The Prognostic Impact of a Positive Vascular Margin on pT3 Clear Cell Renal Cell Carcinoma

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Abbreviations and Acronyms

CSS = cancer specific survival
IVC = inferior vena cava
MRV = main renal vein
NVM = negative vascular margin
PFS = progression-free survival
PVM = positive vascular margin
RCC = renal cell carcinoma

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Editor's Note: This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 530 and 531.

Purpose: We examined the impact of positive vascular margins in patients with pT3 clear cell renal cell carcinoma.

Materials and Methods: After excluding patients with nonvascular positive margins, metastasis, lymph node involvement, neoadjuvant therapy or nonclear cell histology, we identified 224 patients with venous tumor invasion through our institutional database from 1999 to 2013. Kaplan-Meier analysis and log rank tests were used to evaluate whether positive vascular margins were associated with progression-free survival or cancer specific survival.

Results: There were 41 patients (18%) with a positive vascular margin. Margin status was directly related to the level of invasion ($p < 0.0001$). Compared to the negative vascular margin group the positive group had a significantly worse progression-free survival ($p=0.01$) but not cancer specific survival ($p=0.3$). Similarly the level of vascular thrombus invasion was significantly associated with worse progression-free survival ($p=0.02$) but not cancer specific survival ($p=0.4$). The 3-year progression-free survival was worst with inferior vena cava invasion and best with segmental/muscular venous branch invasion (54%, 95% CI 34–70 vs 76%, 95% CI 64–85). Among patients with only main renal vein thrombus, vascular margin status was not associated with progression-free survival ($p=0.5$) or cancer specific survival ($p=0.2$).

Conclusions: In patients with pT3N0/XM0 clear cell renal cell carcinoma positive vascular margins are associated with risk of disease progression. However, the risk of relapse associated with positive vascular margins is driven by the extent of vascular thrombus invasion. These findings suggest that the clinical significance of vascular margin status as currently defined in pT3 clear cell renal cell carcinoma is minimal.

Key Words: kidney neoplasms; thrombosis; neoplasm staging; prognosis; carcinoma, renal cell

Clear cell RCC constitutes the majority of all renal carcinomas and exhibits a propensity to progress locally through growth as a tumor thrombus into successively larger caliber vessels.[1] Up to 10% of all patients diagnosed with clear cell RCC have a tumor thrombus, which may extend beyond the renal vein into the IVC and right atrium. Such disease is classified as stage T3b or T3c, depending on the thrombus level.[2]

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The presence of tumor thrombus is associated with less favorable cancer related outcomes.[3,4] Vascular invasion is a growth pattern reflective of tumor biology and has been suggested to offer prognostic value.[5–7] Various forms of vascular invasion may be difficult to appreciate intraoperatively and may potentially contribute to a PVM. Reporting vascular margin status is standard, although the clinical significance remains unclear.

The 2012 International Society of Urologic Pathology consensus defines a renal vein margin as positive only if there is adherent tumor at the actual margin.[8] There are 3 scenarios in which a PVM may occur (fig. 1). A PVM develops when inking the free-floating edge of an intact tumor thrombus that protrudes from the lumen of the renal vein after transection. This is the most common form of PVM and may be a result of surgical technique or specimen processing because the vessel wall has a tendency to retract beyond the bulging thrombus during fixation.[8] A PVM can also occur when the tumor thrombus grows into and invades the renal vein or IVC wall at the surgical margin. Finally, a PVM occurs when a tumor thrombus extends into the IVC and cannot be manipulated back toward the renal vein intraoperatively. Cavotomy is performed to allow for the evacuation of the tumor thrombus. In this scenario the tumor thrombus protrudes beyond the transected MRV and IVC margins. In this study we determine the prognostic value of PVMs in regard to predicting oncologic outcomes in patients with pT3 clear cell RCC.

MATERIALS AND METHODS

After institutional review board approval patients with pT3 renal tumors who underwent open or minimally invasive radical nephrectomy were retrospectively identified from January 1999 to June 2013. Before surgery all patients underwent routine metastatic evaluation, which included physical examination, cross-sectional radiographic imaging and blood testing. On pathological assessment only patients with evidence of tumor thrombus invasion into the muscular/segmental venous branch, MRV or IVC were included in the study. Patients with metastatic disease at diagnosis, positive surgical margins other than PVMs, node positive disease, neoadjuvant therapy and nonclear cell histology were excluded from the study. A total of 224 patients were eligible for the final analysis.

For patients with IVC thrombus on perioperative imaging all visible tumor thrombus was surgically excised, including resection of the vena caval wall if wall invasion was suspected. We did not routinely perform intraoperative frozen section analysis to assess renal vein margin status. PVMs were identified from pathology reports using the standard pathology criteria that define a PVM as grossly visible tumor protruding beyond the margins of MRV or IVC wall transection.[8]

Routine followup included serial chest and abdominal imaging. Clinical trials in the adjuvant setting were offered to eligible patients with pT3 clear cell RCC at our institution. PFS was defined as time to first discovery of local recurrence or distant metastasis. Local recurrence was defined as recurrence of disease at the site of vascular excision, within or adjacent to the renal fossa. Distant metastasis was defined as recurrence of disease other than local recurrence. CSS was calculated as time from surgery to death due to disease or last known followup, whichever occurred earlier.

Baseline categorical variables were compared between patient groups using Fisher's exact test and continuous variables were compared using rank sum tests. Kaplan-Meier analyses were used to estimate the 3-year probability of PFS and CSS based on vascular margin status and extent of tumor thrombus involvement. Differences in PFS and CSS were determined with the log rank test. Pathological stage was defined according to the 2010 American Joint Committee on Cancer classification.[2] Statistical analyses were performed using Stata® version 13 with $p < 0.05$ considered statistically significant.

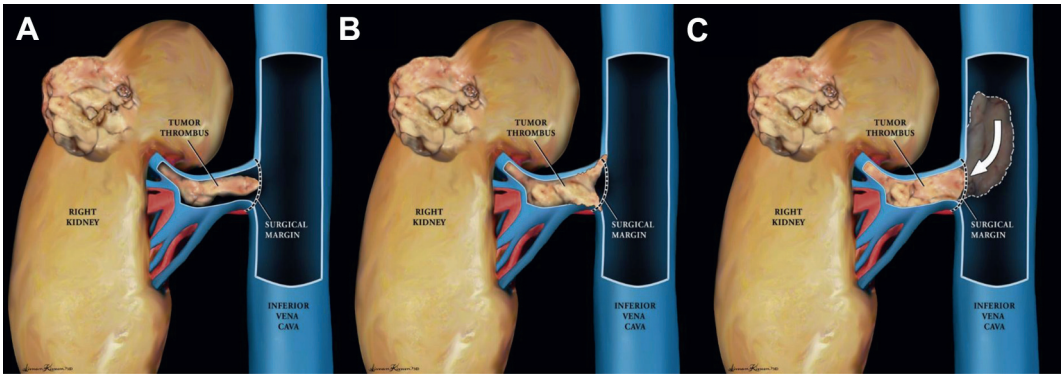

Figure 1. PVMs have 3 sources in T3 disease. *A*, free-floating thrombus protrudes from vein lumen after transection. *B*, microscopic vascular wall invasion from tumor thrombus grows beyond transection margin. *C*, free-floating thrombus extends into IVC and cannot be manipulated back toward MRV. Cavotomy is performed to allow for evacuation of tumor thrombus.