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Kidney Cancer

Impact of Histologic Subtype on Cancer-specific Survival in Patients with Renal Cell Carcinoma and Tumor Thrombus

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Abstract

Background: Although different prognostic factors for patients with renal cell carcinoma (RCC) and vena cava tumor thrombus (TT) have been studied, the prognostic value of histologic subtype in these patients remains unclear.
Objective: We analyzed the impact of histologic subtype on cancer-specific survival (CSS).
Design, settings, and participants: We retrospectively analyzed the records of 1774 patients with RCC and TT who underwent radical nephrectomy and tumor thrombectomy from 1971 to 2012 at 22 US and European centers.
Outcome measurements and statistical analysis: Multivariable ordered logistic and Cox regression models were used to quantify the impact of tumor histology on CSS.
Results and limitations: Overall 5-yr CSS was 53.4% (confidence interval [CI], 50.5–56.2) in the entire group. TT level (according to the Mayo classification of macroscopic venous invasion in RCC) was I in 38.5% of patients, II in 30.6%, III in 17.3%, and IV in 13.5%. Histologic subtypes were clear cell renal cell carcinoma (cRCC) in 89.9% of patients, papillary renal cell carcinoma (pRCC) in 8.5%, and chromophobe RCC in 1.6%. In univariable analysis, pRCC was associated with a significantly worse CSS ($p < 0.001$) compared with cRCC.

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In multivariable analysis, the presence of pRCC was independently associated with CSS (hazard ratio: 1.62; CI, 1.01–2.61; $p < 0.05$). Higher TT level, positive lymph node status, distant metastasis, and fat invasion were also independently associated with CSS.
Conclusions: In our multi-institutional series, we found that patients with pRCC and vena cava TT who underwent radical nephrectomy and tumor thrombectomy had significantly worse cancer-specific outcomes when compared with patients with other histologic subtypes of RCC. We confirmed that higher TT level and fat invasion were independently associated with reduced CSS.
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1. Introduction

Renal cell carcinoma (RCC) represents 2–3% of all cancers [1] with an estimated 65 150 new cases and 13 680 deaths for 2013 in the United States [2]. According to the World Health Organization (WHO), there are at least three major histologic subtypes of RCC: clear cell RCC (cRCC, 80–90%), papillary RCC (pRCC, 10–15%), and chromophobe RCC (chRCC, 4–5%) [3].

Several studies have evaluated the prognostic value of histologic subtype in RCC [4–9]. However, the impact of the three main RCC subtypes on prognosis is inconclusive. Some studies showed a survival advantage for patients with pRCC or chRCC histology relative to that of cRCC, but these reports did not include multivariable analyses [4,6]. Patard et al. performed a multi-institutional international study of 4063 patients and found on multivariable analysis that histopathology was not an independent predictor [9]. This finding was confirmed by Ficarra et al., who analyzed data of patients with centrally reviewed pathology [7]. In contrast, Capitanio et al. reported that histologic subtype as a group was an independent predictor of cancer-specific mortality (CSS) in multivariable analyses using the National Cancer Institute Surveillance Epidemiology and End Results database [5]. Nevertheless, the authors noted that individually neither papillary nor chromophobe histology was distinguishable from clear cell histology. Keegan et al. found that patients with chRCC had improved survival after adjusting for the effect of tumor stage [8]. Pathologic tumor stage remains the strongest prognostic factor in patients with RCC [10]. RCC with tumor thrombus (TT) is found in 4–10% of newly diagnosed RCC patients and associated with poor prognosis, higher Fuhrman grade, and larger tumor size [11]. Although different prognostic factors for patients with RCC and vena cava TT, such as Eastern Cooperative Oncology Group performance status, metastatic status, sarcomatoid features, and concomitant perinephric fat invasion have been extensively documented, the prognostic significance of histologic subtype in patients with RCC and TT has rarely been studied and remains unclear [12,13].

To address this vacuum, we analyzed the impact of histologic subtype on CSS in a large international cohort of RCC patients with TT.

2. Patients and methods

2.1. Patient selection and data collection

This study was approved by the institutional review boards of all participating sites that provided the necessary institutional data-sharing agreements before initiation of the study. A total of 22 US and European centers provided data. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Prior to final analysis, the database was frozen and the final data set was produced for the current analysis. The records of 1774 patients with RCC and vena cava TT who underwent radical nephrectomy and complete tumor thrombectomy between 1971 and 2012 were reviewed. Neoadjuvant and adjuvant treatments were administered at the investigator's discretion to 10.2% of patients, all of whom had metastasis.

2.2. Pathologic evaluation and macroscopic vascular involvement

All surgical specimens were processed according to standard pathologic procedures. Tumor size was evaluated on fixed pathologic specimens. Histologic subtype was determined according to the 1997 WHO Heidelberg classification [14]. pRCC types 1 and 2 were not distinguished in this cohort. Tumor nuclear grade was determined according to the Fuhrman system. Pathologic staging was designated according to the 2009 TNM classification of the American Joint Committee on Cancer [15].

To ensure validity of the pathologic data, two investigators independently reviewed pathology from a subgroup of patients while blinded to patient clinical parameters and the finding of the other reviewer. Interreader reliability measured using the intraclass correlation coefficient was >0.95 for each pathologic characteristic.

2.3. Tumor thrombus level

The Mayo classification was used for the macroscopic vascular involvement [16]. In level I, TT is either at the entry of the renal vein or within the inferior vena cava (IVC) <2 cm from the confluence of the renal vein and the IVC. In level II, TT extends within the IVC >2 cm above the confluence of the renal vein and IVC but still remains below the hepatic veins. In level III, TT involves the intrahepatic IVC. The size of the thrombus ranges from a narrow tail that extends into the IVC to one that fills the lumen and enlarges the IVC. In level IV, TT extends above the diaphragm or into the right atrium.

2.4. Follow-up

Follow-up was performed according to institutional protocols. Patients generally were seen postoperatively at least every 3 mo for the first year, semiannually for the second year, and annually thereafter. Follow-up visits consisted of a physical examination and serum chemistry evaluation including liver function tests and alkaline phosphatase. Diagnostic imaging (eg, ultrasonography, computed tomography of the abdomen/pelvis with intravenous contrast), and chest radiography were performed twice yearly and at the discretion of the treating physician when clinically indicated. When patients died, the cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or

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