

BRIEF REPORT

Increased risk of preoperative venous thromboembolism in patients with renal cell carcinoma and tumor thrombus

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Summary. *Background:* The clinical impact of a tumor thrombus in renal cell carcinoma (RCC) patients awaiting radical nephrectomy and thrombectomy is unknown. *Objective:* To determine the incidence of venous thromboembolism (VTE) in RCC patients with tumor thrombus prior to nephrectomy. *Patients and methods:* We conducted a retrospective cohort study including all late-stage (stage 3–4 excluding T1–2 N0M0) RCC patients who underwent radical nephrectomy at our institution between 1 January 2005 and 1 July 2012. Tumor thrombus was defined as the presence of an intraluminal filling defect in the renal vein, hepatic vein, portal vein, or inferior vena cava, directly extending from a renal mass detected on computed tomography. *Results:* A total of 176 patients were included in the study. Fifty-three (30.1%) patients had tumor thrombus diagnosed on imaging. Three patients with tumor thrombus (5.7%; 95% confidence interval [CI] 1.4–16.8) developed a VTE while awaiting radical nephrectomy, whereas none (0%; 95% CI 0–2.9) of the patients without a tumor thrombus had an event ($P = 0.026$). All three events were deep vein thrombosis. Times from tumor thrombus diagnosis to VTE were 5, 15 and 21 days. *Conclusions:* Tumor thrombus on imaging is a frequent finding among RCC patients awaiting nephrectomy. The presence of tumor thrombus in these patients increases the incidence of preoperative VTE.

Keywords: neoplasm; nephrectomy; renal cell carcinoma; thrombosis; venous thromboembolism.

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Background

Patients with kidney cancers, specifically renal cell carcinomas (RCCs), are at increased risk of venous thromboembolism (VTE), with rates varying between 1.2% and 3.5% [1,2]. Concurrently, tumor thrombus, or the extension of the RCC into the renal vein and inferior vena cava (IVC), also occurs frequently in this patient population, at a reported rate of 5–10% [3]. Venous tumor thrombus disrupts vascular integrity and disturbs venous blood flow, which could potentially increase the risk of VTE. The clinical impact of a tumor thrombus and its potential association with an increased risk of VTE in RCC patients awaiting radical nephrectomy and thrombectomy are unknown. Currently, no evidence or guidelines are available to direct clinical management, and the use of anticoagulant therapy is variable among practitioners. We sought to determine the incidence of VTE in RCC patients with gross tumor thrombus on imaging diagnosis prior to radical nephrectomy and thrombectomy.

Patients and methods

A retrospective cohort study was conducted of all late-stage (stage 3–4 excluding T1–2 N0M0) RCC patients who underwent a radical nephrectomy at our institution, the Ottawa Hospital, between 1 January 2005 and 1 July 2012. Radiologic imaging data were reviewed to identify patients with tumor thrombus seen on imaging. Tumor thrombus was defined as the presence of an intraluminal filling defect in the renal vein, hepatic vein, portal vein or IVC directly extending from a renal mass detected on computed tomography. Patients with gross tumor thrombus on radiographic imaging became the ‘tumor thrombus’ group. The remaining patients, including those with pathology reports subsequently showing vascular involvement, became the ‘control’ group. The date of imaging

diagnosis was defined as the first diagnostic imaging report of suspected RCC.

Patients on anticoagulation therapy or with a VTE event prior to or at cancer diagnosis were excluded. The primary outcome was the incidence of VTE during the time interval between (i) the diagnosis of cancer on imaging and (ii) radical nephrectomy. VTE was defined as proximal lower limb (popliteal vein or more proximal) deep vein thrombosis (DVT) or pulmonary embolism. Both symptomatic and incidental VTE events were included. A two-sided Fisher exact test was used to compare the incidence of VTE between patients in the 'tumour thrombus' and 'control' groups.

Results and discussion

In 1140 charts reviewed of patients diagnosed with kidney cancer, we identified 212 patients with stage 3 or 4 RCC who underwent radical nephrectomy. Of the 212 patients, 36 were excluded: 30 because of VTE prior to or at the time of cancer diagnosis; three because of thrombophilia; and three because prophylactic anticoagulation was used between the time of diagnosis and surgery.

A total of 176 patients were included in the study. The mean age was 62.5 years, and 68.2% were men. The proportion of patients with stage 3 RCC was 51.4% (Table 1). Fifty-three (30.1%) patients had tumor thrombus diagnosed on imaging, and were included in the 'tumour thrombus' group; the remaining 123 patients (69.9%), including six patients (4.9%) with no tumor thrombus on radiographic imaging but evidence of vascular involvement on pathology, were included in the 'control' group. The median times from imaging diagnosis to radical nephrectomy were 24 days (range: 1–213 days) in the 'tumor thrombus' group and 46 days (range: 0–2055 days) in the 'control' group. Three patients in the 'tumour thrombus' group (5.7%; 95% confidence interval [CI] 1.4–16.8) developed a VTE while awaiting radical nephrectomy, whereas none (0%; 95% CI 0–2.9) of the patients in the 'control' group had an event ($P = 0.026$).

Table 1 Baseline characteristics

	No tumor thrombus (control) ($n = 123$)	Tumor thrombus ($n = 53$)	<i>P</i> -value
Mean age (SD)	63.1 (10.7)	61.0 (11.1)	NS
Male, no. (%)	82 (66.7)	38 (71.7)	NS
Stage 3 (%)	63 (51.2)	29 (54.7)	NS
Median days to surgery (range)	46 (0–2055)	24 (1–213)	0.046
Total VTE events, no. (%)	0	3 (5.6)	0.026
IVC, no.	0	2	NS
Lower limb DVT, no.	0	1	NS

DVT, deep vein thrombosis; IVC, inferior vena cava; NS, non-significant; SD, standard deviation; VTE, venous thromboembolism.

All three events were DVTs (two symptomatic and one incidental). All three VTE events were then treated with low molecular weight heparin prior to surgery. Times from tumor thrombus diagnosis to VTE were 5, 15 and 21 days.

This is the first study demonstrating an increased risk of VTE in stage 3 or 4 RCC patients with tumor thrombus awaiting radical nephrectomy. The risk of VTE in our patient population is similar to those reported in other high-risk populations. In a large randomized controlled trial comparing the efficacy of thromboprophylaxis (enoxaparin 20 or 40 mg daily) with that of placebo in hospitalized medically ill patients, the rates of symptomatic DVT in patients receiving placebo were 0.5% and 1.5% at 12 and 110 days, respectively [4]. The American College of Chest Physician guidelines recommend anticoagulant thromboprophylaxis for acutely ill hospitalized medical patients at increased risk of VTE [5]. Therefore, the presence of tumor thrombus in patients with stage 3 or 4 RCC could potentially identify a high-risk subgroup of patients who might benefit from thromboprophylaxis for the limited time period while awaiting surgery. This study is particularly significant in the era of targeted therapies for RCC. Currently, there are studies ongoing to assess the role of neoadjuvant tyrosine kinase inhibitor therapy prior to surgical resection. This could prolong the time between diagnosis and surgery, and theoretically increase the risk for VTE in patients with tumor thrombus. However, prospective studies are required to confirm these findings.

It is important to recognize significant limitations of this study resulting from the retrospective design, leading to potential bias, incomplete information, or misdiagnosis. We tried to minimize selection bias by including all consecutive patients assessed at our institution and fully reviewing the charts in duplicate (two independent reviewers) to ensure proper identification of patients and adjudication of outcome events. Furthermore, the number of events is relatively small, and larger studies are needed to provide more reliable estimates. Similarly, the difference in the median time from imaging diagnosis to radical nephrectomy between the two groups is caused by one patient in the 'tumor thrombus' group who waited 2055 days before undergoing surgery. Finally, it is important to emphasize that, although the results of this study show that the presence of tumor thrombus increases the rate of VTE, we cannot draw any conclusions regarding the potential benefit of primary thromboprophylaxis in this patient population.

To conclude, tumor thrombus on imaging is a frequent finding among late-stage RCC patients awaiting radical nephrectomy. The presence of tumor thrombus in these patients increases the incidence of preoperative VTE. Larger prospective studies are required to confirm these findings and assess the role of thromboprophylaxis in RCC patients with tumor thrombus.

Addendum

M. Carrier and D. Yokom designed and performed research, collected, analyzed and interpreted data, performed statistical analysis, and wrote the manuscript. R. Ihaddadene performed research, and collected, analyzed and interpreted data. G. Le Gal analyzed and interpreted data, provided vital reviews of the manuscript, and wrote the manuscript. P. Moretto, N. Reaume, and C. Canil collected, analyzed and interpreted data, and provided a vital review of the manuscript.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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