spectrum transportability), it is also possible that a model that works well for a specific patient population may not necessarily be the best model for other patient populations (geographic transportability) (16).

The prognostic variables that make our nomogram are age, sex, mode of presentation, tumor size, T stage and presence of lymph nodes. All of these variables have been shown as important prognostic indicators in previous studies (17–26). These variables are also easily available and reproducible, which makes the nomogram easy to be used in real-life clinical practice. However, some points should be mentioned. Categorizing patients in terms of their symptoms may at times be complex, especially when one has to differentiate between local and systemic symptoms on a retrospective analysis. Therefore, we categorized all patients with

Table 3. Published models for the prediction of prognosis before nephrectomy for patients with kidney tumors

	No. of patients	Metastasic disease	Model type	Variables	Endpoint	External validation accuracy
Yaycioglu et al. (1)	296	No	Algorithm	Symptoms Tumor size	DFS	0.651
Cindolo et al. (2)	660	No	Algorithm	Symptoms Tumor size	DFS	0.672
Karakiewicz et al. (3)	2474	Yes	Nomogram	Age Gender Symptoms Tumor size T stage Metastasis	CSS	0.868
Raj et al. (4)	2517	No	Nomogram	Gender Symptoms Lymphadenopathy Necrosis by imaging	DFS	-
Kanao et al. (5)	545	Yes	Algorithm	T stage N stage M stage	CSS	-
Current study	1889	No	Nomogram	Age Gender Symptoms Tumor size T stage Lymphadenopathy	DFS	-

DFS, disease-free survival; CSS, cause-specific survival.

any systemic complaints into systemic group, even if their primary complaint was local symptoms. However, inter-observer variability is always a possibility. For tumor size, we chose to use the largest diameter on CT or MRI. It can be argued that calculation of tumor volume represents the tumor burden more accurately. However, since a largest tumor diameter is easier to calculate and leaves less space for inter-observer variability, we preferred to use it instead. Radiological determination of the exact number of involved lymph nodes may also be problematic. Therefore, we chose to categorize the patients as those with and those without lymph node involvement. There are debates going on over TNM classification and the definition and subcategorization of T stage, which is constantly evolving. It is probable that further refinements on the definition of T stage may be incorporated to the nomogram. However, this subject is to be investigated in the future external validation studies. The limitations of the study are its retrospective nature, relatively short follow-up and the lack of standardized follow-up protocol. On the other hand, the multi-center nature of the study and the number of the enrolled patients are positive aspects. The internal validation of the model resulted in a concordance index of 0.747. This c-index shows that the model has a good accuracy but it is not perfect. The model is yet to be externally validated. There is still room for improvement of the predictive ability of preoperative models. There are efforts to improve the predictive ability of the published postoperative models by integrating molecular markers to these models (27). Improvements on the accuracy of needle biopsy of kidney tumors may allow incorporation of histologic characteristics and tissue molecular markers to the preoperative models as well (28).

CONCLUSIONS

This model predicts the likelihood of the development of cancer recurrence in patients with kidney tumors before nephrectomy. It is a user-friendly nomogram and utilizes easy-to-obtain clinical variables. The model is useful to counsel patients before surgery. It can be used as a tool to enroll patients in clinical trials and to choose which patients would be served best by possible neoadjuvant treatments in the future.

Conflict of interest statement

None declared.

References

1. Yaycioglu O, Roberts WW, Chan T, et al. Prognostic assessment of nonmetastatic renal cell carcinoma: a clinically based model. *Urology* 2001;58:141–5.
2. Cindolo L, de la Taille A, Messina G, et al. A preoperative clinical prognostic model for non-metastaic renal cell carcinoma. *BJU Int* 2003;92:901–5.

3. Karakiewicz PI, Suardi N, Capitano U, et al. A preoperative prognostic model for patients treated with nephrectomy for renal cell carcinoma. *Eur Urol* 2009;55:287–95.
4. Raj GV, Thompson RH, Leibovich BC, et al. Preoperative nomogram predicting 12-year probability of metastaic renal cancer. *J Urol* 2008;179:2146–51.
5. Kanao K, Mizuno R, Kikuchi E, et al. Preoperative prognostic nomogram (probability table) for renal cell carcinoma based on TNM classification. *J Urol* 2009;181:480–5.
6. Kattan MW, Reuter V, Motzer RJ, et al. A postoperative prognostic nomogram for renal cell carcinoma. *J Urol* 2001;166:63–7.
7. Zisman A, Pantuck AJ, Dorey F, et al. Improved prognostification of renal cell carcinoma using an integrated staging system. *J Clin Oncol* 2001;19:1649–57.
8. Frank I, Blute ML, Cheville JC, et al. An outcome prediction model for patients with clear cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade, and necrosis: the SSIGN score. *J Urol* 2002;168:2395–400.
9. Sorbellini M, Kattan MW, Snyder M, et al. A postoperative prognostic nomogram predicting recurrence for patients with clear cell renal carcinoma. *J Urol* 2005;173:48–51.
10. Karakiewicz PI, Briganti A, Chun FK, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. *J Clin Oncol* 2007;25:1316–22.
11. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002;20:289–96.
12. Greene F.L. *AJCC Cancer Staging Manual*, 6th edn. New York, USA: Springer 2002;230–1.
13. Cindolo L, Patard JJ, Chiodini P, et al. Comparison of predictive accuracy of four prognostic models for nonmetastatic renal cell carcinoma after nephrectomy a multicenter European study. *Cancer* 2005;104:1362–71.
14. Hupertan V, Roupret M, Poisson JF, et al. Low predictive accuracy of the Kattan postoperatiğve nomogram for renal cell carcinoma recurrence in a population of French patients. *Cancer* 2006;107:2604–8.
15. Kattan MW. Validating a prognosting model. *Cancer* 2006;107:2523–4.
16. Justice AC, Covinsky KE, Berlin JA. Assesing the generalizability of prognostic information. *Ann Intern Med* 1999;130:515–24.
17. Flanigan RC, Polcari AJ, Hugen CM. Prognostic variables and nomograms for renal cell carcinoma. *Int J Urol* 2011;18:20–31.
18. Russo P, Jang TL, Pettus JA, et al. Survival rates after resection for localized kidney cancer: 1989 to 2004. *Cancer* 2008;113:84–96.
19. Jung EJ, Lee HJ, Kwak C, et al. Young age is independent prognostic factor foe cancer-specific survival of low-stage clear cell carcinoma. *Urology* 2009;73:137–41.
20. Sanchez-Ortiz RF, Rosser CJ, Madsen LT, et al. Young age is an independent prognostic factor for survival of sporadic renal cell carcinoma. *J Urol* 2004;171:2160–5.
21. Karakiewicz PI, Jelders C, Suardi N, et al. Age at diagnosis is a determinant factor of renal cell carcinoma-specific survival in patients treated with nephrectomy. *Can Urol Assoc J* 2008;2:610–7.
22. Patard JJ, Leray E, Rodriguez A, et al. Correlation between symprom graduation, tumor characteristics and survival in renal cell carcinoma. *Eur Urol* 2003;44:226–32.
23. Patard JJ, Leray E, Cindolo L, et al. Multi-institutional validation of a symptom based classification for renal cell carcinoma. *J Urol* 2004;172:858–62.
24. Frank I, Blute ML, Cheville JC, et al. Independent validation of the 2002 American Joint Committee on cancer primary tumor classification for renal cell carcinoma using a large, single institution cohort. *J Urol* 2005;173:1889–92.
25. Ficcara V, Galfano A, Guille F, et al. A new staging system for locally advanced (pT3–4) renal cell carcinoma: a multicenter European study including 2000 patients. *J Urol* 2007;178:418–24.
26. Thompson RH, Cheville JC, Lohse CM, et al. Reclassification of patients with pT3 and pT4 renal cell carcinoma improves prognostic accuracy. *Cancer* 2005;104:53–60.
27. Kim HL, Seligson D, Liu X, et al. Using tumor markers to predict the survival of patients with metastatic renal cell carcinoma. *J Urol* 2005;173:1496–501.
28. Bolenz C, Lotan Y. Decision making in the management of renal cell carcinoma: can nomograms assist? *Eur Urol* 2009;55:296–9.

Appendix: Members of the Uro-oncology Study Group for Kidney Cancer Prognosis

Ayhan Dirim, Baskent University School of Medicine, Department of Urology; Cavit Can, Osmangazi University School of Medicine, Department of Urology; Cag Cal, Ege University School of Medicine, Department of Urology; Abdullah Demirtas, Erciyes University School of Medicine, Department of Urology; Ferhat Ates, GATA Haydarpasa Training Hospital, Department of Urology; Ozgur Ugurlu, Ankara Numune Education and Research Hospital, 2nd Department of Urology; Erem Kaan Basok, Goztepe Education and Research Hospital, 1st Department of Urology; Bugra Icli, Haydarpasa Numune Education and Research Hospital, 1st Department of Urology; T. Alp Ozkan, Kocaeli University School of Medicine, Department of Urology; Recep Buyukalpelli, 19 Mayis University School of Medicine, Department of Urology; Mustafa Kaplan, Trakya University School of Medicine, Department of Urology; Ali Ayyildiz, Ankara Education and Research Hospital, 2nd Department of Urology; Ahmet Soylu, Inonu University School of Medicine, Department of Urology; Gokhan Faydaci, Kartal Education and Research Hospital, 1st Department of Urology; Semih Ayan, Cumhuriyet University School of Medicine, Department of Urology; Murat Lekili, Celal Bayar University School of Medicine, Department of Urology; Hayrettin Sahin, Dicle University School of Medicine, Department of Urology; Mustafa Yucel Boz, Kartal Education and Research Hospital, 2nd Department of Urology; Mustafa Aldemir, Ataturk Education and Research Hospital, Department of Urology; Murat Bozlu, Mersin University School of Medicine, Department of Urology