Stefan Zastrow, Anh Phuong, Immanuel von Bar, Vladimir Novotny, Oliver W. Hakenberg, Manfred P. Wirth

Primary Tumor Size in Renal Cell Cancer in Relation to the Occurrence of Synchronous Metastatic Disease

Erstveröffentlichung in / First published in:

Urologica Internationalis. 2014, 92 (4), S. 462 - 467 [Zugriff am: 19.05.2020]. Karger. ISSN 1423-0399.

DOI: https://doi.org/10.1159/000356325

Original Paper

Urologia Internationalis

Urol Int 2014;92:462–467
DOI: 10.1159/000356325

Received: May 31, 2013
Accepted after revision: October 14, 2013
Published online: March 12, 2014

Primary Tumor Size in Renal Cell Cancer in Relation to the Occurrence of Synchronous Metastatic Disease

Stefan Zastrow[a] Anh Phuong[a] Immanuel von Bar[a] Vladimir Novotny[a]
Oliver W. Hakenberg[b] Manfred P. Wirth[a]

[a]Department of Urology, University Hospital 'Carl Gustav Carus', Dresden, and [b]Department of Urology, University Hospital Rostock, Rostock, Germany

Key Words
Renal cell cancer · Tumor size · Metastasis · Staging · Management

Abstract
Objectives: To investigate the controversially discussed relationship between tumor size and the occurrence of primary synchronous metastatic disease in renal cell cancer (RCC). ***Patients and Methods:*** A consecutive RCC cohort of 2,058 patients (150 primary metastatic) who underwent surgery between 1995 and 2010 was investigated. Rates of synchronous metastases were calculated for stratified groups of tumor size. Uni- and multivariate logistic regression models were calculated for the correlation of tumor size with primary metastatic disease. ***Results:*** The rate of metastatic disease increased with increasing tumor size. Tumor size was significantly correlated with synchronous metastatic disease ($p < 0.001$, c-index 0.772), but for RCCs ≤4 cm in size no significant correlation was found. Regarding tumors ≤5 cm in size, the correlation became significant ($p = 0.028$, c-index 0.621). A multivariate logistic regression model for the prediction of synchronous metastatic disease including tumor size, age and comorbidity yielded a significant c-index of 0.82 and was used to construct a nomogram. ***Conclusion:*** Our data confirm the correlation between tumor size and the rate of synchronous metastatic disease. Small renal tumors <4 cm in size have a low risk of synchronous metastatic disease. The risk becomes significantly associated with tumor size for tumors ≤5 cm.

Introduction

Renal cell cancer (RCC) accounts for over 4% of all malignancies diagnosed in males and over 3% in females. According to recent evaluations, at the time of first diagnosis of RCC, metastatic disease is seen in 25–35% of all cases [1], making curative treatment impossible in most of them. Metastatic disease is related to the size of the primary RCC [2–4]. However, recently this has been challenged for the subgroup of primary RCC <4 cm in diameter [5]. If this were to be confirmed, it would have implications for the treatment of small renal masses.

With increased use of modern imaging techniques [6], the incidence of small renal masses diagnosed incidentally has risen [7]. It is being discussed whether surgical treatment of small incidental renal masses is always warranted or whether it represents overtreatment generally or under certain circumstances, such as high comorbidity and/or short life expectancy. Therefore, less invasive

KARGER

E-Mail karger@karger.com
www.karger.com/uin

0042–1138/14/0924–0462$39.50/0

Stefan Zastrow, MD
Department of Urology
University Hospital 'Carl Gustav Carus'
Fetscherstrasse 74, DE–01307 Dresden (Germany)
E-Mail stefan.zastrow@uniklinikum-dresden.de

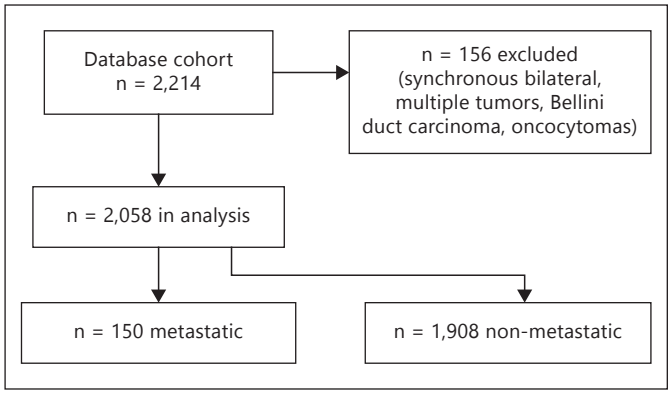

Fig. 1. Consort diagram of the study population and flow within the study.

managements such as cryotherapy, radiofrequency ablation or active surveillance are proposed and are presently being evaluated [8]. However, one caveat of these management approaches to small renal masses is the possibility of undertreatment in cases where synchronous metastatic disease has remained undiagnosed. If there is a considerable risk of metastatic disease in incidental small renal masses, at least full staging would be required before deciding on management. The aim of this study was to evaluate in our own large series of RCC cases treated surgically whether primary tumor size is a reliable predictor for the risk of synchronous metastatic disease in small RCCs and to evaluate other risk factors for metastatic disease in small RCCs in a multivariate model.

Table 1. Tumor characteristics and patient demographics of the whole cohort of RCC cases (WHO TNM classification 2002)

Median age in years (IQR)	64 (14)
Gender, male/female	1,338/720 (65/35)
pT (2002 TNM)	
pT1a	774 (38%)
pT1b	620 (30%)
pT2	232 (11%)
pT3a	185 (9%)
pT3b/c	230 (11%)
pT4	17 (<1%)
cN	
cN0	1,959 (95%)
cN1/2	99 (5%)
cM	
cM0	1,908 (93%)
cM1	150 (7%)
Grading	
G1	250 (12%)
G2	1,486 (72%)
G3	307 (15%)
G4	6 (<1%)
Unknown	9 (<1%)
Median pathological size, cm (IQR)	4.5 (4.0)
Histology	
Clear cell	1,588 (77%)
Papillary	224 (11%)
Chromophobe	194 (9%)
Unclassified	52 (3%)
Most frequent metastatic sites	
Lung	103
Adrenal	38
Bone	36
Liver	20
Brain	10

Patients and Methods

This is a retrospective analysis of a prospectively maintained patient database. The cohort of all consecutive renal tumor cases treated surgically at the Department of Urology of the Technical University Dresden was extracted from our RCC database. Patients had undergone surgery between 1995 and 2010. The database contained 2,214 patients. Cases with multiple or synchronous bilateral tumors, Bellini duct carcinoma or oncocytoma were excluded, leaving 2,058 cases for our analysis (fig. 1). The tumor characteristics and patient demographics are listed in table 1. Table 2 lists the distribution of metastatic patterns in patients with more than one metastatic site.

The standard treatment in our department is open partial nephrectomy, which was performed whenever feasible. Larger tumors or those with central extension and/or vascular infiltration underwent open or laparoscopic radical nephrectomy. Staging included abdominal ultrasound, CT scan and chest X-ray in all cases. Tumors were stratified according to size and the frequency of synchronous metastatic disease in the different groups was calculated.

Patient data were used for modeling a logistic regression model exploring the relationship between primary tumor size and synchronous metastatic disease applying the lrm function of the rms library as described by Harrell et al. [9]. The model test statistics were calculated in an equivalent to a contingency table χ^2 approach. The performance of the model was calculated using the c-index [9]. A c-index of 1.0 indicates a perfect discrimination between patients with different outcome, which was defined as synchronous metastatic disease or no synchronous metastatic disease. A c-index value of 0.5 signifies no discriminatory predictive value at all. Primary tumor size was used as a continuous variable in this model.

Regression modeling initially was done for the whole cohort. For testing the correlation between tumor size and metastatic disease in small tumors exclusively, the same model was constructed for tumors ≤4, ≤5 and ≤6 cm. These different sizes were chosen because the literature describes no correlation for tumors ≤4 cm, but it has not been shown at which size threshold predictive models become valid.

Table 2. Distribution patterns of primary metastatic disease in multiple organs

	Number
Two organs	
Lung, bones	11
Lung, liver	7
Lung, brain	6
Lung, adrenal gland	5
Lung, mediastinum	5
Bone, adrenal gland	2
Lung, thyroid gland	1
Liver, spleen	1
Adrenal gland, abdominal wall	1
Lung, epididymis	1
Liver, pancreas	1
Brain, supraclavicular	1
Three organs	
Lung, liver, bones	4
Lung, liver, adrenal gland	2
Lung, adrenal gland, mediastinum	1
Lung, bones, mediastinum	1
Liver, adrenal gland, mediastinum	1
Lung, adrenal gland, bones	1
Lung, liver, mediastinum	1
Four organs	
Lung, liver, adrenal gland, mediastinum	1
Lung, bones, adrenal gland, brain	1

Table 3. Rates of synchronous metastatic disease in separate groups of primary tumor size

Tumor size, cm	n	M0	M1	% M1
0.2–3.0	428	421	7	1.6
3.1–4.0	363	353	10	2.8
4.1–5.0	299	289	10	3.3
5.1–6.0	236	227	9	3.8
6.1–7.0	199	185	14	7.0
7.1–8.0	147	130	17	11.6
8.1–9.0	107	94	13	12.1
9.1–10.0	93	71	22	23.7
10.1–11.0	65	53	12	18.5
11.1–12.0	28	19	9	32.1
12.1–13.0	27	19	8	29.6
13.1–14.0	22	14	8	36.4
14.1–15.0	17	16	1	5.9
≥15.1	27	17	10	37.0

For better accuracy in predicting the risk of synchronous metastatic disease, a multivariate model was constructed using the covariates age and American Society of Anesthesiologists (ASA) score, again applying the lrm function of the rms library [9]. For testing the significance of the three covariates, Wald testing was applied.

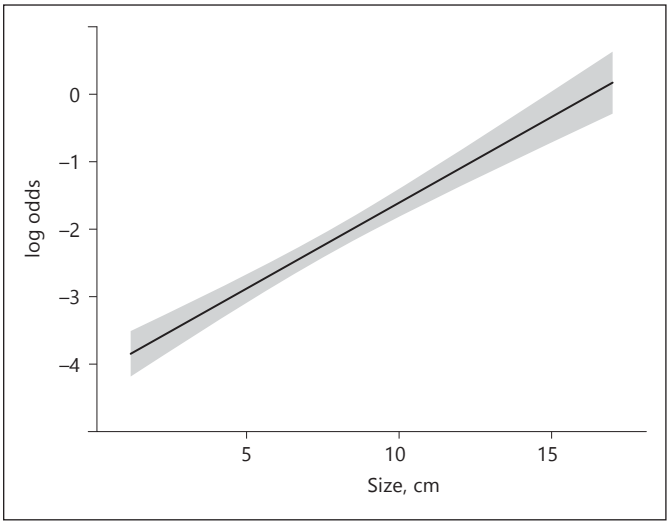

Fig. 2. Regression line of the univariate model showing an increase of the log odds for synchronous metastatic disease with increasing primary tumor size ($p < 0.001$). The calculated c-index of the model is 0.772.

The model was internally validated by the validate function of the rms library and the performance of the model was then calculated using the c-index [9]. Finally, the model was presented graphically as a nomogram using the nomogram function of the rms library.

All statistical analyses were performed using R™, version 2.8.1 (R Foundation for Statistical Computing). The reported p values are two-sided with the statistical significance level set at $p \leq 0.05$.

Results

Within the whole cohort, the rate of synchronous metastatic disease increased with increasing tumor size (table 3). For small renal tumors ≤4 cm in size there was a low risk of synchronous metastatic disease, as only 17/791 (2.1%) patients presented with metastases at first diagnosis in this group. Within the group of small RCCs (≤4 cm) there was an obvious increase in the rate of primary metastatic disease between RCCs ≤3 cm (1.6%) and those with tumors between 3.1 and 4 cm (2.8%), although this observation cannot be validated statistically due to the low number of primary metastases in this group.

The univariate logistic regression model examining the relationship between tumor size and synchronous metastatic disease for the whole study cohort yielded a definite and significant increase in metastatic risk with increasing size of the primary tumor ($p < 0.001$, c-index 0.772; fig. 2). Since data from the literature do question this significant increase for tumors <4 cm in size, the same calculations

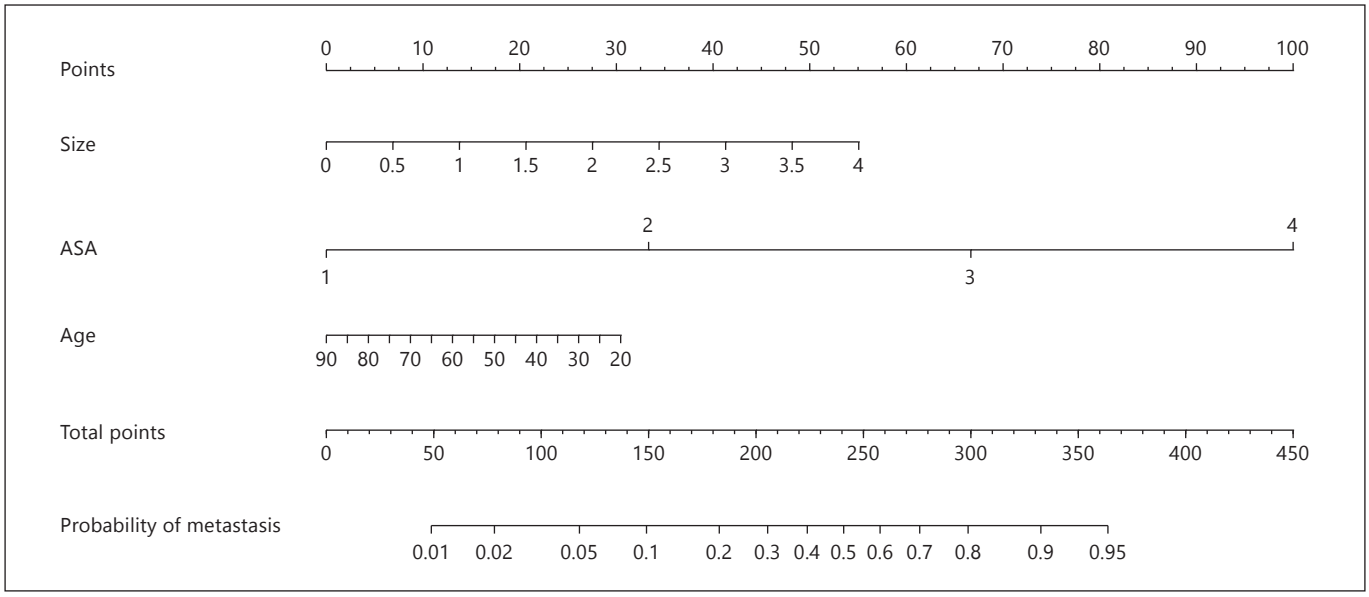

Fig. 3. Nomogram representing a multivariate model for the prediction of synchronous metastatic disease including the variables patient age, ASA score and primary tumor size (cm).

were applied to the group of small RCCs only (≤4 cm) and a comparable logistic regression model was calculated. For these small tumors, however, the logistic regression model did not show a significant association between primary tumor size and metastatic risk ($p = 0.165$, c-index 0.593). This raised the question whether there is a size threshold where the logistic regression model becomes significant. Therefore the regression model was calculated for tumors ≤5 cm and ≤6 cm in size. For both thresholds the model was significant (≤5 cm: $p = 0.028$, c-index 0.621; ≤6 cm: $p = 0.017$, c-index 0.609).

A multivariate predictive model designed to test the predictive power for synchronous metastatic disease included primary tumor size, patient age and ASA score as a comorbidity measure. Inside the model, ASA score ($p = 0.0003$) and tumor size ($p < 0.0001$) were highly significant predictors. Age did not reach significance ($p = 0.3894$). Internal validation of the model produced a c-index of 0.82, i.e. the model was able to predict synchronous metastatic disease with relatively high accuracy. Finally, a nomogram was designed (fig. 3).

Discussion

The plausible notion that primary tumor size correlates with or predicts progression-free and cancer-specific survival is generally accepted and has been shown for many carcinoma entities, including RCC [10–12]. Thus, primary tumor size is an important factor for the management of RCC and also for the management of follow-up.

However, when discussing conservative management in incidentally detected small renal masses, the question of the true risk of synchronous metastatic disease becomes crucial and there is some controversy on this issue [13, 14]. Data from a multicenter study reported a relatively high rate of synchronous metastatic disease in RCCs <4 cm in size [5]. In that series, there was no significant relationship between the rate of synchronous metastatic disease and primary tumor size in tumors <4 cm. However, when not only small tumors but all RCCs were considered, increasing tumor size correlated significantly with the rate of synchronous metastatic disease in other studies [2, 15]. In our RCC database, which has been prospectively maintained since 1995, we could confirm the significant relationship between primary tumor size and the rate of primary metastatic disease.

791 out of the 2,058 patients in our series had primary RCCs with a diameter ≤4 cm, and of those only 2.1% had synchronous metastatic disease. Others reported 9/1,227 (0.7%) patients with primary metastatic disease in RCCs ≤4 cm [4]. Klatte et al. [5] in their multicenter analysis reported a rate of primary metastatic disease of 7, 6, 5 and 8% for RCCs of 0.1–1, 1.1–2, 2.1–3 and 3.1–4 cm in diameter, respectively.

How can such a discrepancy be explained? Looking at the series of Klatte et al. [5] in terms of raw numbers, 34/575 (5.9%) cases of synchronous metastatic disease were reported for RCCs between 0.1 and 3 cm and 8% (38/420) for RCCs between 3.1 and 4 cm in size. Thus, there was a markedly higher rate of synchronous metastatic disease in the group of larger tumors (3–4 cm) among all small RCCs. Pahernik et al. [15] reported 3.0%, 2.6% and 6.0% synchronous metastatic disease in the RCC size groups of 0.1–2, 2.1–3 and 3.1–4 cm, respectively. Their series included a significant number of cases with multifocal tumors, and these represent an increased overall tumor burden; this may lead to an underestimation of the relationship between primary tumor size and synchronous metastatic disease. However, both the series by Pahernik et al. [15] and that by Klatte et al. [5] show a definite increase in the rate of synchronous metastatic disease in RCCs between 3 and 4 cm in size, as does our series. Likewise, a Surveillance, Epidemiology, and End Results database analysis by Lughezzani et al. [3] also found a relatively high rate of synchronous metastatic disease in small RCCs with a definite increase in the larger of the small RCCs (4.8% at ≤1.0 cm, 4.2% at 1.1–2.0 cm, 4.9% at 2.1–3.0 cm and 7.1% at 3.1–4 cm, respectively). Thus, our results are in line with those of others, confirming a certain risk of synchronous metastatic disease in small RCCs <4 cm in diameter which lies between 2.1% (present series) and 5%. However, the risk is much higher in the larger of the small RCCs (3–4 cm) and seems to increase out of proportion in this group – 2.8% (our series) to 8% [5].

It clearly depends on the subgroup of RCC cases included in a given series whether a strong quantitative relationship between tumor size and the rate of synchronous metastatic disease can be calculated. Within the subgroup of small RCCs, statistical significance will be more difficult to reach as the rate of observed cases with metastatic disease will be rather low. This may explain our findings for RCCs ≤4 cm and is in agreement with those of others [5]. Regarding the uncertainty in predicting synchronous metastatic disease in small renal masses ≤4 cm in size, it is of interest to determine when a prediction model would become significant, i.e. whether there is a certain size threshold. We tried to determine such a threshold by calculating models for tumors ≤5 cm and ≤6 cm in size. Interestingly, the model became significant when we extended the cohort to tumors ≤5 cm. This correlation for tumors up to 5 cm shows that even for smaller renal masses tumor size has a predictive potential regarding synchronous metastatic disease.

The second aim of our study was to develop a multivariate model which might better predict the presence of synchronous metastatic disease. This aim was achieved for the whole range of tumor sizes by using readily available parameters such as the ASA score and patient age. Both parameters, although seemingly not directly related to metastatic potential, have been shown to be useful as both patient age and performance, which is related to comorbidity, have been shown to be predictive factors for survival in RCC disease [16–23]. As our database does not include a performance score for all patients, we used the ASA score as an index of comorbidity. The validity of the ASA score as a prognostic factor for survival has recently been shown in a univariate model [20, 21].

Our model performed well for the whole cohort of RCC cases (c-index of 0.82) and thus might have a potential application in cases where the question arises whether additional staging procedures should be performed before deciding on management.

In summary, small RCCs ≤4 cm in diameter have a low but not insignificant risk of synchronous metastatic disease. However, this risk increases considerably in RCCs between 3 and 4 cm in size and becomes significant when tumors up to 5 cm are included in a predictive model. Expectant management of small RCCs bears a definite risk, above all in tumors between 3 and 4 cm in size. Likewise, before undertaking surgical treatment in these cases, additional staging to exclude primary synchronous metastatic disease might be warranted in case of further risk factors such as older age and increased comorbidity.

References

1 Hock LM, Lynch J, Balaji KC: Increasing incidence of all stages of kidney cancer in the last 2 decades in the United States: an analysis of surveillance, epidemiology and end results program data. J Urol 2002;167:57–60.

2 Kunkle DA, Crispen PL, Li T, Uzzo RG: Tumor size predicts synchronous metastatic renal cell carcinoma: implications for surveillance of small renal masses. J Urol 2007;177:1692–1696; discussion 1697.

3 Lughezzani G, Jeldres C, Isbarn H, Perrotte P, Shariat SF, Sun M, Widmer H, Arjane P, Peloquin F, Pharand D, Patard JJ, Graefen M, Montorsi F, Karakiewicz PI: Tumor size is a determinant of the rate of stage T1 renal cell cancer synchronous metastasis. J Urol 2009;182:1287–1293.

4 Thompson RH, Hill JR, Babayev Y, Cronin A, Kaag M, Kundu S, Bernstein M, Coleman J, Dalbagni G, Touijer K, Russo P: Metastatic renal cell carcinoma risk according to tumor size. J Urol 2009;182:41–45.

5 Klatte T, Patard J, Demartino M, Bensalah K, Verhoest G, Delataille A, Abbou C, Allhoff E, Carrieri G, Riggs S: Tumor size does not predict risk of metastatic disease or prognosis of small renal cell carcinomas. J Urol 2008;179:1719–1726.

6 Larson DB, Johnson LW, Schnell BM, Salisbury SR, Forman HP: National trends in CT use in the emergency department: 1995–2007. Radiology 2011;258:164–173.

7 Berland LL, Silverman SG, Gore RM, Mayo-Smith WW, Megibow AJ, Yee J, Brink JA, Baker ME, Federle MP, Foley WD, Francis IR, Herts BR, Israel GM, Krinsky G, Platt JF, Shuman WP, Taylor AJ: Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee. J Am Coll Radiol 2010;7:754–773.

8 Volpe A, Cadeddu JA, Cestari A, Gill IS, Jewett MA, Joniau S, Kirkali Z, Marberger M, Patard JJ, Staehler M, Uzzo RG: Contemporary management of small renal masses. Eur Urol 2011;60:501–515.

9 Harrell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–387.

10 Crispen PL, Boorjian SA, Lohse CM, Leibovich BC, Kwon ED: Predicting disease progression after nephrectomy for localized renal cell carcinoma: the utility of prognostic models and molecular biomarkers. Cancer 2008;113:450–460.

11 Bedke J, Pritsch M, Buse S, Jakobi H, Elsaesser K, Pahernik S, Haferkamp A, Hohenfellner M: Prognostic stratification of localized renal cell carcinoma by tumor size. J Urol 2008;180:62–67.

12 Karakiewicz P, Lewinshtein D, Chun F, Briganti A, Guille F, Perrotte P, Lobel B, Ficarra V, Artibani W, Cindolo L: Tumor size improves the accuracy of TNM predictions in patients with renal cancer. Eur Urol 2006;50:521–529.

13 Smaldone MC, Kutikov A, Egleston BL, Canter DJ, Viterbo R, Chen DY, Jewett MA, Greenberg RE, Uzzo RG: Small renal masses progressing to metastases under active surveillance: a systematic review and pooled analysis. Cancer 2012;118:997–1006.

14 Haramis G, Mues AC, Rosales JC, Okhunov Z, Lanzac AP, Badani K, Gupta M, Benson MC, Mckiernan J, Landman J: Natural history of renal cortical neoplasms during active surveillance with follow-up longer than 5 years. Urology 2011;77:787–791.

15 Pahernik S, Ziegler S, Roos F, Melchior SW, Thüroff JW: Small renal tumors: correlation of clinical and pathological features with tumor size. J Urol 2007;178:414–416; discussion 416–417.

16 Galfano A, Novara G, Iafrate M, Cavalleri S, Martignoni G, Gardiman M, D'Elia C, Patard JJ, Artibani W, Ficarra V: Mathematical models for prognostic prediction in patients with renal cell carcinoma. Urol Int 2008;80:113–123.

17 Bukowski RM, Negrier S, Elson P: Prognostic factors in patients with advanced renal cell carcinoma: development of an international kidney cancer working group. Clin Cancer Res 2004;10(18 Pt 2):6310S–6314S.

18 Motzer RJ, Bacik J, Mazumdar M: Prognostic factors for survival of patients with stage IV renal cell carcinoma: Memorial Sloan-Kettering Cancer Center experience. Clin Cancer Res 2004;10(18 Pt 2):6302S–6303S.

19 Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J: Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530–2540.

20 Brookman-Amissah S, Kendel F, Spivak I, Pflanz S, Roigas J, Klotz T, May M: Impact of clinical variables on predicting disease-free survival of patients with surgically resected renal cell carcinoma. BJU Int 2009;103:1375–1380.

21 de Cássio Zequi S, de Campos ECR, Guimarães GC, Bachega W Jr, da Fonseca FP, Lopes A: The use of the American Society of Anesthesiology classification as a prognostic factor in patients with renal cell carcinoma. Urol Int 2010;84:67–72.

22 Zisman A, Pantuck AJ, Dorey F, Said JW, Shvarts O, Quintana D, Gitlitz BJ, deKernion JB, Figlin RA, Belldegrun AS: Improved prognostication of renal cell carcinoma using an integrated staging system. J Clin Oncol 2001;19:1649–1657.

23 Zisman A, Pantuck AJ, Wieder J, Chao DH, Dorey F, Said JW, deKernion JB, Figlin RA, Belldegrun AS: Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. J Clin Oncol 2002;20:4559–4566.