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Extent of Renal Vein Invasion Influences Prognosis in Patients with Renal Cell Carcinoma

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Abstract

Objective—To compare oncologic outcomes for segmental versus main renal vein invasion (RVI) in patients with renal cell carcinoma.

Patients Methods—Patients undergoing extirpative surgery for RCC at our institution from 2003–2013 were stratified into five groups: T2 (n=135), T3a with fat invasion (n=185), T3a with segmental RVI (n=87), T3a with main RVI (n=64), and T3b disease (n=40). Kaplan-Meier survival analysis and multivariable Cox regression were performed to determine the impact of segmental RVI on recurrence-free survival (RFS) and cancer-specific survival (CSS). Harrell's C index was used to compare the prognostic accuracy of current and proposed staging models.

Results—At a median follow-up of 37 months, both RFS and CSS were significantly worse for patients with main RVI as compared to segmental RVI ($p = 0.03$, $p = 0.009$, respectively). On multivariable analysis, main RVI had an increased risk of recurrence (HR 2.3, 95% confidence interval [CI] 1.1–4.4, $p = 0.03$) and CSS (HR 3.5, 95%CI 1.3–9.9, $p = 0.02$) compared to segmental RVI. Sub-stratifying T3a disease by separating segmental and main RVI improved prognostic accuracy compared to the current staging system for CSS (c indices 0.66 vs 0.59) and RFS (0.70 vs 0.60).

Conclusions—Main RVI is independently associated with worse RFS and CSS than segmental RVI. These findings may have significance for patient counseling and future staging guidelines.

Keywords

kidney cancer; renal cell carcinoma; venous invasion; risk stratification

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Conflicts of interest: none

Introduction

Renal cell carcinoma (RCC) is the eighth most common malignancy, with an estimated 63,920 new cases and 13,860 estimated deaths in the United States in 2014 [1]. RCC has the ability to locally invade venous structures with tumor thrombus that can propagate distally from the segmental renal veins to the main RV, inferior vena cava (IVC) and right atrium. Historically, an estimated 4–10% of cases of RCC are reported to have venous invasion [2]. Venous invasion is a poor prognostic sign, as these tumors are often found with concomitant distant metastases and, even in the absence of metastatic disease, are associated with long-term survival rates of 60% or less [3–5]. Accordingly, the American Joint Committee on Cancer (AJCC) staging manual designates venous invasion as pathologic stage T3, while the prognostic significance of the extent of venous involvement continues to be reviewed and refined [6–8]. In the most recent AJCC 7th edition, both segmental and main renal vein invasion (RVI) were reclassified as T3a [8].

Accurate staging is necessary not only for patient counseling, but to guide post-operative surveillance and to aid in the design of clinical trials evaluating adjuvant therapies. While the prognostic extent of IVC invasion has been widely studied [4, 9–11], less attention has been given to segmental RVI [12].

Given that the impact of segmental RVI has not been fully clarified, we sought to evaluate the oncological significance of segmental RVI compared to main RVI in a cohort of patients with intermediate-term follow-up.

Methods

Our institutional review board-approved renal mass registry (2003–2013) was queried for patients undergoing extirpative surgery for RCC. The following five patient groups were considered: T3a with segmental RVI (without main RVI), T3a with main RVI, T3a with perinephric or sinus fat involvement (without any venous involvement), T2 disease without venous involvement, and T3b (subdiaphragmatic IVC invasion). The latter three groups were chosen to serve as comparator groups to evaluate if either group in the T3a cohort had survival more similar to the staging groups directly above or below T3a. All patients undergo pre-operative cross-sectional imaging with CT or MRI to stage both the local extent of disease and to assess for distant metastases.

Corresponding with the release of AJCC 6th edition in 2002, segmental RVI defined as invasion into a muscle-containing vein branch was specifically evaluated and consistently documented by our surgical pathologists. Patients with concomitant segmental and main RVI were classified as main RVI. Patients with lymph node or distant metastases were excluded from analysis as survival in these patients is likely driven more by their distant disease than the extent of local tumor. Pathologic examination was performed as previously described [13] and in accordance with International Society of Urological Pathology guidelines [14]. Briefly, representative sections were submitted for analysis with at least one section per cm of tumor and additional sections sampled at the discretion of the grossing pathologist in areas suspicious for venous invasion, extension into sinus or perinephric fat or

necrosis. Specimens were reviewed by general surgical pathologists, with daily consultation of urological pathologists for issues relating to grade, stage and margins. Any case where venous invasion was indeterminate was re-reviewed by a single genitourinary pathology (GJN).

Descriptive statistics were used to summarize patient characteristics and pathologic features. Continuous variables were compared with the Wilcoxon rank-sum or Kruskal-Wallis tests and categorical variables with the chi-square test.

Survival analysis was performed using the Kaplan-Meier method to determine recurrence-free survival (RFS) and cancer-specific survival. The log rank test was used to compare survival curves. RFS was calculated from the date of surgery to local or distance recurrence. All patients with RCC undergo physical exam, chest imaging and cross-sectional abdominal imaging within 6 months after surgery and annually thereafter. Metachronous tumors were not considered a recurrence for purposes of this analysis. CSS was calculated from the time of surgery to death from kidney cancer. An annual query of the Social Security Death Index is performed to confirm vital status and date of death for all patients. Additionally, cause of death data is ascertained from the National Death Index. Multivariable Cox proportional hazard models including extent of venous involvement, tumor diameter, nuclear grade, and fat invasion were constructed to adjust for potential confounding. Harrell's c index for the five patient groups in this study using the current AJCC staging system in terms of CSS and RFS was calculated and compared to new proposed staging models. All statistical analysis was performed with Stata 13.1 (StataCorp, College Station, TX). Two-sided p values < 0.05 were considered significant.

Results

A total of 511 patient met inclusion criteria. Table 1 summarizes demographic of the study patients by clinical stage: pT2 (n=135), pT3a with segmental RVI (n=87), pT3a with main RVI (n=64), pT3a with fat invasion (n=185) and pT3b (n=40). In general, T2 patients tended to be younger, have more non-clear cell histology and more low-grade tumors than patients with venous invasion.

Actuarial RFS was compared for T2, segmental RV, main RV and T3b groups using the Kaplan-Meier method. Median follow-up was 37 months. As expected, the worst RFS was seen T3b patients. However, when subdividing the T3a category, patients with segmental RVI and fat invasion had similar survival to T2 patients ($p = 0.08$ and $p=0.3$, respectively) and patients with main RVI had survival similar to T3b patients ($p=0.9$). Main RVI was associated with worse RFS compared to segmental RV ($p = 0.03$). In all groups the vast majority of recurrences were in distant sites rather than local recurrences. Targeted therapy was recommended in all patients with good performance status.

Similar results were seen in terms of CSS. Again, main RVI was associated with worse RFS than segmental RVI ($p=0.009$). CSS for segmental RVI was indistinguishable from T2 disease ($p = 0.6$) or fat invasion (0.8) while main RVI had similar RFS compared to T3b disease ($p=0.6$). Actuarial 3 year RFS was 90.5% for T2, 80.9% for segmental RVI, 93.9%

for fat invasion, 67.9% for main RVI, and 70.7% for T3b disease. Actuarial 3 year CSS was 93.5% for T2, 93.5% for segmental RVI, 96.7% for fat invasion, 80.8% for main RVI and 74.1% for T3b disease.

In an unadjusted Cox proportional hazard model, segmental RVI had a similar risk of recurrence to patients with T2 disease (HR 0.5, 95% confidence interval [CI] 0.2–1.1, $p=0.1$) and improved RFS compared to fat invasion (HR 0.3, 95%CI 0.1–0.8, $p = 0.008$. Main RVI and T3b disease both had significantly higher risk of recurrence compared to segmental RVI (main RVI HR 2.2, 95% CI 1.1–4.4, $p = 0.03$; T3b HR 2.2, 95%CI 1.0–4.7, $p = 0.05$). Likewise, the risk of death from kidney cancer was similar for T2 and segmental RVI (HR 1.3, 95%CI 0.5–3.8, $p = 0.6$) and fat invasion (HR 0.9, 95%CI 0.3–2.5, $p= 0.8$, while main RV and T3b disease had increased risk (main RVI HR 3.6, 95%CI 1.3–10.0, $p = 0.01$; T3b HR 4.7, 95%CI 1.6–13.4, $p = 0.004$). In a multivariable main RVI remained an independent risk factor for recurrence compared to segmental RV (HR 2.2, 95%CI 1.1–4.4, $p = 0.03$). Similarly, in the adjusted model for death from kidney cancer, main RVI was also an independent risk factor when compared to segmental RVI (HR 3.5, 95%CI 1.3–9.9, p value = 0.02) (Table 2).

Table 3 lists Harrell's C indices for CSS and RFS for the 2010 AJCC staging system and 6 alternative staging models. The current staging model using patient in pT2–pT3b groups has a c index for RFS of 0.60 and CSS of 0.59. The model with the best c indices substratified segmental and main RV invasion into separate categories and demoted fat invasion into T2 (model 5, Table 3) with a c index for RFS of 0.70 and RFS of 0.66.

Discussion

Because the prognostic significance of segmental RVI has not been fully characterized, we evaluated the impact of segmental RVI on RFS and CSS in a cohort of patients with intermediate-term follow up. We found that compared to main RVI, segmental RVI was associated with improved RFS and CSS. Furthermore, segmental RVI performed similarly to T2 disease, while main RVI performed similar to T3b disease. These findings have signification ramifications for patient counseling and risk stratification.

Previous studies evaluating the impact of the extent of venous invasion has led to multiple revision of the AJCC staging guidelines. In the AJCC 5th edition, both main RVI and IVC invasion below the diaphragm were considered T3b, while segmental RVI was not included in the staging schema [6]. However, in the 6th edition, segmental RVI was added to the T3b classification along with main RVI and subdiaphragmatic IVC invasion [7]. Multiple studies have evaluated the significance of main RVI versus IVC invasion. Moinzadeh et al found that compared to patients with level I IVC thrombus, patients with main RVI only had improved ten-year survival [9]. In contrast, Kim et al found that on multivariable analysis controlling for stage, grade and performance status, patients with main RVI and subdiaphragmatic IVC invasion had similar survival [4]. Despite the controversy, main RVI and segmental RVI were reclassified as T3a, while abdominal IVC invasion remained T3b in the most recent AJCC 7th edition [8].

The significance of segmental RVI has been less well studied. Feifer and colleagues evaluated a cohort of patients with segmental RVI treated at Memorial Sloan Kettering [12]. With a median follow-up of 18 months, the authors found no difference in recurrence or survival between patients with segmental RVI or main RVI, but both groups had worse survival compared to a composite pT1-T2 cohort. In contrast, we found that there was survival advantage for segmental RVI compared to main RVI in a study with twice the median follow-up. The discrepancy in both OS and RFS becomes more apparent with longer follow-up as seen in our Kaplan-Meier curves.

Segmental renal veins are located in the renal sinus. Invasion of renal sinus fat, lymphatics and venous structures are all thought to contribute to hematogenous and lymphatic spread from RCC [15, 16]. Not surprisingly, there is a high correlation between segmental RVI and renal sinus fat invasion with data to support segmental RVI as the source of renal sinus fat invasion [17]. In this regard, segmental RVI may be a precursor to both renal sinus fat invasion and main RVI. Invasion of the renal sinus fat is also associated with poor survival [18]. In the current study, segmental RVI had statistically similar survival to T2 disease; however it is also possible that this analysis may have been underpowered to detect a difference between these groups.

Taken together, our data support distinct staging categories for segmental RVI and main RVI. These data should be interpreted in the context of other studies to determine whether segmental RVI should be grouped with T2, main RVI should be grouped with T3b, or a new subcategory should be added to the T3 designation. Our data support the substratification of T3a into two groups. While the improvement of the c indices appear only modest, it is of similar magnitude to findings by Thompson et al in which reclassification of the 2002 AJCC pT3 designation improved the c index from 0.55 to 0.61 [10]. In another study, Kim and colleagues found that the prognostic ability of 2010 staging system as a whole compared to the 2002 showed only modest improvement in c indices (0.850 and 0.848).

Limitations of this study include the retrospective nature of the review, limited sample size, limited follow-up and the lack of pathologic re-review. However, at the time of original pathologic analysis, the presence or absence of segmental RVI was specifically documented in a standardized macro used by all surgical pathologists at our institution. Additionally, differences in baseline characteristics, including different proportions of RCC subtypes and surgical approaches in each group could bias the results. Although potential confounding factors were included in the multivariable analysis, it is possible that additional features not accounted for influenced survival and recurrence in this cohort of patients.

Conclusion

Patients with segmental RVI have improved RFS and CSS compared to patients with main RVI, in contrast to their identical staging in the current staging system. In addition, segmental RVI performed similarly to T2 disease, while main RVI performed similar to T3b disease. These data, if externally validated in larger data sets, should be considered in future staging guidelines and when counseling patients on the risk of recurrence.

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References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin.* 2014; 64:9–29. [PubMed: 24399786]
2. Marshall VF, Middleton RG, Holswade GR, Goldsmith EI. Surgery for renal cell carcinoma in the vena cava. *J Urol.* 1970 Apr.103:414–420. [PubMed: 5437743]
3. Wotkowicz C, Wszolek MF, Libertino JA. Resection of renal tumors invading the vena cava. *Urol Clin North Am.* 2008 Nov.35:657–671. viii. [PubMed: 18992619]
4. Kim HL, Zisman A, Han KR, Figlin RA, Belldegrun AS. Prognostic significance of venous thrombus in renal cell carcinoma. Are renal vein and inferior vena cava involvement different? *J Urol.* 2004 Feb.171:588–591. [PubMed: 14713765]
5. Martinez-Salamanca JI, Huang WC, Millan I, et al. Prognostic impact of the 2009 UICC/AJCC TNM staging system for renal cell carcinoma with venous extension. *Eur Urol.* 2011 Jan.59:120–127. [PubMed: 20980095]
6. Fleming, ID.; Henson, J.; Hutter, D.; O'Sullivan; Sobin; Yarbrow. *AJCC cancer staging manual.* Philadelphia: Lippincott-Raven; 1997.
7. Greene, FL. *AJCC cancer staging manual.* Springer; 2002.
8. Edge, S.; Byrd, D.; Compton, C.; Fritz, A.; Greene, F.; Trotti, A. *AJCC Cancer Staging Manual.* 7th edn. New York, New York: Springer; 2010.
9. Moinzadeh A, Libertino JA. Prognostic significance of tumor thrombus level in patients with renal cell carcinoma and venous tumor thrombus extension. Is all T3b the same? *J Urol.* 2004; 171:598–601. [PubMed: 14713768]
10. Thompson RH, Cheville JC, Lohse CM, et al. Reclassification of patients with pT3 and pT4 renal cell carcinoma improves prognostic accuracy. *Cancer.* 2005 Jul 1.104:53–60. [PubMed: 15895375]
11. Ficarra V, Righetti R, D'Amico A, et al. Renal vein and vena cava involvement does not affect prognosis in patients with renal cell carcinoma. *Oncology.* 2001; 61:10–15. [PubMed: 11474242]
12. Feifer A, Savage C, Rayala H, et al. Prognostic impact of muscular venous branch invasion in localized renal cell carcinoma cases. *J Urol.* 2011 Jan.185:37–42. [PubMed: 21074196]
13. Ball MW, Bezerra SM, Gorin MA, et al. Grade heterogeneity in small renal masses: potential implications for renal mass biopsy. *J Urol.* 2015 Jan.193:36–40. [PubMed: 24960470]
14. Trpkov K, Grignon DJ, Bonsib SM, et al. Handling and staging of renal cell carcinoma: the International Society of Urological Pathology Consensus (ISUP) conference recommendations. *Am J Surg Pathol.* 2013 Oct.37:1505–1517. [PubMed: 24025521]
15. Bonsib SM. Renal veins and venous extension in clear cell renal cell carcinoma. *Mod Pathol.* 2007 Jan.20:44–53. [PubMed: 17170742]
16. Bonsib SM. Renal lymphatics, and lymphatic involvement in sinus vein invasive (pT3b) clear cell renal cell carcinoma: a study of 40 cases. *Mod Pathol.* 2006 May.19:746–753. [PubMed: 16547467]
17. Bonsib SM. The renal sinus is the principal invasive pathway: a prospective study of 100 renal cell carcinomas. *Am J Surg Pathol.* 2004; 28:1594–1600. [PubMed: 15577678]
18. Thompson RH, Leibovich BC, Cheville JC, et al. Is renal sinus fat invasion the same as perinephric fat invasion for pT3a renal cell carcinoma? *J Urol.* 2005; 174:1218–1221. [PubMed: 16145373]

Figure 1. Recurrence-free survival stratified by the extent of venous invasion. Main RVI was associated with a greater rate of recurrence than segmental RVI.

Figure 2. Cancer-specific survival stratified by the extent of venous invasion. Main RVI was associated with worse survival as compared to segmental RVI.

Table 1
Patient demographic and pathologic features stratified by venous extent in patients without lymph node or distant metastases

	T3a – Main RV (n=64)	T3a – Segmental RV (n=87)	T3a – Fat invasion only (n=185)	T2 (n=135)	T3b (n=40)	P value
Age	64.4 (54.6 – 75.0)	63.5 (54.9–71.9)	64.1 (55.3–72.1)	59.7 (49.1–68.2)	62.5 (55.9 – 73.0)	0.02
Sex, n (%)						
Female	22 (34.4)	28 (32.2)	48 (26.0)	38 (28.2)	7 (17.5)	0.3
Male	42 (65.6)	59 (67.8)	137 (74.0)	97 (71.8)	33 (82.5)	
RCC Subtype, n (%)						< 0.0001
Clear cell	61 (95.3)	76 (87.4)	110 (59.5)	72 (53.3)	35 (87.5)	
Papillary	2 (3.1)	3 (3.5)	47 (25.4)	37 (27.4)	3 (7.5)	
Chromophobe	0	6 (6.9)	15 (8.1)	16 (11.9)	0	
Other	1 (1.6)	2 (2.3)	13 (7.0)	10 (7.4)	2 (5)	
Fuhrman Grade, n(%) [*]						< 0.0001
1	1 (1.6)	0	4 (2.2)	2 (1.5)	0	
2	21 (32.8)	27 (31.0)	74 (40)	69 (51.1)	5 (12.5)	
3	28 (43.8)	42 (48.2)	82 (44.3)	45 (33.3)	24 (60.0)	
4	13 (20.3)	14 (16.1)	13 (7)	7 (5.2)	10 (25.0)	
Not graded/missing	1 (1.6)	4 (4.6)	12 (6.5)	12 (8.9)	1 (2.5)	
Sarcomatoid Differentiation, n(%)	4 (6.3)	6 (6.9)	9 (4.9)	3 (2.2)	4 (10.3)	0.2
Fat Invasion, n (%)						
Perinephric Fat only	12 (18.8)	14 (16.1)	145 (78.4)	0	10 (25)	< 0.001
Sinus Fat Only	7 (10.9)	26 (29.9)	32 (17.3)	0	5 (12.5)	< 0.001
Both Perinephric and Sinus Fat	3 (4.7)	3 (3.5)	8 (4.3)		2 (3.5)	0.05
Diameter	8.8 (6–11)	5.9 (4.5–8.5)	5.5 (3.5–8.0)	8.6 (8–11)	9.3 (7–12.3)	< 0.0001
Surgical approach, n(%)						
Radical nephrectomy	64 (100)	74 (85.1)		113 (83.1)	40 (100)	< 0.0001
Partial nephrectomy		13 (14.9)		23 (16.9)	0	
Follow-up (months)	43.3 (14.4–82.5)	37.9 (16.5–75.7)	44.4 (21.5–91.3)	48.5 (17.7–79.9)	37.6 (19.5–68.8)	0.4

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	T3a – Main RV (n=64)	T3a – Segmental RV (n=87)	T3a – Fat invasion only (n=185)	T2 (n=135)	T3b (n=40)	P value
Year of Surgery						0.2
2003–2009	44 (68.8)	44 (50.6)	125 (74.4)	87 (64.0)	25 (62.5)	
2010–2013	20 (31.3)	43 (49.4)	43 (25.6)	49 (36.0)	15 (37.5)	

Values are expressed as medians–interquartile range unless otherwise specified

* Chromophobe RCC is not routinely graded at our institution.

Table 2

Cox proportional hazard model for recurrence or death by extent of venous extension

	Recurrence HR (95% CI)	P value	Death from Kidney Cancer HR (95% CI)	P value
Univariate				
T2	0.5 (0.2–1.1)	0.1	1.3 (0.5–3.8)	0.6
T3 Fat Invasion only	0.3 (0.1–0.8)	0.008	0.9 (0.3–2.5)	0.8
T3a Segmental RV	Reference		Reference	
T3a Main RV	2.2 (1.1–4.4)	0.03	3.6 (1.3–10.0)	0.01
T3b	2.2 (1.0–4.7)	0.05	4.7 (1.6–13.4)	0.004
Multivariable *				
T2	0.8 (0.3–1.9)	0.5	1.5 (0.5–4.9)	0.5
T3 Fat Invasion only	0.3 (0.1–0.8)	0.009	1.0 (0.3–3.0)	1.0
T3a Segmental RV	Reference			
T3a Main RV	2.2 (1.1–4.4)	0.03	3.5 (1.3–9.9)	0.02
T3b	1.6 (0.7–3.5)	0.2	3.4 (1.2–10.0)	0.03

* Controlling for nuclear grade, pathologic tumor diameter and fat invasion

Table 3
Harrell's C Index for Cancer-specific and recurrence-free survival in 7 Staging Models

Model	T2	T3a	T3a-1	T3a-2	T3b	RFS C Index	CSS C Index
Reference (2010 AJCC)	T2	Segmental RVI Main RVI Fat Invasion	n/a	n/a	T3b	0.60	0.59
1	T2 Segmental RVI	Fat Invasion Main RVI	n/a	n/a	T3b	0.57	0.61
2	T2 Segmental RVI Fat Invasion	Main RVI			T3b	0.65	0.66
3	T2	n/a	Segmental RVI Fat Invasion	Main RVI	T3b	0.66	0.67
4	T2	Segmental RVI Fat Invasion			T3b, Main RVI	0.66	0.67
5	T2 Fat Invasion		Segmental RVI	Main RVI	T3b	0.70	0.66
6	T2 Segmental RVI Fat Invasion	Main RVI T3b				0.65	0.66