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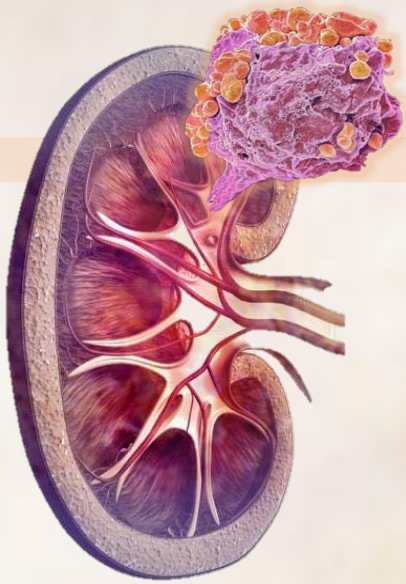

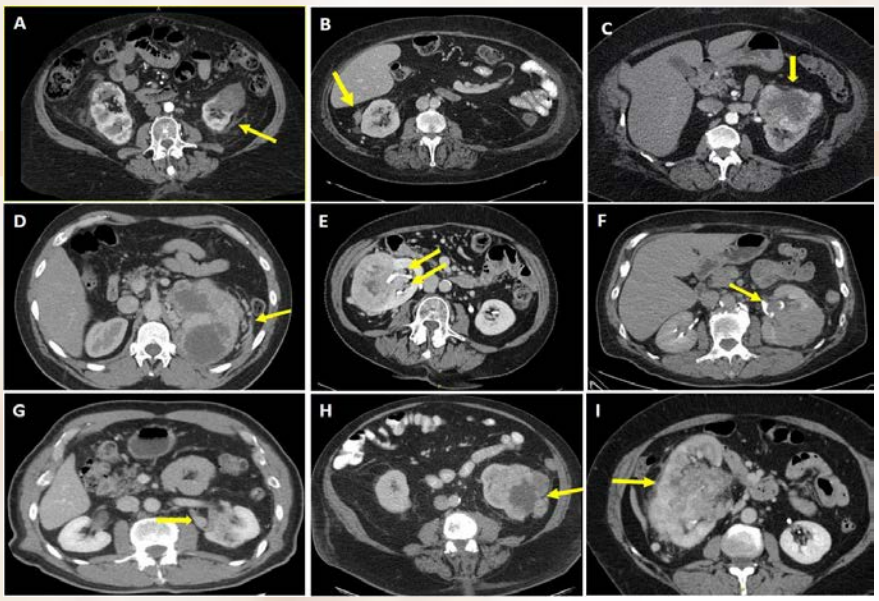

Radiological Correlates of pT3a Kidney Cancer: Importance of Irregular Tumor Sinus Border

The COVID-19 conundrum, vaccines, and cancer care

A Tribute to Dr. Christopher Wood, MD

Moving Kidney Cancer Care Forward: IKCS 2021

Q&A with Medical Director, Kidney Cancer Association

An Educational Service for Medical Oncologists, Hematologist-Oncologists, and Urologists

Based on a 2020 survey of physicians who treat RCC

Recurrence occurred in 52% of patients with stage III RCC within 5 years[1]

More than half of patients with stage III RCC who were treated by 86 physicians had disease recurrence within 5 years after initial therapy[a] regardless of nodal involvement. Out of those who recurred, nearly two-thirds had metastatic recurrence.[1,b]

[a]About 80% of patients received surgery as part of initial therapy.
[b]Based on a 2020 Kantar Health survey of 94 physicians treating a total of 3,089 patients with RCC per month.

In addition, a retrospective review of 465 patients with nonmetastatic RCC (≥pT3a) who were treated surgically, including patients with thrombus, found that approximately 40% of patients developed recurrent disease. The median follow-up was 28.3 months (range: 12.2 to 56.4 months) and the median time-to-recurrence was 9.0 months (range: 4.0 to 20.9 months), with pulmonary, liver, and bone being the most common sites of metastatic recurrence.[2,c]

Assessing each patient's risk of recurrence is important.

[c]Records from 465 consecutive patients with nonmetastatic RCC with tumor thrombus, treated surgically between 2000 and 2012 at 1 of 3 centers, were reviewed, including patients with thrombus present in the renal vein (257 patients, 55.3%), infrahepatic IVC (144 patients, 31.0%), and suprahepatic IVC (64 patients, 13.8%).

RCC = renal cell carcinoma; CT = computed tomography; IVC = inferior vena cava.

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Hypothetical patient.

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ABOUT THE COVER

A graphical illustration of pre-operative assessment of T3a renal cell carcinoma using radiological CT images to facilitate more accurate prediction of pT3a status and thus improve patient-counseling prior to surgery for RCC

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The COVID-19 conundrum, vaccines, and cancer care

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Dear Colleagues,

As 2021 comes to an end while we are bracing for the second pandemic winter, the world faces a new COVID-19 variant Omicron. Like last year, this winter holiday season could turbo-charge COVID-19 spread. Given that Delta variant still has a lot more energy, newly found Omicron variant is adding another layer of uncertainty even among fully vaccinated people. The latest data from the KFF COVID-19 Vaccine Monitor indicates that one in four adults remain unvaccinated with one in seven (14%) continuing to say they will not get vaccinated[1]. We're going to learn how long infection-induced and vaccination mediated protection last as time goes on. The global vaccine rollout wouldn't guarantee cancer patients stay safe, but it would greatly limit the spread of the COVID and also offers reprieve for cancer patients.

Scientific conferences are crucial to keep abreast of the latest breakthroughs for physicians, HCPs, and caregivers etc. At the 2021 International Kidney Cancer Symposium (IKCS) held both in person in Austin Texas, and virtually from November 5th to 6th, oncologists and kidney cancer researchers around the world presented interesting latest research in kidney cancer care. Our IKCS21 conference supplement in this issue showcases advancements in renal oncology presented at the conference. Here is a recap of some interesting research presented at 2021 IKCS. Nizar Tannir MD, et al presented (abstract CTR11)[2] the first long-term conditional survival data, representing the longest phase 3 follow-up (median, 67.7 months) reported for a checkpoint inhibitor combination therapy in aRCC from CheckMate 214 trial (NCT02231749). Results show that nivolumab plus ipilimumab yielded durable survival and response benefits relative to sunitinib in patients with advanced renal cell carcinoma (aRCC). In summary, nivolumab plus ipilimumab yielded durable survival and response benefits highlighted the greater likelihood of long-term clinical benefit relative to sunitinib in patients who had long-term survival. In the phase 3 study (abstract TIP01)[3], S1931/PROBE (NCT04510597), authors hypothesized that in the setting of immune checkpoint based systemic therapy, cytoreductive nephrectomy may result in improvement in overall survival outcomes[2]. A post hoc exploratory analysis from CheckMate 9ER trial has shown that first-line NIVO+CABO demonstrated superiority versus SUN in aRCC patients in the phase 3 CheckMate 9ER trial (abstract CTR12)[4]. In the phase 3 CheckMate 9ER trial (NCT03141177), exploratory analysis demonstrated N+C significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs S in first-line aRCC, irrespective of bone metastasis at baseline, consistent with outcomes in all randomized patients (abstract N22)[5].

Also presented were some interesting results with the use of molecular biomarkers as predictors of response to treatment of kidney cancer. In a multi-institutional real-world study, using gene expression profiling, authors demonstrate differential GEP patterns among ccRCC and nccRCC tumors with nccRCC being strongly associated with the 'proliferative' subtype and angiogenic cluster would be sensitive to VEGF-TKI therapy combination (abstract N26)[6]. In the prognostic analysis (abstract LB47)[7] using epithelial-mesenchymal transition gene expression signature, authors observed EMT and CCP related pathways were enriched in patients with high WT1 expression cohort and the synergistic prognostic impact of EMT in tumors with high CCP score was observed with the potential to improve risk stratification. An ongoing phase 2 study (abstract TIP08)[8], building on the findings from the phase III IMmotion151 trial (NCT02420821), investigates whether patients with clusters enriched in immunogenic/proliferative pathways will have improved outcomes with ipilimumab/nivolumab compared with the control group, and whether patients with angiogenic clusters will have improved outcomes with an immunotherapy/TKI combination compared with the control group.

The impact of COVID-19 vaccination in patients with renal cell carcinoma receiving cancer therapy were also presented. In a population of patients with RCC receiving ICI, COVID-19 vaccination appears to be well tolerated and safe (abstract N19)[9]. In another study (abstract E42)[10], investigators demonstrated that sufficient immune response in RCC patients was observed in patients who received a commercially available COVID-19 vaccine and encourages continued vaccination among RCC patients.

In this issue, Ye *et al* reported that preoperative assessment of T3a RCC in absence of renal vein involvement or lymph node enlargement has potential implications for counseling and prognosis. This study suggests that ITSB and tumor-size associated with pT3a RCC, which could facilitate more accurate prediction of pT3a status and thus improve patient-counseling prior to surgery for RCC. This article is accompanied by a commentary written by Dr. Nirmish Singla. In the obituary section, Dr. Nizar Tannir paid a tribute to late Dr. Christopher Woods, a surgeon and professor at the University of Texas MD Anderson Cancer Center to recognize his contribution to the kidney cancer field. Dr Woods served as an editorial board member of our Kidney Cancer Journal and a chair of Board of Directors at the Kidney Cancer Association. In the IKCS 2021 supplement issue, Dr. Marc Matrana provided a conference coverage for IKCS 2021. For the top abstracts section, I have listed a few important abstracts presented at IKCS21 conference.

In closing, while vaccines give the best hope, newly emerging COVID-19 variants keep complicating our efforts to control the pandemic. It is not safe to let down our guard just yet. Hopefully, in the months to come, the rollout of vaccines worldwide would hit a sweet spot and the virus would get itself trapped. Fingers crossed, everyone. As we look ahead to 2022, we wish a healthy new year to you and your family despite these difficult times. We hope that the new year brings you and your family much happiness and prosperity, and that in time the world will be a safe place again.

Sincerely,

Robert A Figlin, MD

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KCJ ORIGINAL CONTRIBUTION

OPEN ACCESS

Radiological Correlates of pT3a Kidney Cancer: Importance of Irregular Tumor Sinus Border

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Purpose:
Preoperative assessment of T3a renal cell carcinoma (RCC) in absence of main renal vein involvement or lymph node enlargement is challenging but has potential implications for counseling and prognosis.

Materials and Methods:
A retrospective review of 1129 cT1-T3aN0M0 RCC patients managed with partial/radical nephrectomy (PN/RN) in our institution (2012-2014) was performed. Exclusion criteria included radiological evidence of main renal vein involvement or substantial lymphadenopathy. Eleven radiological findings suggestive of aggressive tumor biology or invasive phenotype based on prior literature were assessed for correlation with pT3a status. These included perinephric findings (stranding, enhancing nodule, collateral vessels, or irregular perinephric tumor contour), findings within the sinus (stranding, collecting system invasion, branch vein enlargement, or irregular tumor sinus border [ITSB]), and tumor necrosis, infiltrative features, and tumor size. Radiological assessment was blinded to final pathology. Sensitivity/specificity and logistic regression analyses assessed the performance of each imaging finding for detecting pT3a tumors.

Results:
Median tumor size was 4.0cm and R.E.N.A.L. was 8. Median follow-up was 53 months (IQR:28-64). pT3a tumors were found in 281 patients (25%) and strongly correlated with local and systemic recurrence ($p<0.02$). ITSB was found in 350 patients (31%) and was the strongest predictor of pT3a status. Sensitivity/specificity/PPV/NPV/OR/C-Index for ITSB were 75%/84%/61%/91%/15.8(11.4-21.9)/0.80, for correlation with pT3a, respectively. The best predictive model included ITSB (yes/no) and tumor size as a continuous variable (C-index=0.84). Addition of other imaging findings did not improve the model (C-index=0.84). ITSB was the strongest contributor in all multivariable models and also strongly correlated with recurrence free survival. Inter/intra-observer correlations for assessment of ITSB were 0.89/0.98, respectively.

Conclusion:
Our data suggest that ITSB and tumor-size associate with pT3a RCC, which could impact patient counseling.

KEYWORDS: imaging characteristics, kidney cancer, pathologic stage T3a, renal cell carcinoma

INTRODUCTION

Pathologic T3a (pT3a) status for renal cell carcinoma (RCC) is defined by American Joint Commission on Cancer as tumor extension into the renal vein or its segmental branches, invasion into the collecting system, or extension into the perirenal and/or renal sinus fat but limited to Gerota fascia[1]. Five-year recurrence-free survival (RFS) for patients with pT3a tumors is about 70-80%, substantially reduced when compared to those with organ confined tumors[2]. Some reports suggest worse outcomes for pT3a tumors when managed with partial nephrectomy (PN) rather than radical nephrectomy (RN), although most studies suggest otherwise[3–7] and both are options according to national/international guideline[8,9].

Upstaging of clinical T1-2 (cT1-2) tumors to pT3a occurs in approximately 5-15% of cases[2–6] and has correlated with reduced recurrence-free and cancer-specific survival (CSS); however, it is difficult to identify such patients preoperatively[10]. Pathologic features including tumor size, clear cell histology, higher Fuhrman grade (3-4) and positive surgical margins have all associated with upstaging, but much of this information is not available until after surgery, and it is notable that imaging features were not incorporated into these analyses[11–14]. Traditionally, perinephric stranding or presence of an

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Preoperative	**Number of patients**	1129
	Age (years), median (IQR)	62 (54-70)
	Male, n (%)	738 (65)
	Caucasians n (%)	939 (83)
	BMI (kg/m^2), median (IQR)	30 (26-33)
	Diabetes, n (%)	266 (24)
	Hypertension, n (%)	750 (66)
	Cardiovascular disease, n (%)	124 (11)
	Coronary artery disease, n (%)	101 (9)
	Smoking history, n (%)	644 (57)
	Preoperative eGFR (ml/min/1.73m^2), median (IQR)	75 (62-90)
	CKD (eGFR<60 ml/min/1.73m^2), n (%)	239 (21)
	Symptomatic, n (%)	202 (18)
	RENAL score, median (IQR)*	8(7-10)
Tumor characteristics	**Tumor size (cm), median (IQR)**	4.0 (2.7-5.9)
	pT stage, n (%)	
	T1a	578 (51)
	T1b	218 (19)
	T2a	36 (3)
	T2b	16 (1)
	T3a	281 (25)
	pN1 stage, n (%)	3 (<1)
	pM1 stage, n (%)	1 (<1)
	Histology, n (%)	
	Clear cell carcinoma	771 (69)
	Papillary carcinoma	194 (17)
	Chromophobe carcinoma	91 (8)
	Oncocytic Neoplasm	26 (2)
	Unclassified	15 (1)
	Other RCC	32 (3)
	Sarcomatoid, n (%)	16 (1)
	Rhabdoid, n (%)	36 (3)
	High Tumor grade (III/IV), n (%)	504 (45)
	Positive surgical margins, n (%)	87 (8)
Intraoperative	**Nephrectomy type, n (%)**	
	Partial	837 (74)
	Radical	292 (26)
	Operative Time (min), median (IQR)	286 (243-330)
	EBL (cc), median (IQR)	150 (100-300)
	Intraoperative complication, n (%)	15 (1)

Table 1 | Demographics, tumor characteristics and perioperative outcomes.
Abbreviations: BMI=body mass index; CKD=chronic kidney disease; EBL=estimated blood loss; eGFR=estimated glomerular filtration rate; IQR=Interquartile range; R.E.N.A.L. = (R)adius (tumor size as maximal diameter), (E)xophytic/endophytic properties of tumor, (N)earness of tumor deepest portion to collecting system or sinus, (A)nterior(a)/posterior (p) descriptor, and (L)ocation relative to polar lines. *only available for 442 patients

isolated, enhancing perinephric nodule were considered indicative of pT3a disease, but the former is non-specific and the latter, while having high positive predictive value, is uncommon[2,15–17].

In this study we provide a comprehensive analysis of radiological findings that might correlate with pT3a status, including potential indicators of aggressive tumor biology (e.g. tumor size, infiltrative features, or presence of necrosis or collateral vessels) or signs of locally-invasive phenotype (e.g. involvement of the collecting system or branch veins). Recent studies with restricted numbers of patients or other limitations, suggest that irregular tumor contour may correlate with advanced pathology for RCC and we have also incorporated this into our analysis[18–20]. Our study population includes a large cohort of cT1-T3a patients excluding only those with obvious locally-advanced tumors, such as those clearly involving the main renal vein or exhibiting concerning lymphadenopathy. Our objective is to facilitate more accurate prediction of pT3a status and thus improve patient counseling prior to surgery for RCC[8,21].

2. MATERIAL AND METHODS

2.1. Study participants

After approval from our institutional review board, a retrospective review was performed of all patients who underwent PN/RN at our institution for RCC (2012-2014) (Supplementary Figure 1). Availability of preoperative cross-sectional, contrast-enhanced imaging studies was required. All studies were reviewed to identify cT1-T3aN0M0 RCC cases without main renal vein involvement or substantial lymphadenopathy (total ipsilateral or interaortocaval retroperitoneal lymph-node burden>1.5cm). Demographics, tumor/pathologic characteristics, and clinical outcomes were obtained by retrospective chart review.

2.2 Endpoints and imaging review

Primary endpoint was correlation of radiological findings with pT3a. Radiological findings were chosen for this analysis if they were suggestive of aggressive tumor phenotype or local invasion or were previously implicated in the literature as being correlated with pT3a status. Preoperative imaging studies (CT or MRI) were reviewed in both corticomedullary/nephrographic phases in blinded fashion. Imaging findings included perinephric features (extensive stranding, isolated enhancing nodule in perinephric space, collateral vessels, or irregular perinephric tumor contour), findings within the sinus (extensive stranding, collecting system invasion, branch vein enlargement or filling defect, or irregular tumor sinus border [ITSB]), tumor necrosis[22,23], infiltrative features,[24,25] and tumor size (Figure 1). ITSB was defined as non-spherical or non-elliptical contour for tumor extending into the renal sinus. Any perceived irregularity in tumor contour within the sinus was classified as ITSB. Figure

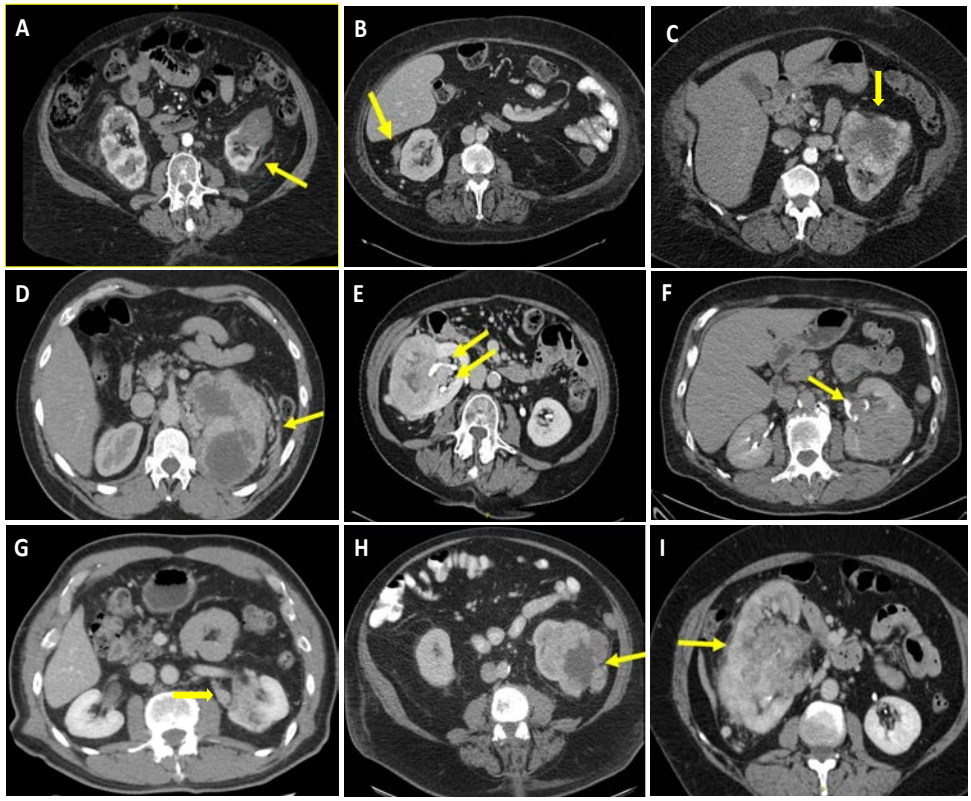

Figure 1. Representative images from pre-operative CT for patients with cT1-T3a renal cell carcinoma demonstrating various imaging findings with possible correlation to pT3a status. Arrows point to relevant findings, including: A) Perinephric stranding; B) Enhancing nodule in the perinephric space; C) Irregular tumor contour in the perinephric space; D) Collateral vessels in perinephric space; E) Irregular tumor sinus border (ITSB); F) Collecting system invasion; G) Branch vein involvement; H) Tumor necrosis; and I) Infiltrative features. Some tumors exhibited more than one of these features and when this was the case all such features were recorded as positive for analysis. Branch vein involvement was suspected whenever there was apparent filling defect or enlargement or soft tissue enhancement within a branch vein not extending into the main renal vein.

2 provides examples of cases that were negative or positive for ITSB.

After preliminary group review of several cases to develop common perspectives, all imaging was reviewed by a radiology fellow (AGR), a urology resident (DAP) and an urologist (YY) and all equivocal findings were also reviewed with both EMR and SCC, staff radiologist and urologist, respectively, to reach consensus. Each radiological finding was assessed as a dichotomized parameter and evaluated for sensitivity/specificity, and C-index relative to pT3a status. If more than one radiological finding was present for a tumor, each was independently included in the analysis. Secondary outcomes included total, local, and systemic RFS from the date of surgery. Intra-observer correlation for ITSB status was determined by repeat blinded review of 50 randomly selected cases. Inter-observer correlation for ITSB-status was assessed by independent and blinded review of 250 randomly selected cases.

2.3. Statistical Analysis

Tumor size was examined both as a continuous and categorical variable. All other parameters were evaluated as dichotomized variables. For each imaging finding the sensitivity, specificity, and concordance-index (C-index) with pT3a status were determined. Multivariable predictive models combining ITSB and other radiological findings were developed using logistic regression analysis and in each instance the C-index and its 95% confidence interval (CI) were determined. Odds ratio (OR) and 95% CI were also estimated for each variable. The 95% CIs were determined by 1000 bootstrap resampling. Multiple nomograms were created with ITSB and tumor size as the base with inclusion of other radiological findings based on multivariable logistic regression models. Kaplan-Meier was used to estimate recurrence-free survival and Log Rank test to compare the survival curves. Statistical analyses were done using R (www.r-project.org).

3. RESULTS

3.1. Patient demographics/tumor characteristics

A total of 1129 RCC patients managed with PN/RN with cT1-T3aN0M0 tumor (excluding only those with main renal vein involvement or substantial lymphadenopathy) were analyzed. Demographic/tumor characteristics were representative for such a patient population (Table 1). Median patient age was 62 years, 65% were male, and 83% Caucasian. Median tumor size was 4.0 cm and median R.E.N.A.L. score was 8. pT3a tumors were found in 281 patients (25%), while the remaining 848 (75%) were pT1-2. High tumor grade (3/4) was observed in 504 patients (45%). Tumor histology included 69% clear cell carcinoma, 17% papillary, 8% chromophobe, and 2% oncocytic neoplasm. Median follow-up was 53 months (IQR:28-64 months). pT3a tumors had significantly worse 5-year RFS compared to pT1-2, at both the local and systemic levels ($p=0.011$ and $p<0.001$, respectively) (Figure 3).

3.2. Correlation of imaging features with pT3a status

ITSB was found in 350 patients (31%), including 61% of pT3a patients, and proved to be the strongest predictor of pT3a (C-index=0.80, Table 2). Sensitivity/specificity/positive predictive value (PPV)/negative predictive value (NPV)/OR (95% CI) for correlation of ITSB with pT3a were

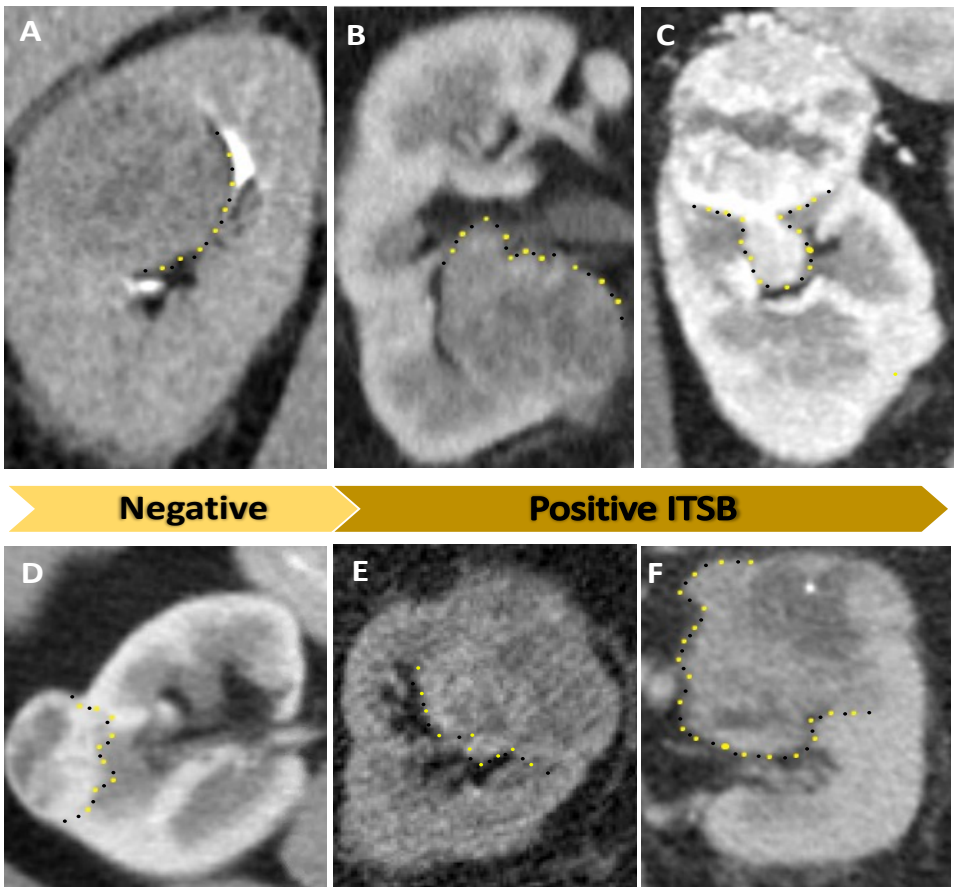

Figure 2. Comparison of CT images of renal tumors illustrating absence versus presence of irregular tumor sinus border (ITSB), including coronal (A-C) and axial (D-F) images. ITSB was defined based on assessment of the tumor contour in the renal sinus, and was considered positive if this was non-spherical or non-elliptical. A) Smooth, round tumor extending into the renal sinus and negative for ITSB; B) Tumor with irregular border in sinus, positive for ITSB; C) Readily-evident irregular tumor border in sinus; D) Tumor with irregular medial border not extending to renal sinus, so negative for ITSB; E) Tumor with irregular tumor border in sinus, positive for ITSB; F) Tumor with markedly irregular sinus border. In summary, any perceived irregularity in the contour of the tumor within the sinus was classified as ITSB.

75%/84%/61%/91%/15.8(11.4-21.9), respectively. ITSB also strongly correlated with RFS [hazards ratio(HR)(95% CI):5.51(3.61-8.41)] (Figure 3D). Interobserver and intraobserver correlations for imaging review of ITSB were 0.89/0.98, respectively. Other than ITSB, tumor size had the next highest C-index of 0.76 (Table 2). All other imaging features demonstrated high specificity (≥0.92) but relatively low sensitivity (all <0.35) and suboptimal concordance-indices (C-indices all 0.51-0.63, Table 2).

3.3. Multivariable models to predict pT3a

Two-variable models were then explored with ITSB as the foundation to determine if the predictive value could be improved. Tumor size as a categorical variable improved the C-index to 0.83, compared to a C-index of 0.80 for ITSB alone (Supplementary Table 1). In multivariable models using ITSB, categorical tumor size, and a third variable, addition of the third imaging feature did not improve the model, with the C-index remaining at 0.83 (Supplementary Table 2).

The best predictive nomogram for pT3a included ITSB(yes/no) and tumor size as a continuous variable (C-index=0.84, Figure 4). Addition of other imaging features to develop an optimal nomogram did not improve the model (C-index remained 0.84, Supplementary Figure 2). ITSB was the most robust contributor in all models.

4. DISCUSSION

pT3a status for RCC correlates with worse prognosis compared to pT1-2 but is difficult to identify preoperatively.[2,10,14] Previous studies analyzed associations between demographics, laboratory values, or pathologic factors and pT3a; however, many of these factors are only available postoperatively and the observed correlations have been modest and of limited clinical utility[11,14]. Our analysis focuses on several imaging-features that suggest aggressive or invasive tumor biology and evaluates their potential correlation with pT3a status. Our study population includes all cT1-T3a patients excluding only those with obvious locally-advanced tumors, such as those clearly involving the main renal vein or exhibiting substantial lymphadenopathy, to provide as robust of an analysis as possible. We purposely did not classify our patient population as cT1-2 versus cT3a, as criteria for doing this are not well-established and our main objective was to determine what features would allow for such differentiation. The recent literature suggests that tumor contour may be a predictive factor for RCC and this characteristic was also prioritized in our analysis[18–20,26].

We found that pT3a was present in 25% of cT1-T3a cases and strongly associated with both local and systemic recurrence. Irregular tumor sinus border (ITSB) was present in 31% of cases and was the strongest predictor of pT3a status in all models tested. Although somewhat subjective - a limitation of many radiologic findings - assessment of ITSB proved to be reproducible. Tumor size as a continuous variable had the second highest predictive value and has the benefit of being highly objective.

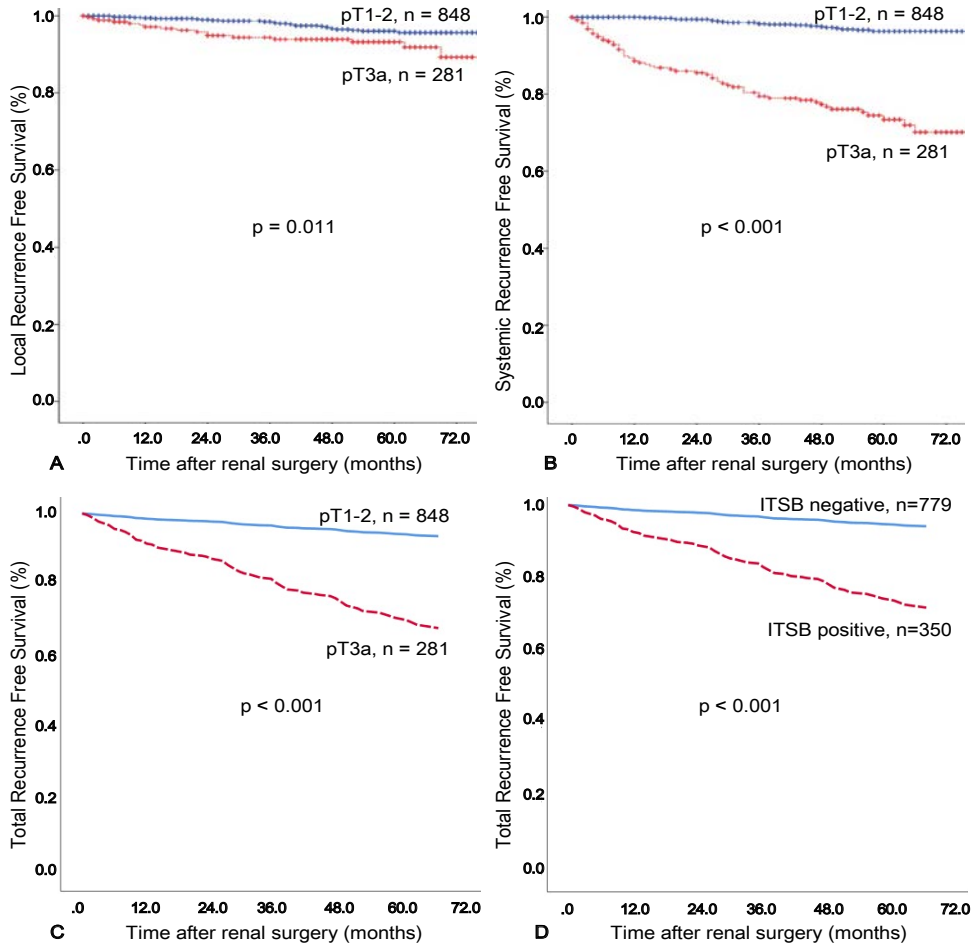

Figure 3. Kaplan-Meier curves comparing recurrence-free survival (RFS) after renal cancer surgery under various conditions, including:
A) Local RFS for pT1-2 versus pT3a tumors; B) Systemic RFS for pT1-2 versus pT3a tumors; C) Total RFS for pT1-2 versus pT3a tumors (RFS at 5 years 94% and 70%, respectively); D) Total RFS for ITSB versus no ITSB (RFS at 5 years 94% and 74%, respectively). ITSB = irregular tumor sinus border. Overall, a total of 41 local recurrences were observed, with 17 in the pT3a cohort (n=281) and 24 in the pT1-2 cohort (n=848). Overall, a total of 79 systemic recurrences were observed, with 59 in the pT3a cohort (n=281) and 20 in the pT1-2 cohort (n=848). Eighteen patients had both local and systemic recurrences. Overall, a total of 65 patients in the pT3a cohort experienced recurrence and 37 pT1-2 patients recurred. A total of 71 ITSB positive patients recurred (n=350) and 31 patients without ITSB recurred (n=779). Local recurrence was defined as recurrence in the ipsilateral kidney or retroperitoneum and systemic recurrence as any recurrence outside of the ipsilateral retroperitoneum.

When tumor size was combined with ITSB the predictive value was strengthened (C-index improved to 0.84), yet addition of other imaging characteristics failed to improve the predictive capacity.

Previous studies have similarly identified irregular tumor contour as a potential predictor of pT3a, although most such studies had significant limitations. Bolster studied 55 RCC cases and found that irregular tumor contour within the sinus had 84% sensitivity for pT3a, and the correlation was significant ($p<0.001$)[18]. Another study with 863 patients evaluated the ability of multi-detector CT to predict renal sinus fat-invasion and found four significant predictors on multivariate analysis, including ITSB (OR 6.83, $p<0.0001$), tumor size greater than 5 cm (OR=7.29, $p<0.0001$), decreased perfusion of the diseased kidney (OR=2.31, $p=0.018$), and lymph-node metastasis (OR=2.97, $p=0.016$)[26]. However, there were only 118 pT3a tumors in this cohort, and many potentially important imaging findings, such as infiltrative features, were not analyzed. Ni studied 60 patients with pT3a RCC and on multivariate analysis, ITSB again proved to be an independent risk factor for renal sinus fat invasion ($p<0.001$)[19]. Based on these reports and our study, which is the largest and most comprehensive to address this topic, irregular tumor contour appears to be a promising predictor of local invasiveness for RCC.

Tumor size has also consistently shown strong predictive value for pT3a in the literature and our study supports this[11,27,28]. A recent meta-analysis by Veccia that examined over 20,000 patients with cT1 RCC, including 1,256 upstaged to pT3a (5.7%), found increasing tumor size to be significantly associated with pT3a ($p<0.001$)[13]. Another study examining the staging accuracy of CT for pT3a found that pT3a tumors were significantly larger than pT1-2 tumors (median 8.0cm vs. 4.5cm, respectively; $p=0.002$)[20]. This is not surprising given previous reports demonstrating strong association between tumor size and aggressive tumor biology for RCC[29].

Previous studies have shown that upstaging from cT1-2 to pT3a occurs in about 5-15% of cases and most suggest that outcomes for upstaged patients are similar when managed with PN or RN[2–7]. Weight examined 2,511 patients with cT1 RCC and found no difference in overall survival or CSS for patients upstaged to pT3a treated with PN versus RN[6]. Similarly, a recent multi-center analysis (n=2,573) found upstaging from cT1-2 to pT3a in 14% of patients and reported that type of surgery (PN vs. RN) was not associated with risk of recurrence[5]. Conversely, Shah, et al. examined 1,250 patients with cT1 disease of which 11% were upstaged to pT3a and found that upstaged cases treated with PN had worse RFS compared to those managed with RN (HR=5.39, $p=0.001$)[3]. Although most recent data suggest that cT1-2 tumors upstaged to pT3a can do well with PN, the Shah study serves as a reminder that

Imaging feature	Presence	Number	pT1-2 (%)	pT3a (%)	Sensitivity (95% CI)	Specificity (95% CI)	C-index (95% CI)	p
Extensive perinephric stranding	No	1079	836 (77)	243 (23)	0.14 (0.1-0.18)	0.99 (0.98-0.99)	0.56 (0.54-0.58)	<0.001
	Yes	50	12 (24)	38 (76)				
Enhancing nodule, perinephric space	No	1111	845 (76)	266 (24)	0.05 (0.03-0.09)	1 (0.99-1)	0.52 (0.51-0.54)	<0.001
	Yes	18	3 (17)	15 (83)				
Irregular shape, perinephric space	No	1014	816 (80)	198 (20)	0.3 (0.24-0.35)	0.96 (0.95-0.97)	0.63 (0.6-0.66)	<0.001
	Yes	115	32 (28)	83 (72)				
Collateral vessels, perinephric space	No	1051	833 (79)	218 (21)	0.22 (0.18-0.28)	0.98 (0.97-0.99)	0.6 (0.58-0.63)	<0.001
	Yes	78	15 (19)	63 (81)				
Sinus stranding	No	1124	848 (75)	276 (25)	0.02 (0.01-0.04)	1 (1-1)	0.51 (0.5-0.52)	<0.001
	Yes	5	0 (0)	5 (100)				
Irregular tumor sinus border (ITSB)	No	779	710 (91)	69 (9)	0.75 (0.7-0.8)	0.84 (0.81-0.86)	0.80 (0.77-0.82)	<0.001
	Yes	350	138 (39)	212 (61)				
Collecting system invasion	No	1035	820 (79)	215 (21)	0.23 (0.19-0.29)	0.97 (0.95-0.98)	0.6 (0.58-0.63)	<0.001
	Yes	94	28 (30)	66 (70)				
Branch venous involvement	No	1067	840 (79)	227 (21)	0.19 (0.15-0.24)	0.99 (0.98-1)	0.59 (0.57-0.61)	<0.001
	Yes	62	8 (13)	54 (87)				
Necrosis	No	959	777 (81)	182 (19)	0.35 (0.3-0.41)	0.92 (0.9-0.93)	0.63 (0.61-0.66)	<0.001
	Yes	170	71 (42)	99 (58)				
Infiltrative features	No	1078	839 (78)	239 (22)	0.15 (0.11-0.2)	0.99 (0.98-1)	0.57 (0.55-0.59)	<0.001
	Yes	51	9 (18)	42 (82)				
Tumor size (cm)	≤4	575	517 (90)	58 (10)			0.76 (0.73-0.79)	<0.001
	>4≤7	371	269 (73)	102 (27)				
	>7≤10	124	47 (38)	77 (62)				
	>10	59	15 (25)	44 (75)				

Table 2: Relationship between imaging features and pathological stage. Abbreviations: CI = confidence interval ote: Sensitivity, specificity and C-index and their 95% CIs are based on 1000 bootstrap resampling.

this is still somewhat controversial.

Our study population differs from those that evaluate pT3a specifically upstaged from cT1-2 in that we did not exclude cT3a patients, except those with obvious locally advanced disease. This likely accounts for our substantially higher incidence of pT3a tumors (25%). Our study design allows us to provide a more comprehensive analysis of imaging features that correlate with pT3a, rather than solely focusing on predictors for upstaging from cT1-2. Studies focused on upstaging from clinically confined to pT3a likely select for patients with microscopic renal sinus or perinephric fat invasion, as more substantial invasion would be suspicious for cT3a and thus more likely to be excluded. In these scenarios, PN could offer equivalent oncologic benefits as RN, as most recent studies have suggested. On the other hand, there are undoubtedly some pT3a patients who would be at risk for poor oncologic outcomes with PN and for whom preoperative identification of T3a status could be important by tipping the balance in favor of RN[8,9,21]. Further studies will be required to examine the potential predictive value of ITSB, and other factors, specifically in the cT1-2 population.

In addition to tumor size and ITSB, nine other imaging features were examined for correlation with pT3a, with most chosen because they had previously demonstrated correlation with pT3a status or were indicative of local-invasion or aggressive tumor biology[15–17,28]. We found that all of these variables were significantly associated with pT3a and demonstrated high specificity; however, low sensitivity and low concordance indices limited their utility, and none of these factors complemented ITSB and tumor size in multivariable models.

In a similar but much smaller study, Sokhi and colleagues examined a multitude of CT findings in 117 patients with pT1-T3a RCC to determine predictors of pT3a, including: tumor necrosis; tumor edge extending to the renal sinus or perirenal fascia; irregularity of tumor contour; accentuated perinephric septa; perinephric stranding; thickening of the perirenal fascia; increased perinephric vascularity; perinephric nodules; and calcification[20]. Most of these variables, some of which overlap those studied in our analysis, were significantly associated with pT3a; however, many were not clinically useful due to poor interobserver agreement. The most useful predictors of pT3a status appeared to be tumor necrosis, irregular tumor contour, and direct contact between tumor and perirenal fascia or renal sinus fat (OR=2.5-3.7; $p<0.05$). Another recent study by Nocera examined 236 patients with cT1 clear cell RCC and developed a model for predicting pT3a at nephrectomy which included age, tumor size, rim location, exophytic position, and polar involvement. pT3a was present in 10.6% of their patients and the accuracy of the model was 81%[30]. Other studies suggest that R.E.N.A.L. nephrometry score and hilar location may also correlate with pT3a status[12,13].

While our analysis provides a comprehensive and blinded evaluation of imaging features and their correla-

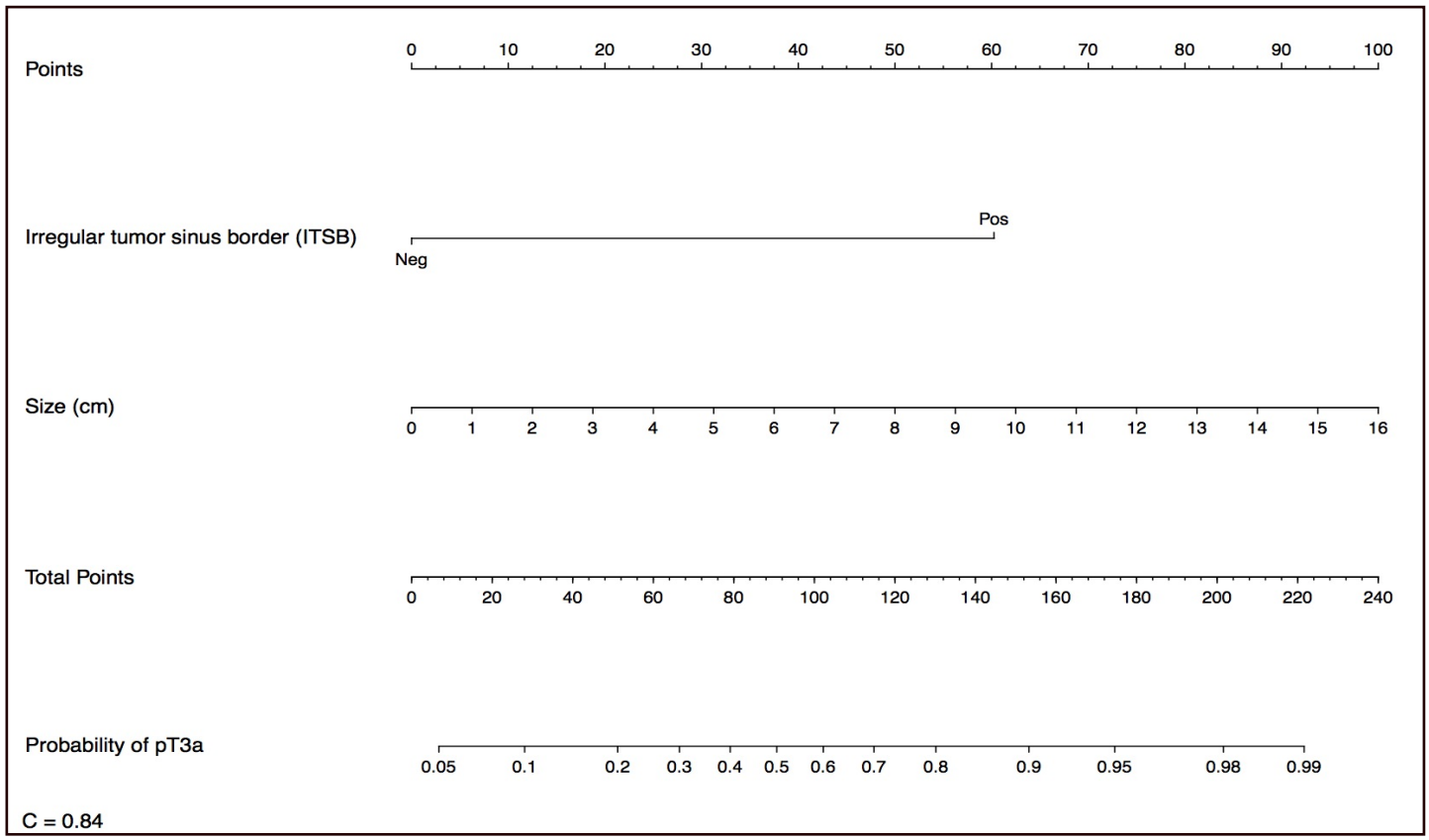

Figure 4. Nomogram for prediction of pT3a status based on pre-operative imaging characteristics. This simple algorithm provided a C-index of 0.84.

tion with pT3a status in a substantial cohort of patients, it is possible that demographic features, laboratory results, or findings from renal mass biopsy might complement ITSB and tumor size and provide an even more accurate preoperative assessment[11–14]. Further studies will be needed to explore these possibilities, and given the retrospective and single-institution nature of our study, independent validation will also be required. Additionally, because our data were generated from a cohort of cT1-cT3a patients, our results may lack generalizability to the more restricted cT1-2 population and this will also require further investigation. While our analysis examined ITSB and pT3a status, specific aspects of pT3a status, such as renal sinus versus perinephric fat invasion, were not assessed individually. Future studies could examine the correlation between ITSB and various cohorts of pT3a, which might be informative. Finally, it could be argued that ITSB is somewhat subjective, although this is a limitation of many other radiologic findings, and our evaluation of this parameter demonstrated strong intra and interobserver reproducibility. In the future, artificial intelligence may further improve this assessment by implementing automatic contouring and recognition.

5. CONCLUSIONS

ITSB and tumor size are readily available and reproducible preoperative imaging findings that can be used to more accurately predict pT3a RCC and thus potentially improve patient counseling. Future studies will be required to externally validate and further explore our findings, including associations between ITSB and specific pathologic findings that qualify a given tumor as pT3a.

SUPPLEMENTAL INFORMATION

Any supplementary information including supplementary figures, supplementary tables, legends, materials and methods can be found online at doi.org/10.52733/KCJ19n4-a1

DISCLOSURES

None of the authors have any disclosures or conflicts of interest to report.

ABBREVIATIONS

CI=confidence interval
CSS=cancer-specific survival
HR=hazard ratio
IQR=interquartile range
ITSB=irregular tumor sinus border
NPV=negative predictive value
OR=odds ratio
RFS=recurrence-free survival
PN=partial nephrectomy
PPV=positive predictive value
RCC=renal cell carcinoma
RENAL= (R)adius (tumor size as maximal diameter), (E)xophytic/endophytic properties of tumor, (N)earness of tumor deepest portion to collecting system or sinus, (A)nterior(a)/posterior (p) descriptor, and (L)ocation relative to polar lines.
RN=radical nephrectomy

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AUTHOR CONTRIBUTIONS

Ye, Yunlin: Developed concept and hypothesis, contributed data collection and analysis; performed the analyses, helped write manuscript, review and revision of manuscript;
Aguilar Palcios, Diego: Developed concept and hypothesis, contributed data collection and analysis; performed the analyses, helped write manuscript, review and revision of manuscript;
Campbell, Rebecca: Developed concept and hypothesis, contributed data collection and analysis, performed the analyses, helped write manuscript, review and revision of manuscript;
Rizk, Alain G: Contributed to data collection, review and revision of manuscript;
Tanaka, H: Contributed to data collection, review and revision of manuscript;
Munoz-Lopez, Carlos: Contributed to data collection, review and revision of manuscript;
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Roversi, Gustavo: Contributed to data collection, review and revision of manuscript;
Li, Jianbo: Data and statistical analysis, writing of manuscript, review and revision of manuscript;
Weight, Christopher J: Developed concept and hypothesis, review and revision of manuscript;
Abouasally, Robert: Developed concept and hypothesis, review and revision of manuscript;
Remer, Erick M, Developed concept and hypothesis, review and revision of manuscript, also helped with data collection;
Campbell, Steven C.: all above activities.

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KCJ COMMENTARY

OPEN ACCESS

How Can We Predict pT3a Kidney Cancer and What Does It Mean?

Commentary for the article "Radiological Correlates of pT3a Kidney Cancer: Importance of Irregular Tumor Sinus Border"

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The ability to predict pathologically advanced renal cell carcinoma (RCC) within the primary tumor upfront can be helpful to guide prognostic counseling and hold implications for both surgical approach and multimodal therapeutic strategies. Herein, the investigators undertook a comprehensive assessment of radiographic features predictive of pT3a stage by querying 11 radiological findings across a robust retrospective cohort of patients with RCC. They found that an irregular tumor-sinus border (ITSB) correlated most strongly with pT3a stage and recurrence-free survival (RFS).

While not explicitly investigated in the present study, predictors for pathological upstaging of small renal masses (cT1a) to pT3a at surgical resection have been investigated previously. This information has been used by some to help dictate the role for or against active surveillance and for or against a nephron-sparing surgical approach. It is important to note, however, that not all pT3a RCC are created equal. First, focal microscopic local invasion constituting pT3a acts different clinically compared to gross invasion constituting pT3a tumors. Furthermore, the pT3a category is quite broad and includes (1) renal sinus fat invasion, (2) perirenal fat invasion, or (3) invasion of the renal vein or segmental branches. The location and pattern of local invasion warrants additional attention biologically to elucidate how similar these subcategories of pT3a truly are and whether further sub-stratification of the pT3a stage is needed.

The cohort investigated notably consisted of either CT or MRI to determine radiographic correlates of pT3a. This naturally begs the question of whether one modality is more reliable than the other in interpreting radiographic parameters such as ITSB. This is important to note, as future applications of this work would be presumably couched in machine learning and radiomic approaches to predicting pT3a stage.

Finally, the role for perioperative systemic therapy in reducing RFS among select, high-risk patients has been a topic of considerable contemporary interest. The adjuvant space has enjoyed recent FDA approval of the immune checkpoint inhibitor pembrolizumab based on the results of the KEYNOTE-564 trial. However, the ability to more accurately predict aggressive, locally advanced disease upfront may lend support to neoadjuvant strategies in select patients with RCC, and in this context we eagerly await the results of the PROSPER-RCC trial among others.

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A Tribute to Dr. Christopher G. Wood, MD

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Tributes to individuals who have passed away share one common purpose: to help us heal. We find comfort by sharing the legacies of the loved ones we've lost. Today we pay tribute to Dr. Christopher G. Wood, Professor of Urology.

November 22, 1963 - November 3, 2021

Dr. Wood passed away at home after a brief illness on November 3, 2021. Chris had a sharp mind, a keen wit and wonderful sense of humor, but above all, he possessed a love for the medical profession, serving his patients and training urology fellows. He is remembered by his colleagues as a surgeon with the highest ethical standards, a selfless mentor dedicated to the training of his fellows and sponsoring them for academic careers in urological oncology.

"Dr. Chris Wood was larger than life and leaves a shining legacy that includes a new generation of urologists whom he educated, trained, mentored, and sponsored and the thousands of lives he saved."

Dr. Wood came to MD Anderson as a urology oncology fellow in 1995 and joined the faculty three years later with a dual appointment as Assistant Professor in Urology and Cancer Biology. He was promoted to Full Professor with Tenure in 2010 and received the Douglas E. Johnson, M.D., Endowed Professorship in Urology in 2012. He served as Deputy Chair of the Department of Urology from 2008 until few months before his death. He operated three days per week and saw more than 50 patients in his clinic one day a week.

During his 26 years at MD Anderson, Dr. Wood operated on more than seven thousand patients and performed radical and partial nephrectomies on five thousand patients. He operated successfully on patients with large, locally advanced renal tumors that other urologists could not remove. Karen Ronquillo, the widow of John Ronquillo whom both Chris and I treated and cared for, described Wood as "the doctor with the confident handshake and warm smile who accepted cases others had written off. Dr. Wood blessed our family by extending my husband's life with a risky, lengthy surgery his local surgeon would not consider."

Chris was considered a legend in the operating room. "He could do things in 40 minutes that other surgeons needed three hours to complete, and he did it better than they ever could do," said Associate Professor Neema Navai, one of Chris' former mentees.

Wood was passionate about education and served as his department CME course chair. He chaired the annual MD Anderson Urology Oncology Conference for 15 years. As part of the renal cell carcinoma (RCC) program, he always included a session in which he'd present challenging cases to a panel of expert urologists and medical oncologists. Then, he'd famously remark, "Don't tell me what you could do, or others would do; tell me what you would do in this case." The "Wood Fire session", as it was known, would become his trademark and a tradition highlighted and looked forward to at the annual International Kidney Cancer symposium (IKCS).

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Throughout his tenure at MD Anderson, Dr. Wood was devoted to developing and sponsoring his fellows, who became known as the "Wood Fellows". "Your success is my success," he often told his mentees. Chris's commitment to his fellows' success was described as "unconditional generosity," by Jose Karam whom Wood recruited to join the faculty of the Urology Department after completing his fellowship under him. Scott Delacroix, a former Wood fellow and now director of urologic oncology at LSU, called his mentor a role model, noting his unparalleled surgical skills and "unwavering support" for his fellows. But beyond that, Delacroix said, "Even with the successes in the field, Chris Wood's most admirable trait was his ability to still be a real down to earth person, devoid of the ego that is all too common in those considered some of the world's best." That sentiment was echoed by Brian Chapin, Associate Professor of Urology at MD Anderson, also a former Wood fellow. "One of the things I admire most about him was his ability to put his own ego aside and elevate others around him."

During his illustrious career, Dr. Wood trained more than 75 urology fellows while serving as director of clinical research in his department for 15 years. But his devotion to education extended beyond the walls of MD Anderson. Dr. Wood committed much of his personal time and energy to the Kidney Cancer Association (KCA). He chaired the annual patient conference every spring for more than 15 years and, for the past six years and until his death, he served as chairman of the KCA Board of Directors. "We'd talk multiple times a week, almost every day. He was such a wonderful sounding board and even better friend. I've literally never known someone so genuinely themselves with no agenda, no ego, who always made me feel like I was enough. He was always unconditional," said Gretchen Vaughan, President and CEO of KCA.

Dr. Wood made significant research contributions to the field of kidney cancer. He pioneered the integration of systemic therapy and cytoreductive nephrectomy in patients with metastatic RCC and neoadjuvant targeted therapy in patients with locally advanced RCC. His laboratory was successful in generating several RCC cell lines and patient derived xenografts, including rare variant types such as translocation RCC and renal medullary carcinoma, which have been used for target discovery and testing novel therapeutics in co-clinical trials. His productive clinical and translational research was published in more than 350 manuscripts. Additionally, he contributed 28 chapters to books on kidney cancer and was honored with more than 40 visiting professorships in the U.S. and abroad.

For the past 20 years, I had the privilege to care for hundreds of patients with RCC who were referred to me by Dr. Wood, and I, in turn, referred hundreds of patients to him for cytoreductive nephrectomies. I thought and hoped our professional partnership would continue until we both retired from MD Anderson.

Our lives were intertwined. My PA for 17 years Zita Dubauskas Lim, his nurse for 22 years Jan Jackson, and his PA for 13 years Reena Cherry, referred to us as '*Ying and Yang*'. I respected Dr. Wood for his surgical skills and judgment and admired his unwavering devotion to and advocacy for his patients. He never said "no" to overbooking a new patient in his clinic. We never argued about the management of a patient, which is rare for a medical doctor and a surgeon. I trusted his surgical skills to operate on the most complex cases, and he trusted my judgment on the management of patients with metastatic disease and the implementation of therapies when indicated.

Once, I told Chris that I realized why we were destined to be BFF. He was amused to learn that he was born the same year as my younger brother and shared my daughter's birthday. This past November 22nd, I celebrated my daughter's seventeenth birthday with her, but I felt a big hole in my heart. Chris's untimely death came on the eve of the 17th IKCS, which he had hoped to attend in Austin despite his failing legs and eyesight.

Dr. Wood passed away 19 days before his 58th birthday. Chris was a loving husband to his wife Colleen and a devoted father to Chris, Jr. and Sarah. He is sorely missed by his family, friends, colleagues, mentees, his longtime administrative assistant and coordinator, his clinic and research staff, and all the people who loved him.

Dr. Chris Wood was larger than life and leaves a shining legacy that includes a new generation of urologists whom he educated, trained, mentored, and sponsored and the thousands of lives he saved. Many of us believe it may take generations to see his equal again.

Essential Peer-Reviewed Reading in Kidney Cancer

The peer-reviewed articles summarized in this section were selected by the Editor-in-Chief, Robert A. Figlin, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research.

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The blood metabolome of incident kidney cancer: A case-control study nested within the MetKid consortium. Guida F et al. PLoS Med. 2021 Sep 20;18(9):e1003786.

Methods and findings: We assessed the association between circulating levels of 1,416 metabolites and incident kidney cancer using pre-diagnostic blood samples from up to 1,305 kidney cancer case-control pairs from 5 prospective cohort studies. Cases were diagnosed on average 8 years after blood collection. We found 25 metabolites robustly associated with kidney cancer risk. In particular, 14 glycerophospholipids (GPLs) were inversely associated with risk, including 8 phosphatidylcholines (PCs) and 2 plasmalogens. The PC with the strongest association was PC ae C34:3 with an odds ratio (OR) for 1 standard deviation (SD) increment of 0.75 (95% confidence interval [CI]: 0.68 to 0.83, p = 2.6 × 10-8). In contrast, 4 amino acids, including glutamate (OR for 1 SD = 1.39, 95% CI: 1.20 to 1.60, p = 1.6 × 10-5), were positively associated with risk. Adjusting for BMI partly attenuated the risk association for some-but not all-metabolites, whereas other known risk factors of kidney cancer, such as smoking and alcohol consumption, had minimal impact on the observed associations. A mendelian randomisation (MR) analysis of the influence of BMI on the blood metabolome highlighted that some metabolites associated with kidney cancer risk are influenced by BMI. Specifically, elevated BMI appeared to decrease levels of several GPLs that were also found inversely associated with kidney cancer risk (e.g., -0.17 SD change [ßBMI] in 1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-16:0/18:2) levels per SD change in BMI, p = 3.4 × 10-5). BMI was also associated with increased levels of glutamate (ßBMI: 0.12, p = 1.5 × 10-3). While our results were robust across the participating studies, they were limited to study participants of European descent, and it will, therefore, be important to evaluate if our findings can be generalised to populations with different genetic backgrounds.

Conclusions: This study suggests a potentially important role of the blood metabolome in kidney cancer aetiology by highlighting a wide range of metabolites associated with the risk of developing kidney cancer and the extent to which changes in levels of these metabolites are driven by BMI-the principal modifiable risk factor of kidney cancer.

Kidney cancer mortality disparities among Hispanics in the US Paulo S Pinheiro 1, Heidy N Medina et al. Cancer Epidemiol. 2021 Jun;72:101938. PMID: 33862414

Methods: Introduction: Kidney cancer incidence is increasing among Hispanics but rate differences by distinct group, such as Cuban, Puerto Rican, and Mexican have not been studied. To fill this knowledge gap, we use mortality data, reflecting fatal kidney cancers, to examine patterns by race-ethnicity, including detailed Hispanic groups, and correlate the mortality rates with each group's prevalence of known kidney cancer risk factors: smoking, obesity, hypertension, diabetes, and chronic kidney disease.

Methods: We used individual-level death data for California, Florida, and New York (2008-2018), and population prevalence data from the National Health Interview Surveys (2008-2018). Age-adjusted mortality rates (AAMRs) and regression-derived mortality rate ratios (MRRs) were computed. Pearson correlation analyses assessed the extent to which group-specific risk factor prevalence explained variability in observed AAMRs.

Results: US-born Mexican Americans and American Indians had the highest rates and MRRs compared to Whites: 1.44 (95 %CI: 1.35-1.53) and 1.51 (1.38-1.64) for Mexican American men and women, respectively, and 1.54 (95 %CI: 1.25-1.89) and 1.53 (95 %CI: 1.15-2.04) for American Indians. In contrast, non-Mexican Hispanics had lower rates than Whites. Among males, positive correlations between AAMRs and smoking, obesity, and chronic kidney disease prevalence by race-ethnicity were found.

Conclusion: Mexican Americans and American Indians are high-risk for fatal kidney cancer. Disparities are only partially attributable to higher smoking and obesity prevalence, and more so among men than women. A shared risk factor profile, as well as possible genetic similarities, may explain their disproportionately higher kidney cancer mortality, but further research is warranted.

Occupational exposure to asbestos and risk of kidney cancer: an updated meta-analysis. Eur J Epidemiol 2021 Sep;36(9):927-936.

Abstract: Limited information is available on carcinogenicity of asbestos on non-respiratory organs. We aimed at conducted an updated systematic review and meta-analysis of cohort studies on occupational exposure to asbestos and risk of kidney cancer. We searched through three databases, PubMed, Embase and Scopus for article published after 2000, and after eliminating duplicates and non-relevant studies, we identified 13 studies. We combined their results with those of 31 non-overlapping studies included in a previous review up to 2000. We conducted a meta-analysis based on random-effects models. The pooled relative risk of kidney cancer for asbestos exposure was 0.94 (95% confidence interval, 0.84-1.04), with no differences according to type of asbestos fiber, geographic region, period of exposure, or estimated quality of the study. Our results showed a lack of association between occupational asbestos exposure and risk of kidney cancer.

Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. Jonasch E et al. 2021 Nov 25;385(22):2036-2046.

Abstract: Background: Patients with von Hippel-Lindau (VHL) disease have a high incidence of renal cell carcinoma owing to VHL gene inactivation and constitutive activation of the transcription factor hypoxia-inducible factor 2a (HIF-2a).

Methods: In this phase 2, open-label, single-group trial, we investigated the efficacy and safety of the HIF-2a inhibitor belzutifan (MK-6482, previously called PT2977), administered orally at a dose of 120 mg daily, in patients with renal cell carcinoma associated with VHL disease. The primary end point was objective response (complete or partial response) as measured according to the Response Evaluation Criteria in Solid Tumors, version 1.1, by an independent central radiology review committee. We also assessed responses to belzutifan in patients with non-renal cell carcinoma neoplasms and the safety of belzutifan.

Results: After a median follow-up of 21.8 months (range, 20.2 to 30.1), the percentage of patients with renal cell carcinoma who had an objective response was 49% (95% confidence interval, 36 to 62). Responses were also observed in patients with pancreatic lesions (47 of 61 patients [77%]) and central nervous

system hemangioblastomas (15 of 50 patients [30%]). Among the 16 eyes that could be evaluated in 12 patients with retinal hemangioblastomas at baseline, all (100%) were graded as showing improvement. The most common adverse events were anemia (in 90% of the patients) and fatigue (in 66%). Seven patients discontinued treatment: four patients voluntarily discontinued, one discontinued owing to a treatment-related adverse event (grade 1 dizziness), one discontinued because of disease progression as assessed by the investigator, and one patient died (of acute toxic effects of fentanyl).
Conclusions: Belzutifan was associated with predominantly grade 1 and 2 adverse events and showed activity in patients with renal cell carcinomas and non-renal cell carcinoma neoplasms associated with VHL disease. (Funded by Merck Sharp and Dohme and others; MK-6482-004 ClinicalTrials.gov number, NCT03401788.).

Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. Choueiri TK et al. 2021 N Engl J Med. Aug 19;385(8):683-694.
Methods: In a double-blind, phase 3 trial, we randomly assigned, in a 1:1 ratio, patients with clear-cell renal-cell carcinoma who were at high risk for recurrence after nephrectomy, with or without metastasectomy, to receive either adjuvant pembrolizumab (at a dose of 200 mg) or placebo intravenously once every 3 weeks for up to 17 cycles (approximately 1 year). The primary end point was disease-free survival according to the investigator's assessment. Overall survival was a key secondary end point. Safety was a secondary end point.
Results: A total of 496 patients were randomly assigned to receive pembrolizumab, and 498 to receive placebo. At the prespecified interim analysis, the median time from randomization to the data-cutoff date was 24.1 months. Pembrolizumab therapy was associated with significantly longer disease-free survival than placebo (disease-free survival at 24 months, 77.3% vs. 68.1%; hazard ratio for recurrence or death, 0.68; 95% confidence interval [CI], 0.53 to 0.87; P = 0.002 [two-sided]). The estimated percentage of patients who remained alive at 24 months was 96.6% in the pembrolizumab group and 93.5% in the placebo group (hazard ratio for death, 0.54; 95% CI, 0.30 to 0.96). Grade 3 or higher adverse events of any cause occurred in 32.4% of the patients who received pembrolizumab and in 17.7% of those who received placebo. No deaths related to pembrolizumab therapy occurred.
Conclusions: Pembrolizumab treatment led to a significant improvement in disease-free survival as compared with placebo after surgery among patients with kidney cancer who were at high risk for recurrence. (Funded by Merck Sharp and Dohme, a subsidiary of Merck; KEYNOTE-564 ClinicalTrials.gov number, NCT03142334.).

The role of stereotactic body radiation therapy and its integration with systemic therapies in metastatic kidney cancer: a multicenter study on behalf of the AIRO (Italian Association of Radiotherapy and Clinical Oncology) genitourinary study group. Franzese C. Clin Exp Metastasis. 2021 Dec;38(6):527-537.
Abstract: Although systemic therapy represents the standard of care for polymetastatic kidney cancer, stereotactic body radiation therapy (SBRT) may play a relevant role in the oligometastatic setting. We conducted a multicenter study including oligometastatic kidney cancer treated with SBRT. We retrospectively analyzed 207 patients who underwent 245 SBRT treatments on 385 lesions, including 165 (42.9%) oligorecurrent (OR) and 220 (57.1%) oligoprogressive (OP) lesions. Most common sites were lung (30.9%) for OR group, and bone (32.7%) for OP group. Among 78 (31.8%) patients receiving concomitant systemic therapy, sunitinib (61.5%) and pazopanib (15.4%) were the most common for OR patients, while sunitinib (49.2%) and nivolumab (20.0%) for OP patients. End points were local control (LC), progression free survival (PFS), overall survival (OS), time to next systemic therapy (TTNS) and toxicity. Median follow-up was 18.6 months. 1, 2 and 3-year LC rates were 89.4%, 80.1% and 76.6% in OR patients, and 82.7%, 76.9% and 64.3% in those with OP, respectively. LC for OP group was influenced by clear cell histology (p = 0.000), total number of lesions (p = 0.004), systemic therapy during SBRT (p = 0.012), and SBRT dose (p = 0.012). Median PFS was 37.9 months. 1, 2- and 3-year OS was 92.7%, 86.4% and 81.8%, respectively. Median TTNS was 15.8 months for OR patients, and 13.9 months for OP patients. No grade 3 or higher toxicities were reported for both groups. SBRT may be considered an effective safe option in the multidisciplinary management of both OR and OP metastases from kidney cancer.

Counterbalancing COVID-19 with Cancer Surveillance and Therapy: A Survey of Patients with Renal Cell Carcinoma. Staehler M et al. Eur Urol Focus. 2021 Nov;7(6):1355-1362.
Background: While providers are challenged with treatment decisions during the coronavirus disease 2019 (COVID-19) crisis, decision making ultimately falls in the hands of patients-at present, their perspective is poorly understood.
Objective: To ascertain renal cell carcinoma (RCC) patients' perspectives on COVID-19 and understand the associated implications for treatment.
Design, setting, and participants: An online survey of RCC patients was conducted from March 22 to March 25, 2020, disseminated through social media and patient networking platforms. The survey comprised 45 items, including baseline demographic, clinicopathologic, and treatment-related information. Patients were additionally queried regarding their anxiety level related to COVID-19 and associated implications for their cancer diagnosis.
Intervention: An online survey study.
Outcome measurements and statistical analysis: Descriptive statistics with graphical outputs were used to characterize survey results.
Results and limitations: A total of 539 patients (male:female 39%:58%) from 14 countries responded. Of them, 71% felt that their risk of COVID-19 infection was higher than the general population, and 27% contacted their physician to establish this. Among patients with localized disease (40%), most (42%) had scheduled surveillance scans within 6 wk-65% were unwilling to delay scans. Among patients with metastatic disease, 76% were receiving active therapy. While most patients preferred not to defer therapy (51%), patients receiving immune therapy regimens were less amenable to deferring therapy than those receiving targeted treatment (20% vs 47%).
Conclusions: Despite high levels of anxiety surrounding COVID-19, many patients with RCC were inclined to adhere to existing schedules of surveillance (localized disease) and systemic treatment (metastatic disease).
Patient summary: The coronavirus disease 2019 (COVID-19) pandemic has prompted many doctors to develop different treatment strategies for cancer and other chronic conditions. Given the importance of the patient voice in these strategies, we conducted a survey of patients with kidney cancer to determine their treatment preferences. Our survey highlighted that most patients prefer to continue their current strategies of kidney cancer treatment and monitoring.