# *Prognostic implications of renal vein involvement in T3a renal cancer*

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***Introduction:*** *The TNM staging system is used globally as the standard for interpreting the extent of cancer. Currently, T3a renal cell carcinoma is classified as tumor extending into the perinephric fat or renal vein. Prognostic outcomes may vary among renal cell carcinomas with renal vein involvement (RVI) versus those with perinephric fat involvement (PFI).*

***Materials and methods:*** *We reviewed the medical records of all patients who underwent radical or partial nephrectomy at our institution by a single group of urologists between 2000 and 2014. After identifying those patients with T3a renal cell carcinoma, we further analyzed their prognostic features. Overall and disease-free survival using Kaplan-Meier analysis with log rank comparison was performed among patients with renal vein involvement and PFI. Gender, smoking status, age at diagnosis, body mass index, tumor grade, tumor size, and tumor histology were also analyzed.*

***Results:*** *Of 139 patients with T3a renal cell carcinoma, 42 patients were found to have RVI, leaving 97 patients with PFI. Mean follow up was 52.1 months (0.3-183.4) versus 28.8 months (0.3-98.0) for patients with PFI and RVI, respectively. Overall survival ($p < 0.048$) and disease-free survival ($p < 0.049$) were significantly lower for patients with RVI.*

***Conclusion:*** *In our study, patients with T3a renal cell carcinoma that have RVI as opposed to PFI have lower overall and disease-free survival. These findings suggest that patient with T3a renal cell carcinoma with RVI should be monitored more closely than their counterparts with only PFI.*

**Key Words:** renal cell carcinoma, renal vein, staging, surveillance

## Introduction

Renal cell carcinoma (RCC) is the 3rd most common urologic malignancy. Surveillance, Epidemiology, and End Results (SEER) data presented by the National Cancer Institute (NCI) estimate 65,340 new cases to be diagnosed in the U.S. in 2018 representing roughly 3.8% of all new cancer cases. They also estimate 14,970 deaths related to RCC in 2018 which would represent 2.5% of all cancer-related deaths. The incidence of RCC has risen by 0.6% each year over the last 10 years and the death toll has been falling by 0.7% each year.[1] RCC takes a high death toll mostly because of its aggressive nature, high rate of early metastasis, and lack of curative therapies in the advanced stages of the disease. Fortunately, increases in survival have mirrored the rising incidence of RCC. Over the last 30 years, the 5 year relative survival has increased from 55.2% to 74.5%.[1] We can attribute all of the above findings to improvements in early detection, advancements in surgical and medical therapy, and improvements in post-treatment monitoring.

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The TNM staging system, which is maintained by the Union for International Cancer Control (IUCC) and followed by the American Joint Committee on Cancer (AJCC), is used globally as the standard for interpreting the extent of all cancers. The 7th edition took effect in 2010 and modified T3a RCC to include tumor extending into the renal vein and perinephric fat, whereas renal vein invasion was previously noted to be classified as T3b. Notably, the 8th edition was recently released and took effect in January of 2017 with no new major changes in RCC staging. In our academic practice, we have observed worse outcomes in patients with T3a RCC extending into the renal vein. With this in mind, we aim to evaluate the differences in overall and disease-free survival in patients with pathologic T3a RCC extending into the renal vein versus those that have extension into the perinephric fat. We hypothesize that patients with T3a RCC with renal vein involvement (RVI) have a worse overall prognosis.

## Materials and methods

First, approval for this project was obtained from our institutional review board. Utilizing the local cancer registry, we identified all patients with pathologic T3a RCC who underwent partial or radical nephrectomy between 2000 and 2014 by a single group of surgeons at our institution. We excluded pediatric patients and those identified as having multiple primary cancers. We examined baseline patient characteristics including gender, age, body mass index (BMI), and smoking status. We also examined tumor characteristics including tumor size, histology, and Fuhrman grade. Kaplan-Meier analysis using the log rank test was utilized to compare overall and disease-free survival. Overall survival served as the primary endpoint and disease-free survival as a secondary endpoint.

## Results

During the study period, 139 patients at our institution who underwent either partial or radical nephrectomy were staged with pT3a RCC based on the 7th edition of TNM classification. Of those 139 patients, 42 (30.2%) were found to have RVI. Patient characteristics of the two subgroups are characterized in Table 1. There were no obvious or statistically significant differences between the two groups in regards to gender ($p = 0.27$), smoking status ($p = 0.15$), BMI ($p = 0.71$), or age ($p = 0.067$). However, patients with RVI tended to be slightly older with a mean age of 65.7 years versus 61.8 years for tumors limited to the perinephric fat.

Tumor characteristics are described in Table 2. There was a statistically significant difference in the histology of the tumors encountered between the two subgroups ($p = 0.03$). T3a RCC with RVI was more likely to have a sarcomatoid pattern (16.3% versus 4.1%). While there were no statistically significant differences in the Fuhrman grade ($p = 0.38$) or tumor size ($p = 0.69$) between the two subgroups, T3a RCC with RVI tended to have a higher Fuhrman grade of 3 or 4 (66.6% versus 51.6%) and this correlated with a larger mean tumor size (8.1 cm versus 6.87 cm).

Overall, 139 patients with T3a RCC were included in survival analysis. Patients with perinephric fat involvement (PFI) had a longer follow up of with a mean of 52.1 months (0.3-183.4). Patients with RVI were followed up for a mean of 28.8 months (0.3-98.0). Kaplan-Meier survival curves using log rank comparison were calculated for overall survival and disease-free survival, Figure 1 and Figure 2. Patients with RVI demonstrated both lower overall survival ($p < 0.048$) and disease-free survival ($p < 0.049$) when compared to tumors with PFI.

TABLE 1. **Patient characteristics**

| | **Perinephric fat involvement** | **Renal vein involvement** | **p value** |
|---|---|---|---|
| Gender | | | 0.2716 |
| Male | 65 (67%) | 26 (60.4%) | |
| Female | 32 (33%) | 16 (37.2%) | |
| Age at diagnosis (yrs) | 61.8 (41-86) | 65.7 (43-87) | 0.0669 |
| Smoking status | | | 0.1587 |
| Current | 19 (21.1%) | 9 (20.9%) | |
| Former | 23 (25.6%) | 5 (11.6%) | |
| Never | 48 (53.3%) | 29 (67.4%) | |
| Body mass index | 31.0 (16.5-78.3) | 30.4 (19.2-60.1) | 0.7087 |

TABLE 2. **Tumor characteristics**

| | Perinephric fat involvement | Renal vein involvement | p value |
|---|---|---|---|
| Fuhrman grade | | | 0.3819 |
| 1 | 2 (2.2%) | 0 | |
| 2 | 41 (46.1%) | 14 (33.3%) | |
| 3 | 31 (34.8%) | 20 (47.6%) | |
| 4 | 15 (16.8%) | 8 (19.0%) | |
| Histology | | | 0.0321 |
| Clear cell | 74 (76.3%) | 33 (76.7%) | |
| Cystic renal cell carcinoma | 1 (1.0%) | 0 | |
| Papillary | 10 (10.3%) | 3 (7.0%) | |
| Chromophobe | 8 (8.2%) | 0 | |
| Sarcomatoid | 4 (4.1%) | 7 (16.3%) | |
| Tumor size (mm) | 68.7 (11-200) | 81 (10-170) | 0.0669 |

## Discussion

The 7th edition of the TNM classification of malignant tumors describes pT3a RCC as tumor infiltrating the perinephric fat, renal sinus, or the renal vein. Previous versions of the TNM classifications stratified renal vein involvement as pT3b RCC. The 8th edition was released and went into effect on January 1, 2017 but there were no major changes to the TNM classification of renal tumors warranting discussion. Under the current guidelines, treatment and management of pT3a RCC invading the renal vein is the same as those localized to the perirenal fat and carries a similar disease prognosis.

Our study indicates that T3a RCC with RVI portends a worse prognosis which is at odds with the changes of the TNM classification in 2009. Previous studies have illustrated similar outcomes in pT3a RCC with extension into perirenal sinus fat and perinephric fat;[2,3] however, few studies demonstrate similar outcomes when factoring renal vein extension. A 2008 study by

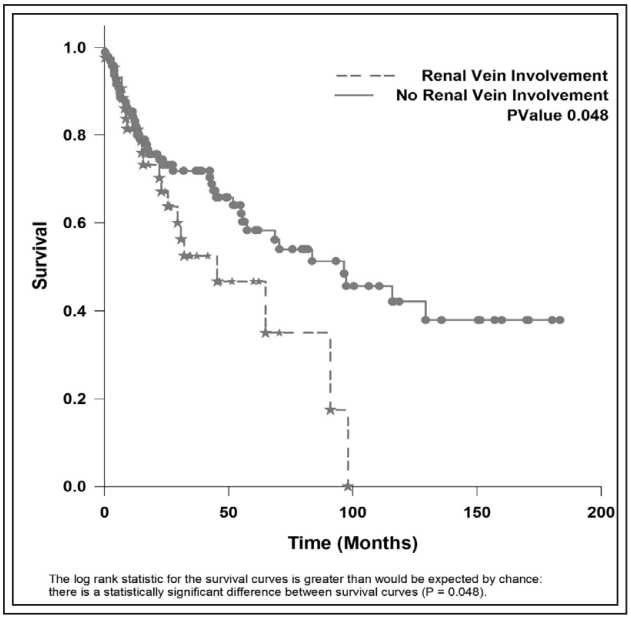


**Figure 1.** Kaplan-Meier analysis demonstrating overall survival between T3a RCC with renal vein involvement versus perinephric fat involvement.

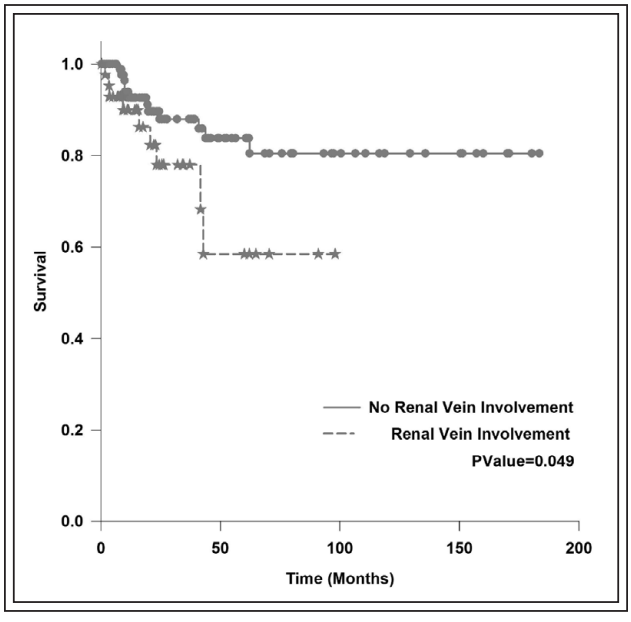


**Figure 2.** Kaplan-Meier analysis demonstrating disease-free survival between T3a RCC with renal vein involvement versus perinephric fat involvement.

Terrone et al presented data that showed 5 year CSS was 63.3% for invasion of perinephric fat only, 60.6% 5 year CSS when invasion of sinus fat occurs, and 48.6% with renal vein invasion. Median survival was 132.5 months, 101.0 months, and 59.0 months in the three groups, respectively. Their data also identified that simultaneous venous and fat involvement carried an adverse prognosis with 5 year CSS of 27.5% and a median survival of 18.0 months. It is worth noting though that this subgroup included tumors that both invaded the renal vein and IVC.[3] Da Costa et al did not replicate these results in a retrospective study in 2011. Da Costa et al stratified patients into three groups: fat invasion, renal vein invasion, and both fat and renal vein invasion. Their study found that survival was similar between fat invasion only and renal vein invasion only at 5 year follow up (75% DSS and 72% DSS p = 0.91), but patients with concomitant fat invasion and RVI had a significantly decreased disease specific survival (27% p = 0.02).[4] We did not analyze those with both RVI and PFI in our study.

Data observing outcomes specifically related to the renal vein have been limited. A retrospective study by Chen et al found that patients with PFI lend a more favorable prognosis when compared to tumors with RVI. They demonstrated decreased disease-free survival if the tumor includes the renal vein,[5] similar to our findings.

The current study also demonstrated that tumors with RVI were associated with poor prognostic factors related to their malignancy. In 1997, the TNM classification introduced a threshold tumor size of 7 cm to stratify patients as either pT1 or pT2. While tumor size is not incorporated in the TNM classification of pT3 RCC, tumor size has been found to directly relate to patient survival. Tumors larger than 7 cm have been shown to predict poor outcomes in pT3a RCC.[6-8] Siemer et al conducted a study using a modified T classification, grouping pT1/pT3a RCC < 7 cm together and pT2/pT3a RCC > 7 cm together. Analysis determined that increased tumor size over the 7 cm cut off in pT3a RCC correlated as a negative prognostic indicator for survival.[8] Additional analysis of tumor size has shown that pT3a tumors greater than 7 cm had similar prognosis to pT3b RCC, while those smaller than 7 cm had similar outcomes as pT2 RCC.[7] In a retrospective study, Yoo et al determined that tumor size was the most significant prognostic factor of pT3a RCC. That study showed that pT3a RCC larger than 7 cm was associated with rapid tumor progression and death when compared to tumors smaller than 7 cm.[9] Our study found that the RVI group had a larger tumor size with a mean tumor size of 8.1 cm. These findings were further supported in a study by Chen et al that revealed that tumors extending into the renal vein were larger (median 7.2 cm) than tumors localized to perinephric fat (median 5.5 cm).[5] Our data revealed consistent findings to the aforementioned studies. This correlation with larger tumor size may serve to additionally explain the lower overall survival of our patients with RVI.

Sarcomatoid tumors are a well-established, aggressive histologic variant of RCC. They are associated with adverse outcomes and decreased overall survival.[10-12] In a study by Trudeau et al, sarcomatoid RCC was associated with more advanced disease, specifically higher grade disease, higher stage of disease, and larger tumor burden.[11,12] Five year survival rates for regional sarcomatoid RCC is estimated to be between 15%-32%.[13] Localized sarcomatoid RCC has a median survival of 17 months.[14] The overall median survival for both local and/or distant sarcomatoid renal cell carcinoma is 5-9 months.[12,13,15] According to prior studies, sarcomatoid differentiation is discovered in approximately 5%-8% of all RCC.[10,13,16] Interestingly, our data revealed that patients with pT3a tumors with RVI had a higher likelihood of sarcomatoid malignancy, evident in 16.3% of our patients compared to 4.1% of pT3a tumors with PFI. Certainly, this plays a role in the decreased overall survival of our RVI cohort. This finding may also signify the tendency of this aggressive variant to invade central structures versus spread peripherally.

The Fuhrman grading system is a widely used predictor of prognosis and metastasis of renal cell carcinoma. Fuhrman grades stratify the tumor into four grades (I-IV) based on morphologic characteristics including pathologic stage, tumor size, cell arrangement, cell type, and nuclear grade.[17] Advanced Fuhrman grades of III and IV have been shown to indicate adverse cancer specific survival outcomes. According to a recent study by Smith et al, 5 year survival outcomes for low grade RCC was 75.5% versus 54.7% for high grade tumors.[18] In our current study, advanced Fuhrman grades III and IV were significantly more prevalent in the RVI group. Our data showed that 66.6% of all pT3a RCC with RVI had advanced grades of malignancy as compared to 51.6% of pT3a tumors with PFI.

Our findings underscore the importance of taking extra caution in patients with RVI as it relates to post-surgical monitoring. At our institution, we rely on the guidelines provided by the National Comprehensive Cancer Network (NCCN) to establish appropriate patient follow up. Currently, the recommendations for the follow up of stage II/III RCC allow for physician preference and judgment in determining both the

interval and method of renal imaging following baseline CT or MRI. Based on our findings, we advocate for decreased intervals between screening with imaging studies that allow for higher sensitivity and specificity for detecting recurrence in patients with pT3a RCC with RVI.

While our study's findings support our hypothesis, the study is not without limitations. The study is retrospective in nature with a limited number of patients with RVI versus those with PFI. Additionally, previous studies looking at renal vein involvement have illustrated that it is the concomitant renal vein and perinephric fat involvement rather than either involvement alone that carries the poor prognosis. Including this association in analysis could further strengthen the validity of our conclusions. Lastly, it is difficult to discern what role the higher proportion of well-established adverse prognostic factors (increased tumor size, increased sarcomatoid histology, higher percentage of advanced Fuhrman grade) of the RVI group played in the decreased overall survival of this group as compared to the PFI group versus the finding of RVI on its own. Certainly, analysis of a larger patient population may help to clarify this question.

## Conclusion

Despite limitations in our study, the results support the hypothesis that RVI portends a worse prognosis when compared to PFI. These tumors are generally larger, higher grade, and histologically more aggressive. The decreased overall and disease specific survival may be explained in part by these negative prognostic tumor characteristics and certainly warrant their own consideration. Extra caution should be taken with RVI patients as it relates to post-surgical monitoring. An argument may even be warranted to re-adjust the TNM classification to better reflect the prognostic implication of these findings if similar results are encountered at a larger scale. □

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