

Metastatic Bone Disease is Associated with Muscle Loss and Reduced Survival in Kidney Cancer

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INTRODUCTION: Cachexia is a multifactorial syndrome characterized by muscle loss and is responsible for 20–40% of cancer-related deaths, yet no FDA-approved therapies exist. Preclinical studies suggest that metastatic bone disease may contribute to muscle wasting, but this relationship has not been evaluated in clinical populations. Kidney cancer frequently metastasizes to bone, is associated with cachexia, and is characterized by relatively long survival. Thus, the purpose of this study was to evaluate the relationship between metastatic bone disease, muscle loss, and survival in kidney cancer patients.

METHODS: Following IRB approval, we retrospectively identified 293 patients (196 males and 97 females) with either localized kidney cancer at diagnosis, metastatic disease outside bone, or metastatic disease to bone using a comprehensive cancer center registry. Clinical and demographic variables, treatments, and body composition metrics were abstracted via chart review. Body composition was quantified over time for a subset of 99 patients at the L3 vertebral level using AI-assisted segmentation software (Voronoi Analytics), capturing skeletal muscle, subcutaneous adipose tissue, and visceral adipose tissue. Longitudinal changes were analyzed using linear regression, and overall survival was assessed with Kaplan–Meier and multivariable Cox proportional hazards models.

RESULTS: At diagnosis and over time, patients with metastatic bone disease had significantly lower BMI compared to those with localized or non-osseous metastatic disease (**Figure 1a**). Skeletal muscle loss was also significantly greater in the bone metastasis cohort (**Figure 1a/c**). Linear regression demonstrated that Black race and bone metastasis at diagnosis were the strongest predictors of muscle loss (**Figure 1b**). Survival analyses showed worse outcomes for patients with bone metastases and >20% skeletal muscle mass, which was the most powerful predictor of mortality in multivariate analysis (**Figure 2**).

DISCUSSION: This study provides the first clinical evidence that metastatic bone disease is strongly associated with accelerated skeletal muscle loss and reduced survival in kidney cancer patients. These findings extend prior preclinical observations into the clinical setting and suggest that the skeleton is not merely a site of tumor colonization but may also act as a driver of systemic muscle wasting. Importantly, the observation that severe muscle loss is a strong predictor of mortality highlights the need to consider cachexia as a modifiable determinant of outcomes, not just a byproduct of advanced disease. Future work will investigate underlying mechanisms, including inflammatory and bone–muscle signaling pathways, leveraging preclinical models and biobank specimens to identify novel therapeutic targets.

SIGNIFICANCE/CLINICAL RELEVANCE: These findings support the concept that preventing muscle wasting by targeting bone metastases may represent a novel therapeutic strategy for cancer cachexia. Incorporating body composition metrics into routine clinical assessments may also improve risk stratification and guide early intervention strategies in kidney cancer patients.

IMAGES AND TABLES:

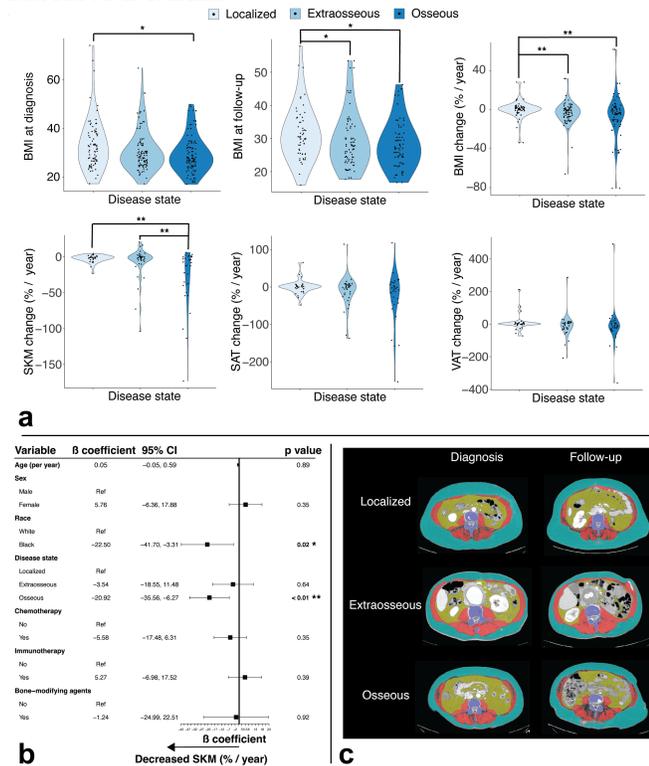


Figure 1. Osseous metastatic disease is associated with loss of skeletal muscle (SKM) in persons with renal cell carcinoma (RCC). Violin plots show changes in body composition over time by disease state (a). Multiple linear regression shows race and osseous disease associated with decreased SKM (b). Representative images (median of SKM for each group) of artificial intelligence assisted body composition analysis of CT scans are shown in c, with red indicating SKM. Each datapoint represents an individual person in A. * = $p < 0.05$. ** = $p < 0.01$.

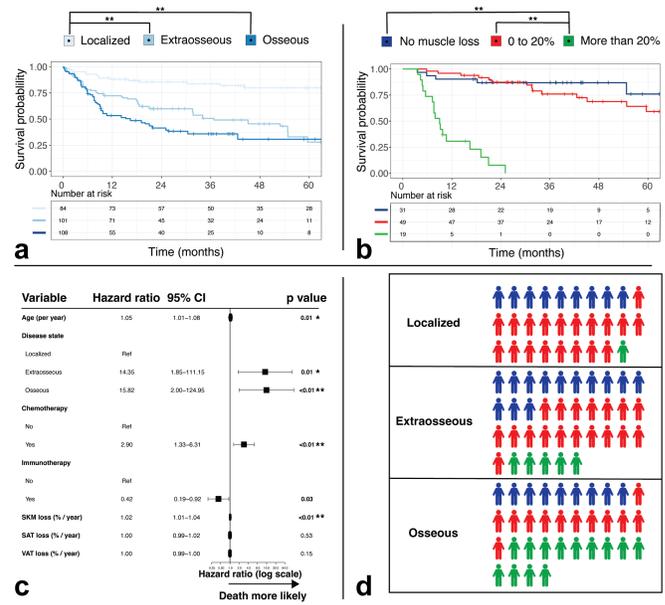


Figure 2. Osseous metastatic disease and loss of skeletal muscle (SKM) is associated with survival in persons with renal cell carcinoma (RCC). Data summarize findings from a retrospective chart review at my institution. Data obtained from medical records (clinical) and artificial intelligence assisted analysis of CT scans (body composition). Kaplan-Meier curves show that patients with osseous metastatic disease have worse survival (a) than other disease states, and that those with more than 20% loss of SKM per year have worse survival than those with no or 0-20% SKM loss per year (b). Multiple Cox regression analysis identified SKM loss of 20% and osseous disease as having the first and second highest risk of death, respectively (c). (d) provides a visual representation of individual persons in each disease category (localized, extraosseous metastasis, and osseous metastasis) with no muscle loss (blue), 0-20% (red), and more than 20% (green). * = $p < 0.05$. ** = $p < 0.01$.