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The association of peri-tumoral vascularity and stage, grade, and histopathologic features in renal cell carcinoma

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ABSTRACT

Aims and Objectives: This study aimed to investigate the relationship between the presence of peritumoral vessels in CT scan images of Renal Cell Carcinoma (RCC) patients, the histopathological status of the tumor, and the TNM stage of the tumor.

Methods and Materials: This retrospective study was conducted by reviewing the clinical records of patients. The histopathological information of the patients, encompassing the grade and the histological type of the tumor was extracted. The images of the CT scan and other imaging modalities were then reviewed by an experienced radiologist to determine the TNM stage of the tumor and presence of peritumoral vessels. Logistic regression analysis was performed to assess the predictive power of the presence of peritumoral vessels in determining the pathology and stage of the tumor.

Results: We included 66 patients in our study. The mean age was 69 ± 6.4 among the patients. Among 20 patients with detected peri-tumoral vein, 18 (90%) had T3 stage cancer (p-value=0.041), 11 (55%) had N1 stage cancer (p-value=0.009), and 6 (30%) had present metastasis (p-value=0.011). Existence of peri-tumoral vein was significantly associated for 5.66 times increased odds of higher stage T cancer, 4.55 times increased odds lymph node involvement, and 6.14 times increased odds of having metastasis. Further detail regarding 95% CI and significance level is summarized in Table 2.

Conclusion: The existence of collateral vessels exhibited a significant correlation with aggressive clinicopathological features, poor differentiation, and poor staging. This relationship emphasizes its relevance to the selection of RN and open surgery in clinical decision-making.

Keywords: renal cell carcinoma, cancer grade, cancer stage, tnm, peri-tumoral vein.

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INTRODUCTION

Cancer poses a significant global public health challenge, with kidney cancer encompassing malignant tumors in both parenchymal tissue and the renal pelvis in adults. Renal pelvis tumors constitute approximately 10% of kidney tumors, with Renal Cell Carcinoma (RCC) accounting for 90% of malignancies. RCC alone represents about 2% of all cancers, and its incidence has been on the rise. In 2008, there were 270,000 reported cases, resulting in 116,000 deaths globally [1,2]. Key risk factors for RCC include obesity, smoking, hypertension, genetic predisposition, aging, male gender, and exposure to substances like petroleum products, asbestos, and polyethylene. The genetic and hereditary forms of RCC are associated with kidney cell cancer and syndromes such as hereditary leiomyoma, Birt-Hogg-Dubé, and von Hippel-Lindau. RCCs are categorized into clear cell, papillary, chromophobic, onco-cytic, and collecting duct types based on their histopathologic features. Clear cell tumors, the most common type, have a poorer prognosis and account for over 80% of metastatic cases. Many RCC patients remain asymptomatic until the disease advances, with the classic triad of hematuria, flank pain, and palpable flank mass observed in 9% of cases, signaling advanced local disease [3-5].

In general, treatment planning is tailored to each patient's specific conditions. Therefore, evaluating prognostic factors is crucial for making individualized treatment decisions, estimating the likelihood of tumor recurrence, planning patient follow-up, and providing counseling. Prognostic factors for Renal Cell Carcinoma (RCC) can be categorized as follows: 1) Anatomical factors included in the TNM classification system; 2) Histological factors, such as RCC type, nuclear grade, sarcomatous features, vascular invasion, tumor necrosis, and invasion of the collecting system and perirenal fat; 3) Clinical factors, including performance status, localized symptoms, cachexia, anemia, and platelet count; 4) Molecular factors like VEGF [6-8].

The TNM staging system is recommended for scientific and clinical use, but continuous updates are necessary. The most recent version was published in 2009, with a supplement in 2012, and its prognostic value has been confirmed in various studies. Tumor size, venous invasion, renal capsular invasion, adrenal and lymph node involvement, and distant metastasis are included in the TNM classification system [3,4]. The Fuhrman nuclear grade is widely accepted for grading RCC, with prognosis worsening as histopathological grade and stage increase. The

extension of the thrombus into the renal vein is a unique feature of RCC, impacting TNM stage and typically observed in T3a stage and later. Controversy exists regarding the prognosis of venous thrombosis following RCC. Current consensus suggests that a completely removed thrombus during surgery does not hold special prognostic significance. RCC tumors often exhibit a vascular tendency, influencing prognosis. Angiogenesis in RCC involves the growth of new vessels around and inside the tumor. Studies have shown that angiogenesis is associated with malignancy and metastasis in various tumors, including RCC. The clear cell type of RCC has a higher tendency to vascularize, while papillary and chromophobe types have a lower tendency [9-11].

Few studies have explored the relationship between the TNM staging of RCC and the presence of peritumoral vessels. Limited research has investigated the association between the pathological status of RCC and peritumoral vessels. This study aimed to investigate the relationship between the presence of peritumoral vessels in CT scan images of RCC patients, the histopathological status of the tumor, and the TNM stage of the tumor.

METHODS AND MATERIALS

This retrospective study was conducted by reviewing the clinical records of patients who were referred to Shahid Hashminejad Kidney and Urinary Tract Center in Tehran from April 1, 2011, to April 1, 2016.

Inclusion criteria were as follows: Patients diagnosed with renal cell carcinoma. Absence of tumor thrombosis. Having a contrast-enhanced CT scan. Presence of tumor histopathological information (determined through pathological examinations on the surgical specimen).

Firstly, the demographic information of the patients, including age and gender, was extracted from the clinical files and entered into the checklist. Subsequently, the histopathological information of the patients, encompassing the disease grade based on the Forman criteria and the histological type of the tumor (clear cell, papillary, chromophobe, onco-cytic, collecting duct, and other unclassified types), was extracted from their clinical files and recorded in the checklist. The images of the CT scan and other imaging modalities were then reviewed by an experienced radiologist. The TNM stage of the tumor and the presence of peritumoral vessels were determined by the radiologist and recorded in the checklist. The criteria for identifying peritumoral vessels included an asymmetric and irregular increase in vessel density in the periphery of the affected kidney and inside the renal fascia, often associated with numerous arterial and venous shunts.

After the data were collected, they were entered into SPSS version 20. In the descriptive section, qualitative data were expressed as ratios and percentages. In the analytical statistics section, chi-square tests, independent t-tests, and Pearson's correlation tests were employed. Additionally, logistic regression analysis was performed to assess the predictive power of the presence of peritumoral vessels in determining the pathology and stage of the tumor.

RESULTS

Finally, we included 66 patients (36 males and 30 females) in our study based on our eligibility criteria. The mean age was 69±6.4 among the patients with no significant difference between males and females (p-value=0.670). The existence of peri-tumoral veins was significantly higher among those with higher-stage carcinomas. Among 20 patients with detected peri-tumoral vein, 18 (90%) had T3 stage cancer (p-value=0.041), 11 (55%) had N1 stage cancer (p-value=0.009), and 6 (30%) had present metastasis (p-value=0.011). Further detail is summarized in Table 1.

Tab. 1. Peri-tumoral vascularity and characteristics of renal carcinoma

		Peri-tumoral Vein		p-value
		N (n=46)	Y (n=20)	
T	I	17 (36.96%)	2 (10%)	0.041
	II	2 (4.35%)	0	
	III	27 (58.70%)	18 (90%)	
N	0	39 (84.87%)	9 (45%)	0.009
	1	7 (15.22%)	11 (55%)	
M	0	43 (93.48%)	14 (70%)	0.011
	1	3 (6.52%)	6 (30%)	
Stage	I	31 (67.39%)	5 (25%)	0.014
	II	1 (2.17%)	2 (10%)	
	III	12 (26.09%)	11 (55%)	
	IV	2 (4.35%)	2 (10%)	
Grade	I	18 (40%)	2 (10%)	0.023
	II	15 (33.33%)	6 (30%)	
	III	11 (24.44%)	12 (60%)	
	IV	1 (2.22%)	0	
Pathology	Clear Cell	35 (76.09%)	17 (85%)	0.416
	Papillary	11 (23.91%)	3 (15%)	
Vein Size		-	5.76±4.99	-

Based on the logistic model, the existence of peritumoral vein was significantly associated with increased odds for higher stage cancer based on the TNM staging model. Existence of peri-tumoral vein was significantly associated for 5.66 times increased odds of higher stage T cancer, 4.55 times increased odds lymph node involvement, and 6.14 times increased odds of having metastasis. Further detail regarding 95% CI and significance level is summarized in Table 2.

Tab. 2. Odds ratio of peri-tumoral vascularity for cancer stage

		T	N	M
Peri-tumoral Vein	N	-		
	Y	5.66 (1.16 – 27.56)	4.55 (1.38 – 15.02)	6.14 (1.35 – 28.74)
p-value		0.032	0.013	0.019

DISCUSSION

The imaging characteristics of renal cell carcinoma exhibit variability, with tumor size, invasion, and necrosis being suggested as correlates with tumor staging and prognosis. Therefore, the identification of specific imaging features that can guide clinical practice and predict patient outcomes holds significant importance. RCC is characterized by hypervascularity attributed to elevated production of vascular endothelial growth factor activated by hypoxia-inducible factor [12-15]. Extensive evidence indicates an association between high angiogenesis levels and poor prognosis in RCC. While micro-vessel density is commonly used for assessing intra-tumoral angiogenesis through immunohistochemical staining, the presence and role of collateral vessels on preoperative imaging in RCC remain less explored [16-19]

A study noted a significant correlation between the presence of peritumoral vascularity and tumor size in each subtype of RCC, consistent with our findings. Correspondingly, an angiography study in the past indicated that Wilms' tumors with collateral vessels tended to have a larger size compared to those without collaterals [3,13,20,21]. Our results align with these observations, and a retrospective study supported the notion that collateral vessels were indicative of locally advanced renal cancer6. Furthermore, a separate study in the USA highlighted that the presence of collateral vessels on preoperative MRI independently predicted a high-grade clear cell type [16-19].

In our study, collateral veins were more frequently observed than collateral arteries, possibly due to the lower blood pressure in the venous system. The identified collateral veins included the gonadal, renal, adrenal, intercostal, and lumbar veins, along with the inferior vena cava, aligning with previous publications. Notably, collateral arteries and veins often coexisted. For instance, a renal tumor situated in the peripheral renal parenchyma close to a perforating artery could stimulate the perirenal arterial plexus, causing partial blood flow from the tumor in this region to return through the perirenal venous complex [8,9,22]. Consequently, the coexistence of collateral arteries and veins was observed in certain cases. Additionally, in our study, tumors with collateral vessels showed a higher incidence of necrosis, suggesting that these tumors may experience faster growth, surpassing their blood supply and eventually leading to necrosis [18,19,21]

Surgical resection remains the primary treatment for localized RCC, but there is ongoing debate about the optimal surgical approach, particularly for early-stage RCC. Radical nephrectomy (RN) is effective but carries a potentially higher risk of renal dysfunction. Nephron-Sparing Surgery (NSS) may offer similar oncological outcomes with better preservation of renal function but is associated with technical complexity. Therefore, decisions should consider patient physical status, comorbidities, surgeon expertise, and surgical complexity [9,23,24]. The RENAL scoring system categorizes renal masses by complexity, aiding in surgical planning. Our study revealed a significant association between patients with collateral vessels and higher RENAL scores, suggesting that the presence of collateral vessels on preoperative CT could serve as a factor in estimating surgical complexity. Another study noted that RN was commonly performed on renal masses with moderate to high complexity, while NSS was primarily used for low-complexity lesions [10,25,27].

Another study also noted that patients undergoing RN had elevated RENAL scores compared to those undergoing NSS. These findings indicate that the presence of collateral vessels serves as an independent predictor for both RN and open surgery. The increased blood loss and higher rate of intraoperative blood transfusion observed in patients with collateral vessels in our study may be attributed to higher tumor complexity and increased collateral circulation [10,25-27]. As the trend leans towards greater utilization of NSS and minimally invasive surgery, our results suggest that patients with collateral vessels may prioritize RN and open surgery due to higher surgical complexity. If minimally invasive surgery is still chosen, surgeons should remain vigilant to the heightened risk of bleeding during the operation [28-30]. Additionally, these results revealed that patients with collateral vessels had higher SSIGN scores and poorer overall survival compared to those without collateral vessels, suggesting that the presence of collateral vessels may serve as a prognostic indicator and assist clinicians in deciding on subsequent treatments.

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