Associations between body composition, ClearCode34, and clinical outcomes in localized clear cell renal cell carcinoma

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Background: Emerging evidence suggests that pre-surgical body composition is a prognostic factor for cancer outcomes. Lower skeletal muscle quantity and radiodensity have been associated with renal cell carcinoma (RCC) outcomes in other studies, while reports of the relationship between visceral adipose tissue and RCC outcomes have been inconsistent. Mechanisms underlying these associations are unclear but may relate to tumor biology. We leveraged a large molecular epidemiology study of localized clear cell renal cell carcinoma (ccRCC) patients to examine how pre-surgical body composition features were associated with survival post-nephrectomy as well as ClearCode34 status, a previously validated prognostic gene expression signature.

Methods: The RESOLVE study at Memorial Sloan Kettering Cancer Center is a retrospective study of 1,239 patients with stage I-III ccRCC undergoing nephrectomy without systemic therapy. Pre-surgical CT scans at the third lumbar vertebrae were segmented for the cross-sectional areas and radiodensities of skeletal muscle, subcutaneous adipose and visceral adipose tissues using Automatica software. Formalin-fixed, paraffin-embedded tumor tissue samples were available for 929 patients, which were sent to the University of North Carolina at Chapel Hill and assayed for gene expression. RNA was extracted from these samples and analyzed using the Nanostring nCounter system on a custom panel of 356 genes, including the 34 genes used in the ClearCode34 assay. Of the 929 patients with tumor tissue available, gene expression data from 837 patients (90.1%) passed RNA extraction and data QC. Samples were classified into either ccA or ccB ClearCode34 classes using a reference data set and PAM (prediction analysis of microarrays) centroid-based classification.

Results: Of the 837 patients in our analytic sample, 219 (26%) had ccB tumors. Men, patients with high stage or grade tumors, and patients with chronic kidney disease prior to nephrectomy were more likely to present with ccB tumors. Lower skeletal muscle density (SMD) was significantly associated with lower five-year DFS [HR (95% CI) per 10 HU decrease in SMD: 1.7 (1.2, 2.3)]. While no other body composition features were significantly associated, we also observed nonsignificantly increased HRs for VATI and VATD [HR (95% CIs): 1.3 (0.8, 2.0) and 1.5 (0.9, 2.7), respectively].

ClearCode34 subtype was significantly associated with five-year DFS, where patients with ccB tumors had poorer DFS [HR (95% CI): 1.7 (1.1, 2.5)] compared to patients with ccA tumors. Notably, we observed no significant associations between any body composition features and ClearCode34 in univariable analyses. However, in multivariable models that accounted for all body composition variables simultaneously as well as age and sex, lower SMD emerged as significantly associated with ccB subtype [OR (95% CI) per 10 HU decrease in SMD: 1.3 (1.0, 1.7)].

Conclusions: Our findings suggest that the associations observed between body composition features and clinical outcomes in ccRCC may be related to tumor biology. Lower pre-surgical SMD, which may represent myosteatosis and metabolic dysregulation in ccRCC patients, was associated with both decreased five-year DFS and an increased likelihood of presenting with a more aggressive ccB tumor. Future studies should investigate body composition features related to ccRCC prognosis and additional markers of tumor biology, such as immune-related gene expression patterns, to extend these findings.

Keywords: Kidney cancer; body composition; ClearCode34; clear cell renal cell carcinoma; renal cell carcinoma survival