Metastatic Tumor Burden Does Not Predict Overall Survival Following Cytoreductive Nephrectomy for Renal Cell Carcinoma: a Novel 3-Dimensional Volumetric Analysis

Michael L. Blute Jr, Timothy J. Ziemlewicz, Joshua M. Lang, Christos Kyriakopoulos, David F. Jarrard, Tracy M. Downs, Matthew Grimes, Fangfang Shi, Michael A. Mann, and E. Jason Abel

OBJECTIVE To compare 1-dimensional (1D) and 3-dimensional (3D) volume measurements and determine whether primary tumor (PT) burden is predictive of overall survival (OS) following cytoreductive nephrectomy (CN) for metastatic renal cell carcinoma (mRCC).

MATERIALS AND METHODS Records and imaging studies of patients with mRCC treated with CN from 2006 to 2015 were included, with tumor volumes measured by a faculty radiologist blinded to clinical outcomes using Advantage Workstation Volume Share (Ver 4.6, GE, Waukesha, WI).

RESULTS Complete PT and metastatic tumor volumes were measured for 67 patients. For 15 (22.3%) patients, 1D volume was within ±10% of the measured 3D volume. In 40 (59.7%) patients, the 1D calculated PT volume was >10% of the actual 3D volume.

Fractional percentage of tumor volume (FPTV) removed during CN was calculated using the formula PT volume/(PT + met volume). FPTV was not associated with OS when analyzed as a continuous variable.

Patients were divided into 2 groups based on previously published cut point of 90% FPTV. No differences between cohorts in age, gender, grade, subtype, number of metastatic sites, performance status, Memorial Sloan Kettering Cancer Center risk group, or International Metastatic Renal Cell Carcinoma Database Consortium risk group were identified. OS was not different between cohorts (P = .38).

CONCLUSION 1D measurements of PT diameter frequently overestimate mRCC PT volume. In patients with mRCC selected for CN, the ratio of primary to metastatic tumor does not predict OS. UROLOGY 100: 139–144, 2017. © 2016 Elsevier Inc.

The optimal role of cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (mRCC) has recently been re-evaluated with the development of newer systemic therapies. Level 1 evidence for improved overall survival (OS) following CN was provided by 2 randomized trials of patients with mRCC during the immunotherapy era.[1,2] Contemporary evidence supporting treatment with CN is provided from large multicenter retrospective studies of patients treated with targeted therapies.[3,4] However, patient selection for CN is critically important,[5] which has been recognized since the earliest reports of surgery for patients with mRCC.[6]

The overall amount of metastatic tumor burden has been cited as a prognostic factor in many studies, and the initial series of CN frequently excluded patients if they had a large metastatic tumor burden relative to the primary tumor (PT).[7,8] In a retrospective study of 55 patients with mRCC, Pierorazio et al published the first formal analysis of the prognostic ability of the amount of tumor removed during CN, or fractional percentage of tumor volume (FPTV).[9] Interestingly, the authors found that FPTV >90% was associated with significantly better disease-specific survival

Financial Disclosure: *The authors declare that they have no relevant financial interests.*

From the Department of Urology, University of Wisconsin School of Medicine and Public Health, Madison, WI; the Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI; and the Division of Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI

Address correspondence to: E. Jason Abel, M.D., F.A.C.S., Department of Urology, University of Wisconsin School of Medicine and Public Health, UW Medical Foundation Centennial Building, 1685 Highland Avenue, Madison, WI 53705-2281. E-mail: abel@urology.wisc.edu

Submitted: July 8, 2016, accepted (with revisions): September 8, 2016

http://dx.doi.org/10.1016/j.urology.2016.09.016
0090-4295

compared with FPTV <90%, 11.6 vs 2.9 months. Similarly, Barbastefano et al found significant differences in progression-free survival if FPTV was <90% for 46 patients with mRCC in a retrospective analysis of patients treated with targeted agents following CN.[10] Both studies calculated the PT and metastatic volumes using axial imaging to measure tumor dimensions, similar to the Response Evaluation Criteria in Solid Tumors.[11] However, it is unclear if the calculated 1-dimensional volumes (1D volume) are accurate representations of the actual tumor volumes because RCC tumors are irregularly shaped.

With recent improvements in image processing technology, accurate measurement of 3-dimensional tumor volume (3D volume) is possible using images from standard computed tomography or magnetic resonance imaging. The objective of this study is to evaluate differences between measured 3D volume and calculated volume from 1D measurement and determine whether 3D-measured PT burden is predictive of OS following CN for mRCC in the targeted therapy era.

MATERIALS AND METHODS

Following institutional review board approval, clinical and radiographic data were reviewed for patients with mRCC treated with CN from 2006 to 2014 (targeted therapy era) at a single institution. Patients were excluded if all preoperative cross-sectional imaging was unavailable or if metastatic disease was not measurable. Longest axial diameter and volume for all primary and metastatic lesions were measured by 2 independent reviewers who were blinded to clinical outcomes. Volumetric measurements of the primary and metastatic lesions were assessed using Advantage Workstation Volume Share (Ver 4.6, GE, Waukesha, WI). Advantage Workstation Volume Share software uses slice thickness, image matrix, and field of view to determine voxel size. Semiautomated delineation of the tumor allowed determination of the involved voxels with resultant volume reported in cubic centimeter.[12]

Patients were assigned as favorable, intermediate, and poor risk according to definitions from the Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk models.[13,14] Univariable and multivariable Cox proportional hazards analysis was used to identify associations with prognostic factors, including volumetric measurements and OS. FPTV removed during CN was calculated by dividing the PT volume by the sum of metastatic tumor volumes. OS was estimated using the Kaplan-Meier method and compared using the log-rank test. Variables with a P value <.05 were considered significant. Statistical analysis was done using SAS version 9.2.

RESULTS

A total of 67 patients with mRCC who underwent CN were available for analysis. Clinical and pathologic characteristics are shown in Table 1. Median patient age was 63.3

Table 1. Patient and disease characteristics

Characteristics	Overall (n = 67) N (%)	FPTV ≥90% n = 18 (26.9%)	FPTV <90% n = 49 (73.1%)	*P* Value
Median age (IQR)	62.3 (55-67.7)	61.6 (55-67.2)	62.5 (55.6-72.2)	.56
Gender				.76
Male	48 (71.6)	36 (73.5)	12 (66.7)	
Female	19 (28.4)	13 (26.5)	6 (33.3)	
Nuclear grade				.52
1, 2	14 (21.2)	10 (20.8)	4 (22.2)	
3	30 (35.5)	20 (41.7)	10 (55.6)	
4	22 (33.3)	18 (37.5)	4 (22.2)	
Histologic subtype				.69
Clear cell	58 (86.6)	43 (87.8)	15 (83.3)	
Non-clear cell	9 (13.4)	6 (12.2)	3 (16.7)	
Nodal status				.39
N0/Nx	44 (65.7)	34 (69.4)	10 (55.6)	
N1	23 (34.3)	15 (30.6)	8 (44.4)	
Number of metastatic sites				.9
1	41 (61.2)	30 (61.2)	11 (61.1)	
≥2	26 (38.8)	19 (38.8)	7 (38.9)	
Karnofsky performance status				.9
<80	4 (6.0)	46 (93.9)	17 (94.4)	
≥80	63 (94.0)	3 (6.1)	1 (5.6)	
MSKCC risk group				.32
Favorable	6 (9)	6 (12.2)	0	
Intermediate	48 (71.6)	33 (67.4)	15 (88.3)	
Poor	13 (19.4)	10 (20.4)	3 (16.7)	
IMDC risk group				.15
Favorable	7 (10.5)	7 (14.3)	0	
Intermediate	40 (59.7)	26 (53.1)	14 (77.8)	
Poor	20 (29.8)	16 (32.7)	4 (22.2)	
Received targeted therapy	38 (56.7)	10 (55.6)	28 (57.1)	1.0

FPTV, fractional percentage of tumor volume; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; MSKCC, Memorial Sloan Kettering Cancer Center.

Table 2. Univariable and multivariable analysis for OS

		Univariable			Multivariable		
Variable		HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age		0.99	0.96-1.03	.65			
Gender	Male	ref					
	Female	1.19	0.63-2.24	.59			
Grade	1, 2	ref					
	3	1.7	0.75-3.84	.21			
	4	2.7	1.13-6.68	.03	2.2	0.89-5.53	.08
IMDC risk group	Favorable	ref					
	Intermediate	2.2	0.67-7.35	.2			
	Poor	2.9	0.80-10.3	.1			
MSKCC risk group	Favorable	ref					
	Intermediate	3.3	0.78-13.7	.1			
	Poor	8.5	1.7-41.3	.01	3.9	0.83-18.6	.09
Karnofsky PS	≥80	ref		.4			
	<80	1.7	0.53-5.65				
Primary tumor volume		1	1-1.001	.17			
Primary tumor diameter		0.8	0.99-1.008	.77			
FPTV ≥90%		1	0.98-1.02	.77			

Abbreviation as in Table 1.

years (interquartile range [IQR] 55.3-67.9) and the median follow-up was 12 months (IQR 5-28). For the entire population, the median PT volume was 353 cm^3 (IQR 157-642) and the median metastatic site volume was 15 cm^3 (IQR 4-33). Median PT diameter was 9.8 cm (IQR 7.7-12.9) and median diameter for all metastatic lesions was 4.3 cm (IQR 25-91). The median Karnofsky performance status was 90 (IQR 90-100), with median PT volume of 329.5 cm^3 (IQR 175.5-579.5) and median metastatic site volume of 14 cm^3 (IQR 4-33). The median PT diameter was 9.8 cm (IQR 7.8-12.7) and the median diameter for all metastatic lesions was 4.2 cm (IQR 2.5-9.1).

Using the previously published cut point of 90% FPTV, patients were divided into 2 groups. A total of 49 (73.1%) patients had ≥90% of their tumor burden removed at CN, whereas 18 (26.9%) patients had ≤90% FPTV. There were no differences between FPTV ≥90% and FPTV <90% cohorts with regard to age, gender, tumor grade, histologic subtype, number of metastatic sites, performance status, MSKCC risk group, or IMDC risk group. During follow-up, 49 (73%) of patients have died of their disease. Fifty-eight patients had clear cell histology (86.6%), whereas 22 (33.3%) patients had nuclear grade 4 tumors. The anatomic distribution of metastatic sites at presentation for each patient is shown in Supplementary Figure S1. Forty-one (61.2%) patients had 1 metastatic site at presentation, and 25 (38.8%) patients had 2 or more metastatic sites at diagnosis.

Using 1D axial measurement and formula for volume of a sphere ($4/3pir^3$), the calculated 1D volume was compared with the measured 3D volume (Supplementary Fig. S2). For 15 (22.3%) patients, the calculated volume was within ±10% of the measured 3D volume. In 12 (17.9%) patients, 3D tumor volume was underestimated by >10% using volume calculated from a single dimension. In 40 (59.7%) patients, the PT volume was overestimated by >10% of the actual 3D volume using 1D volume calculations. In 12 (18.1%) patients, 1D volume overestimated the 3D volume by >100%.

Cox proportional hazards regression models were used to identify associations with OS among known prognostic variables including measured volumes and FPTV (Table 2). Measured PT volume, diameter, and FPTV were not associated with OS (P = .17, 0.77, 0.77). Median OS for all patients was 16.7 (IQR 8.3-36.4) months. No difference in OS was demonstrated between FPTV ≥90% and FPTV <90% cohorts after Kaplan-Meier analysis (Fig. 1). Additional analyses demonstrated that FPTV was not associated with OS when considered as a continuous variable, (P = .77; HR 1.00; 95% CI 0.99-1.02) or when 75% FPTV was used as a cut point for cohorts (P = .34; HR 1.53; 95% CI 0.64-3.65).

DISCUSSION

CN remains part of the multidisciplinary treatment paradigm for many patients with mRCC based on evidence from phase 3 clinical trials with immunotherapy and retrospective studies with targeted therapies.[1-4] Although few studies have been designed to identify patients who are most likely to benefit from CN,[15] bulky metastatic disease has long been considered a relative contraindication to cytoreductive surgery in mRCC.[5,7-10] However, the studies that originally investigated whether metastatic tumor volume is prognostic for poor outcomes did not directly measure tumor volumes but instead used calculated volumes from 1D measurements.[9,10] The current study has demonstrated that calculated volumes from single measurements were accurate for only 22% of the tumors analyzed. Using a 1D analysis for volume was likely to overestimate PT volumes, including 18% of tumors for which calculated volumes were more than 100% of actual volumes. Using a 3D volume analysis, the percentage of tumor volume removed at CN was not associated with OS, and bulky metastatic disease should not be a contraindication for surgery in well-selected patients.

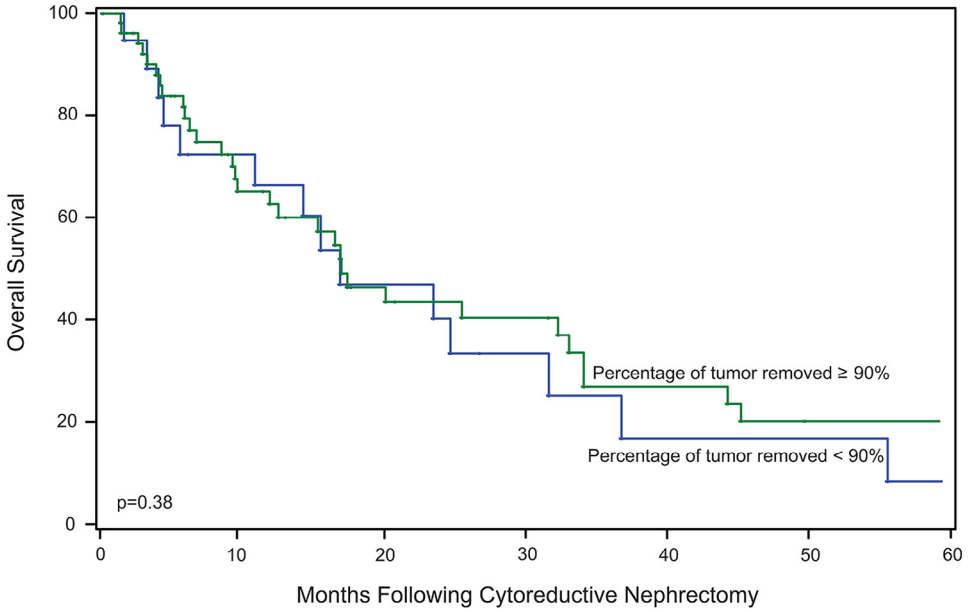

Figure 1. Kaplan-Meier estimate of survival by percent volume of tumor removed at cytoreductive nephrectomy. (Color version available online.)

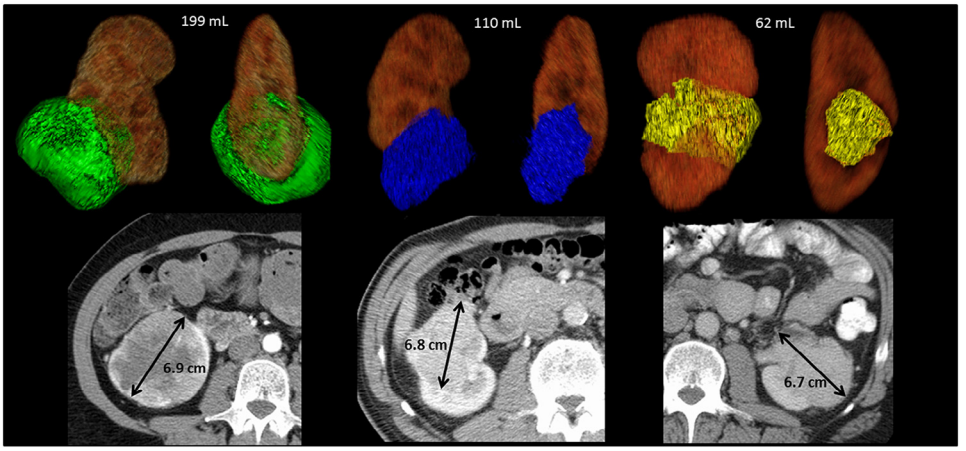

Figure 2. Three primary renal cell carcinoma tumors have similar maximum diameters but actual tumor volumes are widely variable. Calculated volume for tumor with diameter 6.8 cm is equal to 165 cm^3. (Color version available online.)

RCC PTs and metastases are not regular geometric solids. Calculations based on measuring a single dimension are frequently inaccurate, and actual tumor volumes may vary widely despite similar axial 1D measurements (Fig. 2). In the geometric formula for the volume of a sphere, the radius is cubed and any tumor with a large unidimensional measurement may be disproportionately represented if not spherical, as well as any variability in the unidimensional measurement being magnified in the volume calculation. Interestingly, unidimensional measurement error has been noted to increase with irregularly marginated tumors, whereas directly measured 3D volume maintains accuracy regardless of the regularity of tumor borders.[16] Given this large possibility for error with volume calculated from a unidimensional measurement, it is important to measure 3D tumor volumes directly before evaluating whether the FPTV is prognostic for OS in mRCC. The present study is the first to use commercially available image processing software to render actual 3D volumetric measurements of the primary and metastatic tumors in mRCC so that volume characteristics could be accurately evaluated as a prognostic factor.

Several prognostic systems have been developed and validated to stratify patients with mRCC based on expected OS.[13,14,17] Patients who are defined as poor risk have OS less than 1 year and are unlikely to benefit from CN.[4] In the current study, the FPTV ≥90% and FPTV <90% cohorts were similar, with no significant differences between MSKCC and IMDC risk grouping at baseline. Interestingly, Cox proportional hazards models failed to identify any association with FPTV and OS, when analyzed as a continuous variable. Furthermore, median OS in FPTV

≥90% and FPTV <90% cohorts was almost identical (16.6 vs 16.7 months, $P = .38$), which further suggests that metastatic tumor volume relative to PT volume is a poor prognostic factor for OS.

Whereas the optimal role of upfront CN in patients treated with targeted therapy is being investigated in the Clinical Trial to Assess the Importance of Nephrectomy (www.clinicaltrials.gov, NCT00930033), new immune checkpoint inhibitors have been approved for mRCC treatment and have shown promising results in a recent randomized phase 3 clinical trial.[18] Although the mechanism for benefit with CN in patients treated with interferon was unknown, 1 prominent theory is that surgery removes the immunologic sink of the PT.[19] With increased enthusiasm and further development of immune checkpoint inhibitors for mRCC,[20] CN may provide a benefit for patients by removing the immunosuppressive effect of primary RCC tumors similar to observations during the prior immunotherapy era for mRCC treatment.

The results of this study contradict a dogma in mRCC treatment by failing to show an association with OS in patients with large metastatic tumor burden relative to the PT. However, the studies that established this dogma were small retrospective studies that used 1D methods to evaluate tumor volume.[7-10] Using 3D measurements of the PTs in this cohort, we were able to directly measure the volume of tumor burden removed during CN, which was not associated with OS. A recent study by de Bruijn et al also measured tumor volume with an institutional segmentation technique and similarly failed to find any association with survival outcomes,[21] although only 39 patients in this study were treated with CN. Given the lack of evidence with improved techniques for measuring tumor volume, metastatic tumor burden should not be used as a prognostic variable when selecting patients for CN. Limitations of this study include the retrospective analysis, and potential selection bias associated with this study type. Because all patients were selected for surgery, we cannot assess whether FPTV is predictive for patients who were treated nonsurgically. This selection represents clinical practice and even in randomized studies, patients selected for CN may not be representative of all patients. Given the retrospective design, it is likely that there were differences in treatment of individual patients although we did not identify significant differences between cohorts with respect to age, tumor grade, use of targeted therapy, number of metastatic sites, performance status, IMDC grouping, and MSKCC grouping. Multivariable analysis was used to evaluate the association with OS and tumor burden, but it remains possible that unmeasured differences between groups contributed to the observations.

CONCLUSION

Calculation of tumor volumes using a 1D measurement is not accurate when compared with 3D volumetric measurement. In patients with mRCC selected for CN, the ratio of primary to metastatic tumor volume does not predict OS.

References

1. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med*. 2001;345:1655-1659.
2. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet*. 2001;358:966-970.
3. Choueiri TK, Xie WL, Kollmannsberger C, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. *J Urol*. 2011;185:60-66.
4. Heng DYC, Wells JC, Rini BI, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol*. 2014;66:704-710.
5. Abel EJ, Wood CG. Cytoreductive nephrectomy for metastatic RCC in the era of targeted therapy. *Nat Rev Urol*. 2009;6:375-383.
6. Middleton RG. Surgery for metastatic renal cell carcinoma. *J Urol*. 1967;97:973-977.
7. Robertson CN, Linehan WM, Pass HI, et al. Preparative cytoreductive surgery in patients with metastatic renal cell carcinoma treated with adoptive immunotherapy with interleukin-2 or interleukin-2 plus lymphokine activated killer cells. *J Urol*. 1990;144:614-617, discussion 617-618.
8. Fallick ML, McDermott DF, LaRock D, Long JP, Atkins MB. Nephrectomy before interleukin-2 therapy for patients with metastatic renal cell carcinoma. *J Urol*. 1997;158:1691-1695.
9. Pierorazio PM, McKiernan JM, McCann TR, Mohile S, Petrylak D, Benson MC. Outcome after cytoreductive nephrectomy for metastatic renal cell carcinoma is predicted by fractional percentage of tumour volume removed. *BJU Int*. 2007;100:755-759.
10. Barbastefano J, Garcia JA, Elson P, et al. Association of percentage of tumour burden removed with debulking nephrectomy and progression-free survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. *BJU Int*. 2010;106:1266-1269.
11. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst*. 2000;92:205-216.
12. Lubner MG, Dustin Pooler B, del Rio AM, Durkee B, Pickhardt PJ. Volumetric evaluation of hepatic tumors: multi-vendor, multi-reader liver phantom study. *Abdom Imaging*. 2014;39:488-496.
13. 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.
14. Heng DYC, Xie WL, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol*. 2009;27:5794-5799.
15. Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? *Cancer*. 2010;116:3378-3388.
16. Petrick N, Kim HJ, Clunie D, et al. Comparison of 1D, 2D, and 3D nodule sizing methods by radiologists for spherical and complex nodules on thoracic CT phantom images. *Acad Radiol*. 2014;21:30-40.
17. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol*. 2013;14:141-148.
18. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803-1813.
19. Pantuck AJ, Belldegrun AS, Figlin RA. Cytoreductive nephrectomy for metastatic renal cell carcinoma: is it still imperative in the era of targeted therapy? *Clin Cancer Res*. 2007;13:693s-696s.

20. Bedke J, Kruck S, Gakis G, Stenzl A, Goebell PJ. Checkpoint modulation—a new way to direct the immune system against renal cell carcinoma. *Hum Vaccin Immunother*. 2015;11:1201-1208.
21. de Bruijn RE, Nijkamp J, Noe A, et al. Baseline tumor volume in assessing prognosis of patients with intermediate-risk synchronous metastatic renal cell carcinoma. *Urol Oncol*. 2016;34:258, e7-e13.

APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2016.09.016.