Does a Venous Tumor Thrombus Exclude Renal Transitional Cell Carcinoma? Implications for Neo-Adjuvant Treatment Strategies

JOHANNES HUBER[1], DOGU TEBER[1], GENCAY HATIBOGLU[1], VALENTIN POPENECIU[1], HILDEGARD JAKOBI[1], PETER HALLSCHEIDT[2], SASCHA PAHERNIK[1] and MARKUS HOHENFELLNER[1]

Departments of [1]Urology, [2]Diagnostic and Interventional Radiology, University of Heidelberg, Heidelberg, Germany

Abstract. *Background: A venous tumor thrombus (VTT) is well-known in renal cell carcinoma, but we experienced a series of five patients with VTT due to renal transitional cell carcinoma (TCC). Our study aimed to determine the incidence and clinical relevance of this entity. Patients and Methods: From our prospectively-maintained tumor database, we identified 102 patients with renal TCC according to postoperative histology and analyzed the incidence of VTT in renal TCC from 1990 to 2010. Results: Five out of 102 patients with TCC (5%) had a VTT. None of these five patients experienced gross haematuria and we presumed correct diagnosis preoperatively in one out of five patients. Univariate analysis revealed that TNM stage and resection status were inferior in the VTT group. All five patients from the VTT group died from their disease, with a median survival of 8.9 months. With regard to all diagnosed VTT, the effective incidence of vena cava involvement in RCC was 48-fold higher than in renal TCC. Conclusion: A VTT is very suggestive of renal cell carcinoma. However, before neo-adjuvant treatment, the diagnosis should be assured whenever there is doubt.*

The formation of a venous tumour thrombus (VTT) is a well-known phenomenon in renal cell carcinoma (RCC) (1, 2). During the past decades, its surgical treatment and prognostic relevance have been investigated in detail: Radical surgery is the only option of long-term survival, and vena cava involvement represents an independent negative prognostic factor compared to a renal vein thrombus (1-3). The latter finding resulted from a multi-center cohort of 1,192 patients suffering from renal cell cancer with venous involvement (3).

VTT caused by other oncological entities has been rarely described (4). Concerning transitional cell carcinoma (TCC) of the upper urinary tract, there are just a few case reports (5) with the largest series to date comprising of three patients (6). Considering these massively-divergent numbers, the finding of a VTT in preoperative imaging is very suggestive of renal cell cancer. However, our clinical experience gave rise to doubts as we treated four patients with renal TCC presenting with a VTT within a 2-year interval. In contrast, several large-scale studies on TCC of the upper urinary tract have not reported on this phenomenon (7-9). We assume that this aspect was believed to be an exception and therefore considered unimportant.

Because of its potential importance for judging on preoperative imaging and prognosis, we systematically investigated this entity. The aim of our study was to determine the incidence and clinical relevance of VTT in renal TCC.

Materials and Methods

Patient selection. From our prospectively-maintained tumor database (10), we identified 102 patients with postoperative histological confirmation of renal TCC (renal pelvis or calices) from 1990 to 2010. We reviewed their reports of preoperative cross-sectional imaging and assigned patients accordingly either to the group with (n=5) or without (n=97) a VTT. As a cross check for the presence of a VTT, we relied on intraoperative findings and the pathologist's report.

Study parameters. We reviewed age, sex, body mass index, Eastern Cooperative Oncology Group (ECOG) performance status, the presence of an additional malignancy, type and year of surgery, TNM stage, grade, resection (R) status, and histological type. Moreover, we estimated glomerular filtration rate (GFR) according to the simplified formula of the "Modification of Diet in Renal Disease" study (11) and calculated it prior to surgery and before discharge. Median follow-up to assess overall and cancer specific survival was 32 (range=0.2-212) months. For the VTT group, we

Correspondence to: Johannes Huber, MD, Ph.D., Department of Urology, Medical Faculty Carl Gustav Carus, TU of Dresden, Fetscherstr. 74, D-01307 Dresden, Germany. Tel: +49 35145818954, Fax: +49 3514584333, e-mail: johannes.huber@uniklinikum-dresden.de

Key Words: Kidney, transitional cell carcinoma, renal cell carcinoma, venous tumour thrombus, neo-adjuvant treatment.

Table I. *Univariate analysis of clinical data.*

Variable	No venous extension n=97	Venous extension n=5	*p*-Value
Median age (years)	68 (42-89)	66 (47-89)	0.87
Gender (male)	64 (66%)	3 (60%)	0.78
Median BMI (kg/m^2)	26.6 (17.3-45.2)	23.7 (19.1-29.4)	0.09
ECOG performance status			0.023
0	56 (58%)	0 (0%)	
1	28 (29%)	3 (60%)	
2	8 (8%)	2 (40%)	
3	5 (5%)	0 (0%)	
Type of surgery			0.016
Kidney-sparing	6 (6%)	0 (0%)	
Nephrectomy	22 (23%)	4 (80%)	
Nephroureterectomy	69 (71%)	1 (20%)	
GFR (ml/min/1.73 m^2)			
Preoperative	63 (6-116)	49 (17-100)	0.49
Before discharge	46 (1-87)	35 (9-83)	0.66
Additional malignancy	64 (66%)	4 (80%)	0.52
Year of surgery			0.015
1990-2000	54 (56%)	0 (0%)	
2001-2010	43 (44%)	5 (100%)	
Follow-up (years)	2.8 (0-17.6)	0.7 (0.2-5.0)	0.08

BMI: Body mass index; GFR: glomerular filtration rate; ECOG: Eastern Cooperative Oncology Group.

Table II. *Univariate analysis of pathological features.*

Variable	No venous extension n=97	Venous extension n=5	*p*-Value
Stage			<0.001
Ta	24 (25%)	0 (0%)	
T1	20 (21%)	0 (0%)	
T2	3 (3%)	0 (0%)	
T3	37 (38%)	0 (0%)	
T4	13 (13%)	5 (100%)	
N Status			<0.001
N0	76 (78%)	3 (60%)	
>N0	21 (22%)	2 (40%)	
M Status			0.031
M0	88 (91%)	3 (60%)	
M1	9 (9%)	2 (40%)	
Grading			0.054
G1	9 (9%)	0 (0%)	
G2	60 (62%)	1 (20%)	
G3	28 (29%)	4 (80%)	
R Status			<0.001
R0	79 (81%)	0 (0%)	
Rx	5 (5%)	0 (0%)	
R1 or R2	13 (13%)	5 (100%)	

complemented outcomes with data from patient records, and we assessed symptoms, suspected and differential diagnoses, preoperative staging, curative *vs*. palliative intent, and details of surgery. Moreover, we recorded complications according to the Clavien-Dindo classification (12).

Statistics. We present categorical data by absolute and relative frequencies, and continuous variables by median and range (minimum and maximum). For comparing groups, we used the Chi-square test and the Mann-Whitney *U*-test. We estimated overall and cancer-specific survival using the Kaplan-Meier method and assessed differences between groups by applying the log-rank test. Moreover, we complemented median survival data with the 95% confidence interval (95% CI). Due to the sample size of five in the smaller group, we decided not to perform logistic regression analysis (13). We performed all calculations with SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA), and all statistical tests were two-sided with significance level set at $p<0.05$.

Ethics. We performed all actions in accordance with the Declaration of Helsinki in its latest version and respected current data protection requirements. The Institutional Review Board of the University of Heidelberg approved the protocol of our prospectively conducted tumour database (no. 207/2005) (10). This required oral and written informed consent to be obtained from every patient.

Results

Entire collective of renal TCC. Out of 102 patients with renal TCC, 66% (67/102) were male, and median age was 68 (range=42-89) years. Five out of 102 patients (5%) had a VTT. It was limited to the renal vein in two patients, reached level II in two patients (extending more than 2 cm above the renal vein but below the intrahepatic vena cava), and reached level IV in one patient (extending above the diaphragm into the right atrium).

Table I shows the univariate analysis of clinical data. Patients with venous involvement had a worse performance status ($p=0.023$) and a higher rate of radical nephrectomy without ureterectomy ($p=0.016$). We treated all five cases with VTT during the past decade ($p=0.015$), but the main reason for shorter follow-up ($p=0.08$) in this group was poor survival. Univariate analysis of pathological features (Table II) revealed that negative prognostic features were more frequent in the VTT group. All five patients with venous involvement showed T4 stage disease and no R0 (both $p<0.001$). N Status ($p<0.001$) and M status ($p=0.031$) were inferior in the VTT group. Only worse grading did not reach significance ($p=0.054$).

Accordingly, overall ($p=0.002$) and cancer-specific ($p<0.001$) survival were shorter in the VTT group. All five patients from the VTT group died from their disease after a median survival of 8.9 (95% CI=2.3-15.5) months. In the other group without VTT, median overall survival was 76.2 (95% CI=49.0-103.4) months. As only 31 out of 97 patients died from their disease, median cancer-specific survival was not reached in the group without VTT.

Table III. *Clinical data and treatment course of five patients with venous tumor thrombus.*

Gender/ age (years)	Symptoms	Suspected diagnosis	Differential diagnosis	Venous tumour thrombus	Preoperative staging	Intent	Surgery	Complications (Clavien-Dindo classification) (12)	Pathological diagnosis	Survival (months)
m/77	None	RCC	Urothelial carcinoma	Level IV	M0	Curative	Nephrectomy and thrombectomy with use of heart-lung machine	IVa	T4 N0 G2 R1	9
m/47	None	RCC	-	Level II	M0	Curative	Nephrectomy and thrombectomy	None	T4 N0 G3 R1	60
f/66	Flank pain	RCC	Lymphoma (excluded with biopsy)	Level II	M1	Palliative	Nephrectomy, vena cava resection, and graft reconstruction	II	T4 N1 G3 R1	6
m/58	Flank pain, weight loss	Urothelial carcinoma	-	Vena renalis	M1	Palliative	Nephroureterectomy	II	T4 N3 G3 R2	3
f/89	Flank pain, weight loss	RCC	Urothelial carcinoma	Vena renalis	M0	Curative	Nephrectomy (no ureterectomy considered because of high age)	None	T4 N0 G3 R1	13

Renal TCC sub-group with T4-stage disease. In total, there were 18 patients with T4 stage disease, giving a VTT incidence of 28% (5/18) in this sub-group. In this negatively-selected sub-group of T4 tumors, there was no difference in overall (p=0.64) and cancer-specific (p=0.97) survival between patients with or without VTT. As reported above, all five patients from the VTT group died from their disease after a median survival of 8.9 (95% CI=2.3-15.5) months. The other 13 patients with T4 tumors but without VTT had a median overall survival of 7.7 (95% CI=6.3-9.0) months and a median cancer-specific survival of 9.9 (95% CI=6.1-13.6) months.

Clinical course of patients with renal TCC and VTT. We summarize on the clinical data and treatment course of five patients with VTT in Table III. Two patients were asymptomatic, three reported flank pain, and two reported weight loss. None of the patients experienced gross haematuria. We presumed correct diagnosis in one out of five patients, and in two more, TCC was the main differential diagnosis. In an 89-year-old patient with a vena renalis thrombus, we discussed TCC as a relevant differential diagnosis. However, we decided not to perform endoscopic diagnostics because there would have been no therapeutic consequence for reasons of age. In two patients with vena cava involvement, we discussed specific differential diagnoses and performed percutaneous tumour biopsy once to exclude lymphoma. The biopsy result suggested collecting duct carcinoma, but did not allow for a conclusive diagnosis because of extensive tumour necrosis. VTT involving the vena cava made RCC the primarily suspected diagnosis in three cases, which accounted for the decision to perform radical nephrectomy.

Two patients had no complications, two had a grade II complication (blood transfusion, pancreatic fistula), and one patient had a grade IVa complication (intermittent haemodialysis and massive transfusion). Only one of five patients with VTT experienced long-term survival of 60 months.

Discussion

At 2%, the low frequency of TCC in cases with a vena cava tumor thrombus essentially accounts for the diagnostic challenge. However, an accurate differential diagnosis between TCC and RCC is most valuable for adequate treatment decision-making. Remarkably, in patients with renal TCC, evidence of VTT on preoperative imaging permits for very good prediction of TNM stage, R status, and survival.

Besides other diagnostic options, balancing differential diagnoses largely relies on known incidences. For renal TCC, even a vague estimate is impossible. In our surgical cohort, the relative frequency of VTT was 5% (5/102) concerning all stages of renal TCC and 28% (5/18) in those with T4 stage disease. Therefore, VTT was unexpectedly frequent in T4 renal TCC, but it had no additional impact on prognosis in this negatively-selected group.

Limited evidence from the literature. Microscopic lymphovascular invasion is present in about 20% of patients with TCC of the upper urinary tract and represents an independent predictor of recurrence-free and cancer-specific survival (14). However, little is known about macroscopic vascular invasion. The number of published cases of renal TCC causing VTT is small. Only 10 more cases have been added (15-22) since Miyazato *et al*. reported the 18th case according to their literature review (5). A synopsis of these 28 cases confirms advanced stages of high-grade disease with a very poor prognosis as joint features. Unfortunately, no conclusions can, therefore, be drawn concerning the incidence of VTT in renal TCC.

In our series, the frequency of renal TCC invading the inferior vena cava was 3% (3 out of 102). Including the two cases with a vena renalis thrombus, the rate of VTT was 5% (5 out of 102). Before 2000, conservative management might have been more frequent because all our reported VTT cases dated from the past decade (Table I). As we were only able to assess surgically-treated patients, the actual incidence is probably even higher. On the other hand, the relatively high frequency in our single-center sample could result from a selection bias. Therefore, it should be verified in some of the large multi-centric collectives published recently (7, 8, 23). For example, a large study on 2,299 patients with invasive upper-tract TCC included 171 cases with T4 stage disease (23). These numbers should allow for a good assessment of the true incidence of VTT in renal TCC.

Implications for clinical decision-making. To provide an estimate on the frequency of TCC with regard to all diagnosed VTT, we further assessed the number of patients with RCC and VTT extension into the vena cava treated at our center. Therefore, we updated our published series (1) to cover the same time interval. Of 1,505 RCC cases 144 involved the inferior vena cava (9.6%): 44 cases reached level I, 41 cases level II, 30 cases level III, and 29 cases level IV. Hence, the frequency of TCC in all patients presenting with a vena cava tumor thrombus was three out of 147 (2%).

The incidence of vena cava involvement in RCC is known to range from 4% to 10% of newly-diagnosed patients (24) and with 9.6% (144 of 1,505) our collective meets the upper limit. This number is about three times higher than the 3% frequency (3 out of 102) in our patients suffering from renal TCC. However, the effective incidence in everyday clinical routine is dominated by the diverging frequency of the diseases at our centre: Within two decades, we operated on 1,505 RCC cases, but only on 102 cases of renal TCC. Therefore, the effective incidence of vena cava involvement in RCC is 48-fold higher.

Because of this huge difference, it holds true that a VTT is very suggestive of RCC. However, it cannot unequivocally identify RCC. To clarify this uncertainty is of utmost importance whenever neoadjuvant treatment is considered, because targeted therapy has encouraging efficacy in RCC (25), while results in TCC are generally poor (26). Therefore, when doubts arise from cross-sectional imaging (27), additional diagnostic measures should be taken to identify the true aetiology. Selective ureteral cytology should be very effective as patients with VTT usually suffer from high-grade TCC (Table II) (9). Additionally, diagnostic ureteroscopy with endoluminal tumour biopsy can be performed. Percutaneous biopsy is another option that we chose in one case to exclude lymphoma. However, the histological diagnosis can also be misleading.

We have shown VTT to be a strong integrating negative prognostic parameter in renal TCC (Table II). Therefore, correct diagnosis is vital for clinical decision-making in these few patients. All of them had T4 stage disease, and stage is the most dominant prognostic factor (28). Moreover, while cytoreductive surgery is a valid strategy in metastatic RCC (29), it has no benefit on survival in metastatic TCC and can therefore only be considered an option for palliation (9). In metastatic disease, or when a VTT indicates advanced TCC, platinum-based chemotherapy and multimodal approaches including radiation therapy might be preferable (9). Depending on the patient's preference and performance status, best supportive care should also be considered. Summarizing, careful patient counselling relies predominantly on identifying the correct aetiology. A better assessment of the true incidence of VTT in renal TCC could further contribute to this task.

Strength and limitations of the study. This is the first study to investigate the incidence and clinical meaning of VTT in renal TCC. Because of the unexpectedly high incidence of VTT, the present study contributes important information to future research. Further questions arise from several limitations: Above all, the study is of an uncontrolled, retrospective nature. Moreover, the sample size is small due to the rarity of this disease. The latter might also bring into question the calculated incidence and reduce the value of comparative statistics. Larger multi-center collectives could overcome this problem and at the same time reduce possible bias caused by the special characteristics of a single-centre study. Therefore, the existing collectives (7, 8) should be analyzed concerning the incidence of VTT in renal TCC in order to corroborate or correct our results.

Conclusion

A VTT is very suggestive of RCC. However, if neoadjuvant treatment is considered, the diagnosis should be assured by biopsy whenever there is doubt. Our study suggests VTT as a strong integrating negative prognostic parameter in renal TCC. The unexpectedly high frequency of 5% (5 out of 102) could, however, result from a selection bias in our single-center sample and should be verified in larger collectives from multiple institutions. A better assessment of the true incidence of VTT in renal TCC could further contribute to clinical decision-making.

Funding

None.

References

1 Haferkamp A, Bastian PJ, Jakobi H, Pritsch M, Pfitzenmaier J, Albers P, Hallscheidt P, Muller SC and Hohenfellner M: Renal cell carcinoma with tumor thrombus extension into the vena cava: Prospective long-term follow-up. J Urol *177*: 1703-1708, 2007.

2 Staehler G and Brkovic D: The role of radical surgery for renal cell carcinoma with extension into the vena cava. J Urol *163*: 1671-1675, 2000.

3 Wagner B, Patard J-J, Méjean A, Bensalah K, Verhoest G, Zigeuner R, Ficarra V, Tostain J, Mulders P, Chautard D, Descotes J-L, De La Taille A, Salomon L, Prayer-Galetti T, Cindolo L, Valéri A, Meyer N, Jacqmin D and Lang H: Prognostic value of renal vein and inferior vena cava involvement in renal cell carcinoma. Eur Urol *55*: 452-459, 2009.
4 Concepcion RS, Koch MO, McDougal WS, Stewart JR and Merrill WH: Management of primary non-renal parenchymal malignancies with vena caval thrombus. J Urol *145*: 243-247, 1991.
5 Miyazato M, Yonou H, Sugaya K, Koyama Y, Hatano T and Ogawa Y: Transitional cell carcinoma of the renal pelvis forming tumor thrombus in the vena cava. Int J Urol *8*: 575-577, 2001.
6 Leo ME, Petrou SP and Barrett DM: Transitional cell carcinoma of the kidney with vena caval involvement: report of three cases and a review of the literature. J Urol *148*: 398-400, 1992.
7 Isbarn H, Jeldres C, Shariat SF, Liberman D, Sun M, Lughezzani G, Widmer H, Arjane P, Pharand D and Fisch M: Location of the primary tumor is not an independent predictor of cancer specific mortality in patients with upper urinary tract urothelial carcinoma. J Urol *182*: 2177-2181, 2009.
8 Ouzzane A, Colin P, Xylinas E, Pignot G, Ariane MM, Saint F, Hoarau N, Adam E, Azemar MD, Bensadoun H, Cormier L, Cussenot O, Houlgatte A, Karsenty G, Bruyère F, Maurin C, Nouhaud FX, Phe V, Polguer T, Roumiguié M, Ruffion A, Rouprêt M, French Collaborative National Database on UUT-UC: Ureteral and multifocal tumours have worse prognosis than renal pelvic tumours in urothelial carcinoma of the upper urinary tract treated by nephroureterectomy. Eur Urol *60*: 1258-1265, 2011.
9 Rouprêt M, Zigeuner R, Palou J, Boehle A, Kaasinen E, Sylvester R, Babjuk M and Oosterlinck W: European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. Eur Urol *59*: 584-594, 2011.
10 Huber J, Herpel E, Jakobi H, Hadaschik BA, Pahernik S and Hohenfellner M: Two decades' experience with a prospective biobank for urologic oncology: research, clinical care, and the patients' view. Urol Oncol *31*: 990-996, 2013.
11 Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G and Foundation NK: National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med *139*: 137-147, 2003.
12 Dindo D, Demartines N and Clavien P-A: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg *240*: 205-213, 2004.
13 Peduzzi P, Concato J, Kemper E, Holford TR and Feinstein AR: A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol *49*: 1373-1379, 1996.
14 Novara G, Matsumoto K, Kassouf W, Walton TJ, Fritsche H-M, Bastian PJ, Nez-Salamanca JIM, Seitz C, Lemberger RJ, Burger M, El-Hakim A, Baba S, Martignoni G, Gupta A, Karakiewicz PI, Ficarra V and Shariat SF: Prognostic role of lymphovascular invasion in patients with urothelial carcinoma of the upper urinary tract: an international validation study. Eur Urol *57*: 1064-1071, 2010.
15 Fariña Pérez LA, Pesqueira Santiago D, San Miguel Fraile P and Delgado Sánchez-Gracián C: Images in urology. Transitional cell renal carcinoma and tumor thrombus in vena cava. Actas Urol Esp *33*: 1041, 2009 (in Spanish).
16 Cerwinka WH, Manoharan M, Soloway MS and Ciancio G: The role of liver transplantation techniques in the surgical management of advanced renal urothelial carcinoma with or without inferior vena cava thrombus. Intern Braz J Urol *35*: 19-23, 2009.
17 Caso J, Seigne J, Back M, Spiess PE, Pow-Sang J and Sexton WJ: Circumferential resection of the inferior vena cava for primary and recurrent malignant tumors. J Urol *182*: 887-893, 2009.
18 Ian C, Marshall GB, Sadler DJ and Gray RR: Answer to case of the month #130. Transitional cell carcinoma of the renal pelvis with local hepatic and venous invasion. Can Assoc Radiol J *59*: 83-85, 2008.
19 Cilliers G, Naidoo A, Ackermann C, Parsons JJ and Andronikou S: Renal vein thrombosis in transitional cell carcinoma. Australas Radiol *51*: B62-B63, 2007.
20 Kawashima A, Takao T, Takaha N, Nishimura K, Nonomura N, Okuyama A, Tsujimoto Y and Aozasa K: Renal pelvic cancer with tumor thrombus in the vena cava inferior: a case report. Hinyokika Kiyo *50*: 869-872, 2004 (in Japanese).
21 Ord J, Potter M, Reynard J and Cranston D: Transitional cell carcinoma of the kidney invading the inferior vena cava, treated by excision and grafting, with a review of vena cava replacement. BJU Int *92*: e38-e40, 2003.
22 Juan Y-S, Jang M-Y, Shen J-T, Chou Y-H, Huang C-H and Hsieh T-J: Transitional cell carcinoma of the renal pelvis with extension into the inferior vena cava: a report of two cases. Kaohsiung J Med Sci *19*: 362-367, 2003.
23 Lughezzani G, Jeldres C, Isbarn H, Sun M, Shariat SF, Alasker A, Pharand D, Widmer H, Arjane P, Graefen M, Montorsi F, Perrotte P and Karakiewicz PI: Nephroureterectomy and segmental ureterectomy in the treatment of invasive upper tract urothelial carcinoma: a population-based study of 2299 patients. Eur J Cancer *45*: 3291-3297, 2009.
24 Marshall VF, Middleton RG, Holswade GR and Goldsmith EI: Surgery for renal cell carcinoma in the vena cava. J Urol *103*: 414-420, 1970.
25 Harshman LC, Yu RJ, Allen GI, Srinivas S, Gill HS and Chung BI: Surgical outcomes and complications associated with presurgical tyrosine kinase inhibition for advanced renal cell carcinoma (RCC). Urol Oncol *31*: 379-385, 2013.
26 Zhu Z, Shen Z and Xu C: Targeted therapy for advanced urothelial cancer of the bladder: Where do we stand? Anticancer Agents Med Chem *12*: 1081-1087, 2012.
27 Jeong YB and Kim HJ: Is it transitional cell carcinoma or renal cell carcinoma on computed tomography image? Urology *79*: e42-e43, 2012.
28 Olgac S, Mazumdar M, Dalbagni G and Reuter VE: Urothelial carcinoma of the renal pelvis: a clinicopathologic study of 130 cases. Am J Surg Pathol *28*: 1545-1552, 2004.
29 Flanigan RC, Mickisch G, Sylvester R, Tangen C, van Poppel H and David Crawford E: Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol *171*: 1071-1076, 2004.

Received December 9, 2013
Revised January 3, 2014
Accepted January 7, 2014