Title: Impact of Radiation Therapy on Skeletal-Related Events in Renal Cell Carcinoma Patients Receiving Immune Checkpoint Inhibitors: A Retrospective Cohort Study

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Significance & Hypothesis
Bone metastases and pathological fractures remain a significant source of morbidity in patients diagnosed with renal cell carcinoma (RCC). Immune-checkpoint inhibitors (ICI) have become a cornerstone of the treatment of RCC; however, their impact on skeletal-related events remains unclear. We hypothesized that patients receiving ICI + radiation therapy (RT) would demonstrate higher rates of skeletal-related events, including bone metastasis, pathological fracture, and surgical intervention, compared to those receiving ICI alone.

Innovation
This study directly compares skeletal-related event rates between ICI alone and ICI combined with radiation therapy in RCC, providing early clinical data to guide risk stratification and surveillance.

Approach (Materials & Methods)
We conducted a retrospective cohort study of 67 patients with RCC treated with immunotherapy alone (ICI, n=44, 65.7%) vs immunotherapy plus radiation therapy (ICI + RT, n=23, 34.3%). Primary outcomes included bone metastasis, pathological fracture, and surgical intervention. Secondary outcomes included treatment-related complications and mortality. Categorical variables were compared using Fisher's exact test or chi-square testing as appropriate, and continuous variables were analyzed using independent samples t-tests.

Results
All demographic characteristics were similar between the two groups. The ICI + RT group was more likely to have higher tumor grades than ICI alone (87.0% vs 56.8%; p=0.044). Bone metastases were identified in 28.8% of patients overall, most commonly involving the spine (47.4%). Pathological fractures occurred in 23.9% of patients, of whom 56.2% required surgical stabilization. Rates of bone metastasis (23.3% vs 39.1%, p=0.254), ICI-related complications (52.3% vs 56.5%, p=0.942), and surgical intervention (11.4% vs 17.4%, p=0.481) did not differ significantly between the two groups, although numerically higher rates of skeletal complications were observed in ICI + RT patients. The ICI + RT group had approximately 2.5-fold higher risk and 3.4-fold higher odds of pathologic fracture compared with ICI alone, representing a trend toward increased fractures that did not reach significance (OR=0.294; RR=2.46; p=0.068). Among the ICI + RT group, radiation therapy side effects occurred in 13% of patients. Disease recurrence (26.2% vs 47.6%) and mortality (29.5% vs 34.8%; p=0.783) were similar between the two groups.

Discussion & Impact
In this cohort of RCC patients treated with immunotherapy, skeletal-related events were common, with nearly one quarter experiencing pathologic fractures and over half of those requiring surgical intervention. While most outcomes did not differ significantly between groups, patients receiving ICI + RT demonstrated a trend toward higher fracture risk. These findings suggest that patients with advanced or higher-grade disease who require multimodal therapy may represent a higher-risk population and should be counseled appropriately.