Reassessing the 8 cm Rule: Systematic Threshold Testing and Polynomial Modeling Expose the Limits of Conventional Osteosarcoma Staging

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INTRODUCTION: The relationship between tumor size and patient survival in osteosarcoma is not well-defined, and the 8 cm tumor size cutoff used in the American Joint Committee on Cancer (AJCC) staging system is based on limited data. This study's objective is to precisely characterize the nature of the tumor size-mortality relationship in osteosarcoma to determine if it acts as a continuous or discrete risk factor.
METHODS: We conducted a retrospective cohort study of 2,467 osteosarcoma patients using data from the Surveillance, Epidemiology, and End Results (SEER) database (2000-2021). As a publicly available de-identified dataset, it did not require institutional review board approval or informed consent. Patient characteristics were summarized, including the sex distribution (52.6% male). We used multivariable Cox regression, systematic threshold testing (40-150 mm) with Holm correction, propensity score matching, and bootstrap validation to analyze the data.
RESULTS: Out of 2,467 patients, the median tumor size was 85 mm, and the median follow-up was 82 months. The mortality rate was 39.7% (n=979). Each 10 mm increase in tumor size was independently associated with a 6.4% higher hazard of death after adjusting for age, sex, tumor site, grade, surgery, radiation, and chemotherapy (HR = 1.064, 95% CI: 1.054-1.074, $p < 0.001$). Systematic threshold testing across all clinically relevant cutpoints demonstrated significant associations (HR range: 1.70-1.96), with no single optimal cutpoint identified. Kaplan-Meier analysis showed that median survival for small tumors (≤67 mm) was 138 months, 96 months for medium tumors (68−104 mm), and 58 months for large tumors (≥105 mm). Propensity score matching further confirmed the independent prognostic effect of tumor size, demonstrating significantly worse survival for patients with large tumors than those with small tumors (HR = 1.492, 95% CI: 1.297-1.717, $p < 0.001$). Propensity score matching of 991 patient pairs showed an HR of 1.492 (95% CI: 1.297-1.717, $p<0.001$). Polynomial testing indicated a linear relationship ($p=0.253$).
DISCUSSION: This study provides one of the most comprehensive analyses to date on the prognostic significance of tumor size in osteosarcoma. Leveraging a suite of advanced statistical techniques, the research found a continuous dose-response relationship between tumor size and cancer-specific mortality, a finding that challenges the current 8 cm cutoff used in the AJCC staging system which assumes a clear binary risk distinction. The findings demonstrate that even small increases in tumor size are associated with consistent, incremental rises in mortality risk without evidence of threshold effects, aligning with biological principles like increasing genetic heterogeneity and angiogenesis that become more pronounced with tumor growth. Our findings are strengthened by the use of rigorous statistical methods, including systematic threshold testing across a wide clinical range with bootstrap validation confirming the stability and reproducibility of the findings. The study's large sample size and consistent results across different analyses provide a dependable framework, however, important study limitations include the retrospective design and the potential for unmeasured confounding from factors not captured in the SEER database, such as detailed treatment protocols or patient performance status. Ultimately, the findings argue against a singular 8 cm threshold and support adopting continuous or risk-weighted modeling in future staging systems to better reflect the prognostic impact of tumor size.
SIGNIFICANCE/CLINICAL RELEVANCE: This study provides a quantifiable, continuous risk estimate for tumor size in osteosarcoma, which can be incorporated into future risk calculators and staging systems. It has the potential to guide more personalized treatment strategies and improve prognostic discussions by moving beyond a fixed binary threshold.

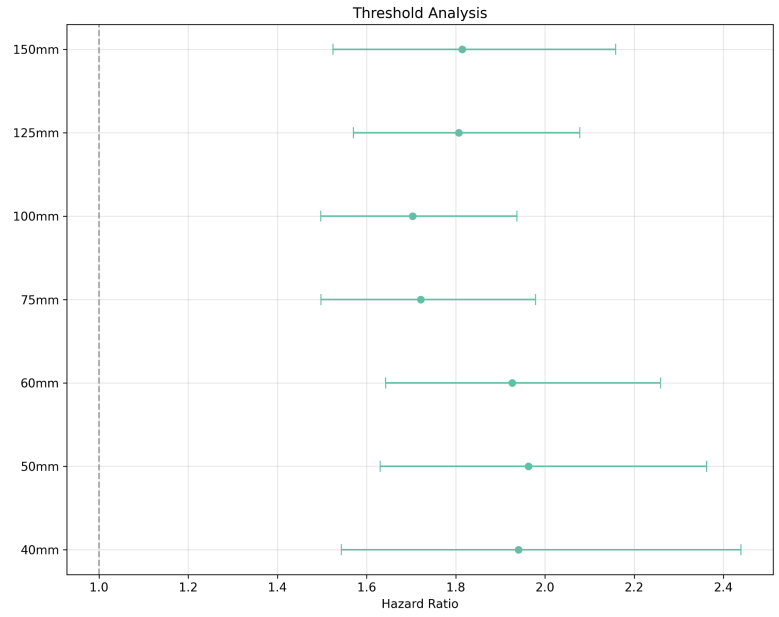

Figure 1. Forest Plot of Hazard Ratios for Multiple Tumor Size Thresholds (Holm-Corrected)
All tested thresholds were determined to be statistically significant: 40 mm threshold (HR= 1.94, 95%-Confidence Interval [95%-CI]: 1.54-2.44), 50 mm (HR= 1.96, 95%-CI: 1.63-2.36), 60 mm (HR= 1.93, 95%-CI: 1.64-2.26), and 75 mm (HR= 1.72, 95% CI: 1.50-1.98). Higher cut points showed similar moderate effects: 100 mm (HR= 1.70, 95%-CI: 1.50-1.94), 125 mm (HR= 1.81, 95%-CI: 1.57-2.08), and 150 mm (HR= 1.81, 95%-CI: 1.53-2.16, all $p<0.001$)