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Prognostic Impact of Muscular Venous Branch Invasion in Localized Renal Cell Carcinoma

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Abstract

Objective—Beginning with the 2002 AJCC staging system, renal sinus muscular venous branch invasion has prognostic equivalence with renal vein invasion (RVI) in renal cell carcinoma. To validate this presumed equivalence, we compared patients with isolated MVBI to those with RVI and to those without any confirmed vascular invasion.

Methods—From routine cataloging at Memorial Sloan-Kettering Cancer Center, we identified 500 patients who underwent partial or radical nephrectomy from 2003 to 2008. After excluding patients with metastasis or non-cortical RCC pathology, 85 patients with MVBI (+) were identified. Patients with pT1-2 MVBI (–) (n = 259) or RVI (+) (n = 71) disease served as comparison groups. A multivariable Cox model was used to control for tumor characteristics, using the Kattan RCC nomogram.

Results—In multivariable analysis, the risk of recurrence in the pT1-2 MVBI (–) group was lower than in the MVBI (+) group (HR 0.06, 95% CI 0.02–0.18; $p < 0.001$). Patients with RVI (+) had similar recurrence rates to those with MVBI (+) (HR 0.80, 95% CI 0.39–1.65; $p = 0.6$). Overall survival rates were higher in the MVBI (–) group than in the other groups.

Conclusion—Patients with MVBI have inferior outcomes compared to those with pT1-2 disease. This confirms the adverse prognosis of MVBI and supports pathologic upstaging. The prognosis of MVBI is similar to that of RVI, although we can't exclude the possibility of a difference. Our findings underscore the importance of close patient follow-up and careful pathologic assessment of the nephrectomy specimen.

Keywords

renal cell carcinoma; muscular venous branch invasion; vascular; prognosis; TNM stage

BACKGROUND

Management strategy for renal cell carcinoma begins with precise pathological staging. The identification and validation of new clinical and pathological prognostic factors have prompted an evolution of the American Joint Committee on Cancer TNM staging system. In 2002, the sixth edition contained numerous modifications, most notably the incorporation of additional pathologic findings for extrarenal tumor extension sites into the pT3a category, which included renal sinus fat, perinephric fat, and the ipsilateral adrenal gland. Recent reports have shown that invasion of the renal sinus is associated with poor clinical

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outcomes.¹⁻² Data regarding the prognosis of intravascular tumor extension prompted the establishment of the 2002 pT3a-pT3c criteria.³⁻⁴

The recent adoption of the updated seventh edition in 2010 included several important modifications specifically related to stage III RCC. RSF and PNF invasion (classified as pT3a in the sixth edition,) as well as isolated renal vein invasion (pT3b in the sixth edition) are now both classified as pT3a. These modifications are an attempt to correct numerous demonstrated shortcomings of the 2002 criteria.⁵ As in the sixth edition, extension of the vascular thrombus to a supradiaphragmatic level distinguishes pT3c from pT3b. An additional noteworthy change is the upstaging of ipsilateral adrenal invasion to pT4. Despite the incorporation of MVBI and the presumed prognostic equivalence of MVBI and RVI, the independent contribution of pathologically confirmed MVBI is not well established. Our aim was to evaluate the independent prognostic significance of MVBI as an isolated pathological finding, with the goal of assessing the validity of current stage III modifications in the seventh edition AJCC staging

MATERIALS AND METHODS

After receiving institutional review board approval at MSKCC, we retrospectively identified 500 patients with RCC who were treated with surgery from January 2003 through August 2008. The chosen time frame represents a contemporary series in which standardized techniques were used for the pathologic assessment of renal sinus MVBI within the specimen by a team of dedicated uropathologists at our institution. Prior to 2003, documentation of MVBI, although routine, was not completed in a standardized manner. Exclusion criteria included metastasis on presentation (n = 41), as well as carcinoid, Wilms' tumor, metanephric adenoma or oncocytoma histology (n = 44), leaving 415 patients available for analysis. We identified 85 patients with pathologically assessed pT1-2 N0M0 disease with MVBI without associated RVI. They are referred to as "isolated MVBI" or "MVBI (+)" in the subsequent text. Similar exclusions were used to identify two comparison cohorts, one with pT1-2 tumors without MVBI (n = 259) and a second with pT3a tumors and renal vein invasion (AJCC 2010) with or without associated MVBI (n = 71).

We used Kaplan-Meier methods to compare patterns of recurrence and overall survival in patients with pT1-2 MVBI (–) tumors, patients with isolated MVBI and patients with RVI (+). To account for potential confounders, we controlled covariates via the MSKCC-developed postoperative RCC nomogram in a multivariable Cox regression model.⁶ When calculating predicted probability, the nomogram uses stage as defined in the fifth edition AJCC Cancer Staging Manual (1997) and histological subtype. The 1997 criteria do not incorporate invasion of renal hilar tissues or structures, thus allowing us to effectively evaluate MVBI as a factor while adjusting for other differences in staging. We additionally completed a sensitivity analysis with identical statistical methodology for patients with only conventional clear cell histology. Time to recurrence was defined as the time to first discovery of local or systemic tumor reappearance. Although numerous clinical trials are available for adjuvant therapy in RCC⁷, the rates of referral for adjuvant therapy in patients who underwent nephrectomy (n= none of the included patients received adjuvant therapy, and surveillance as well as surgical and systemic treatments in the salvage setting were undertaken according to best practice guidelines⁸.

RESULTS

Table 1 shows the characteristics of the 415 patients included in these analyses, separately for those pT1-2 MVBI (–), RVI (+) and MVBI (+). Characteristics of patients with MVBI (+) were similar to those with RVI (+). Patients with pT1-2 MVBI (–) were slightly younger

than those with RVI (+) or pT1-2 MVBI (+) (median ages 61 and 64 years, respectively). PT1-2 MVBI (–) patients had comparatively smaller and lower grade tumors than either patients with MVBI (+) or RVI (+) (median size 3.3 cm vs 5.5 and 7.5 cm; 66% grade 1–2 compared to 27% and 30%, respectively).

Overall, 36 patients experienced a recurrence of kidney cancer: 16 patients with pT1-2 MVBI (+), 15 with RVI (+) and 5 with pT1-2 MVBI (–) pathologies. The median time to last follow-up for those who did not experience a recurrence was 1.5 years. Fig. 1 shows the Kaplan-Meier curve for the probability of being recurrence-free for each group. Overall, as shown in Table 2, patients with pT1-2 MVBI (–) tumors were less likely to experience a recurrence than those with MVBI (+) disease (HR for pT1-2 MVBI (–) vs MVBI (+) 0.06, 95% CI 0.02–0.18; $p < 0.001$). We did not find any evidence that patients with RVI (+) tumors had significantly worse recurrence rates than those with MVBI (+) tumors (HR for RVI (+) vs MVBI (+) 0.80, 95% CI 0.39–1.65; $p = 0.5$). These results were not importantly changed after adjustment for the nomogram-predicted probability of recurrence.

The results were similar when overall survival was evaluated (fig. 2). In total, 34 patients died after receiving treatment for kidney cancer: 10 patients with MVBI (+), 15 with RVI (+) and 9 with pT1-2 MVBI (–) disease. Those with pT1-2 MVBI (–) had a lower risk of death than those with MVBI (+) (HR for pT1-2 MVBI (–) vs MVBI (+) 0.13, 95% CI 0.05–0.33; $p < 0.001$). In contrast, we did not find any evidence that those with RVI (+) disease had a higher rate of death than those with MVBI (+) (HR for RVI (+) vs MVBI (+) 0.77, 95% CI 0.34–1.78; $p = 0.5$). Again, these results were not importantly changed after adjustment for the nomogram-predicted probability of death (Table 2).

Sensitivity Analysis: Clear Cell Histology Only

Three hundred and seven patients presented with clear cell histology, of which 71 had isolated MVBI, 53 had RVI (+) and 183 had pT1-2 MVBI (–) tumors. Of this subgroup, 27 patients recurred and 25 died (fig. 3). The results for this cohort were not importantly different from our findings on all combined RCC histologies. The 3-year probability of being free from recurrence was 97% (95% CI 91%–99%) for pT1-2 MVBI (–) tumors, 74% (95% CI 57%–86%) for RVI (+) and 61% (95% CI 38%–78%) with MVBI (+). The 3-year probability of survival was 95% (95% CI 86%–98%) for stage T1-2 MVBI (–) disease and 74% (95% CI 54%–87%) for RVI (+). We found no evidence that patients with RVI (+) had worse recurrence or survival rates than those with MVBI (+) (HR for recurrence 0.88, 95% CI 0.39–1.99; $p = 0.8$ and HR for death 0.93, 95% CI 0.35–2.50; $p = 0.9$). In contrast, patients with pT1-2 MVBI (–) tumors had significantly lower recurrence rates and better survival than those with MVBI (+) (HR for recurrence 0.06, 95% CI 0.02–0.23; $p < 0.001$; HR for death 0.15, 95% CI 0.05–0.48; $p = 0.001$).

DISCUSSION

In our investigation, we have demonstrated that MVBI is associated with both recurrence and death after treatment for RCC. We found no evidence that MVBI (+) patients had better recurrence or survival rates than those with RVI (+); however, due to the small number of patients and the wide confidence intervals we cannot exclude the possibility that there are unrecognized differences between these groups. We further compared our MVBI (+) cohort to patients with pT1-2 MVBI (–) pathology. In this analysis, the pT1-2 MVBI (–) cohort had significantly better recurrence and survival rates compared with MVBI (+) patients. These results were similar in clear-cell-only histology sensitivity analysis, an important observation due to the higher rates of vascular invasion in the clear cell lesions^{9–10}. This underscores the significance of MVBI assessment in terms of patient prognosis and follow-up planning. While current post-operative surveillance strategy is based principally on

pathologic staging⁸, our results could prompt limiting variability in adherence to recommended surveillance regimens in patients with MVBI. Routine pathologic investigation for MVBI should be encouraged.

The American Joint Committee on Cancer continues to modify existing RCC TNM staging based on accumulated clinical and pathological data. The sixth edition incorporated several vital additions specific to the adverse prognosis attributed to invasion of highly vascular and lymphatic-rich central renal structures.³ RSF invasion and MVBI figured centrally in validating these revisions.¹ Patients with previously identified stage pT2 tumors were upstaged at significant rates as a result of these changes.¹¹ Additional reports refining the prognostic relationships of RSF, PNF, and adrenal invasion further supported staging modifications.^{2, 5, 12–14} Although microscopic vascular invasion is associated with poor outcomes in both localized and advanced RCC,^{9, 15} the classification of vascular invasion is not standardized.¹⁶ Despite heightened focus on vascular invasion,^{17–18} prompting inclusion of MVBI in the sixth and seventh edition staging systems, few studies have identified this specific finding or correlated it with patient outcome.

Although the sixth AJCC staging edition is externally validated, several details associated with adrenal and RSF invasion as well as tumor size merited further attention.⁵ Improvements in histological and imaging techniques^{19–22} combined with recent clinical evidence have prompted the re-categorization of RSF, MVBI and RVI as pT3a in the recently published seventh edition AJCC.⁵ This movement maintains the essential prognostic equivalence between RVI and MVBI. Despite some controversy regarding the significance of tumor thrombus extension,²³ caval thrombus was defined as pT3b and pT3c, based on extension beyond the diaphragm.²⁴

Some authors believe that RSF invasion occurs secondarily to MVBI in the vast majority of cases.¹⁰ Until recently, the anatomical and pathophysiological mechanisms underlying the negative prognostic value of MVBI were poorly understood. A 2007 study elegantly described the steps of invasion that connect MVBI to RSF invasion.¹⁰ In this study, venous involvement was found to be a precursor to RSF invasion. Interestingly, correlation between gross sections and histology revealed that the majority of tumor nodules found in the sinus fat had evidence of pre-existing small venous branch invasion.¹⁰ A transvascular approach for sectioning of the gross specimens was found to be crucial in refining the detection, as this approach revealed cases of discontinuous tumor extension, which may otherwise have gone undetected. While microscopic vascular invasion is known to be an independent prognostic factor,^{9, 15} this was the first study to mechanistically define the invasion sequence.

In demonstrating an independent prognostic implication of MVBI, our data supports the upstaging of MVBI lesions to stage III detailed in both the sixth and seventh edition staging sequences. Recent analyses have also supported the AJCC update and certainly corroborate our current findings. In a retrospective single-institution study, prognostic differences were examined between extrarenal extension (including MVBI) and renal vein and/or vena cava tumor thrombus.¹⁷ The combination of extrarenal extension with vascular thrombus was found to have a worse prognosis than either factor alone. Importantly, these data demonstrated in univariate analysis that the presence of tumor thrombus but not the level of extension was a predictor of disease-specific mortality. While the prognostic consequence of tumor thrombus level remains controversial,^{25–27} our data support an independent risk associated with MVBI irrespective of the renal vein invasion. Our results, however, do not parallel the findings of a 2005 study,²⁸ which developed a revised pT3a classification system based on the experience of a single institution. While our data suggest that the prognosis in patients with RVI (+) is similar to those with only MVBI (+), the other study

found a survival disparity between RVI (+) (54.7%) and MVBI (+) (42.4%) Nevertheless, the divergence of results could be explained by our unique focus on MVBI rather than the surrogate of RSF invasion used elsewhere. Although MVBI (+) and RSF invasion are closely associated, the added strict pathologic assessment of MVBI is likely responsible for the statistically equivalent outcomes in our groups. The establishment of MVBI as a distinguishing prognostic factor between pT3a and pT2 stages and as a primary mode of metastasis is also supported by our analysis.¹⁰⁻¹¹

Potential limitations of our study merit discussion. Pathology data from our series was collected retrospectively from previously filed reports and not from specimen reassessment. This shortcoming is tempered by the meticulous renal hilar assessment methodology and documentation present at our institution since 2003, a methodology we similarly advocate to other institutions. Secondly, while we were able to adjust for tumor characteristics in the multivariable analysis via the nomogram-predicted probability of recurrence, there may be other factors that could partially explain our findings. Unfortunately, due to the low number of events, we were unable to control separately for each tumor characteristic (tumor size, grade, clinical presentation, stage). A multi-institutional collaborative effort by institutions with expertise in treating renal cell carcinoma would be provide a larger sample size through which full validation of the seventh edition of the AJCC staging system would be possible.

CONCLUSIONS

Patients with tumors that invade muscle containing branches of the renal vein have similar recurrence-free probability and overall survival to patients with renal vein invasion. Muscular venous branch invasion also independently distinguishes patients with pT3a from pT1-2 pathologies on the basis of recurrence and survival. Our data supports the recent AJCC seventh edition staging criteria for RCC and underscores the importance of meticulous pathologic inspection of renal hilar structures and clear reporting to the operating surgeon of MVBI. Patients found to have MVBI merit close follow-up and consideration for entry into adjuvant therapy trials.

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Number at risk						
pT1-T2 MVBI (-)	259	177	107	79	45	11
pT3a RVI(+)	71	41	28	15	7	4
pT3a MVBI (+)	85	41	17	5	1	0

Stages are identified following the AJCC Cancer Staging Manual, seventh edition.

Fig. 1.

Kaplan-Meier curve for probability of being free from recurrence. Dashed line indicates pT1-2 MVBI (-), dotted line pT3a RVI (+) and solid line pT3a MVBI (+).

Number at risk						
pT1-T2 MVBI (-)	259	179	109	80	45	12
pT3a RVI (+)	71	50	35	18	11	6
pT3a MVBI (+)	85	42	18	6	1	0

Stages are identified following the AJCC Cancer Staging Manual, seventh edition.

Fig. 2.

Kaplan-Meier curve for probability of survival. Dashed line indicates pT1-2 MVBI (-), dotted line pT3a RVI (+) and solid line pT3a MVBI (+).

Number at risk						
pT1-T2 MVBI (-)	183	117	72	52	28	8
pT3a RVI(+)	53	31	21	13	6	3
pT3a MVBI (+)	71	35	16	5	1	0

Stages are identified following the AJCC Cancer Staging Manual, seventh edition.

Fig. 3.

3-year recurrence-free probability for clear cell carcinoma sensitivity analysis. Dashed line indicates pT1-2 MVBI (-), dotted line pT3a RVI (+) and solid line pT3a MVBI (+).

Table 1

Patient characteristics

	No. MVBI (+)* (%)	No. RVI (+) (%)	No. pT1–2 MVBI (–) (%)
Lymph node dissection	44 (52)	32 (45)	40 (15)
American Society of Anesthesiologists score:			
1	4 (5)	0	10 (4)
2	33 (40)	34 (49)	150 (59)
3	43 (52)	36 (51)	94 (37)
4	3 (4)	0	1 (0)
Histology:			
Conventional clear cell	71 (84)	53 (75)	183 (71)
Papillary	1 (1)	3 (4)	37 (14)
Chromophobe	13 (15)	14 (20)	39 (15)
Grade (only clear cell Ca): [†]			
1–2	19 (27)	13 (30)	109 (66)
3	33 (47)	24 (56)	49 (30)
4	18 (26)	6 (14)	6 (4)

* Stage pT3b,¹ pT3a.⁵

[†] In 277 patients.

Table 2Cox proportional hazards regression models predicting recurrence or death by stage⁵

Group	Recurrence HR (95% CI)	Death HR (95% CI)
Univariate:		
pT3a MVBI (+)	Referent	Referent
pT3a RVI (+)	0.80 (0.39–1.65)	0.77 (0.34–1.78)
pT1-2 MVBI (–)	0.06 (0.02–0.18)	0.13 (0.05–0.33)
Multivariate: *		
pT3a MVBI (+)	Referent	Referent
pT3a RVI (+)	0.82 (0.38–1.75)	0.67 (0.28–1.57)
pT1-2 MVBI (–)	0.07 (0.03–0.21)	0.14 (0.05–0.34)
Univariate: †		
pT3a MVBI (+)	Referent	Referent
pT3a RVI (+)	0.88 (0.39–1.99)	0.93 (0.35–2.50)
pT1-2 MVBI (–)	0.06 (0.02–0.23)	0.15 (0.05–0.48)

* Adjusted for nomogram probability of recurrence.

† Sensitivity analysis of clear cell histology only.