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## Defining the Most Informative Intermediate Clinical Endpoints for Predicting Overall Survival in Patients Treated with Radical Prostatectomy for High-risk Prostate Cancer.

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**BACKGROUND:** Given the prolonged natural history of clinically localized, high-risk prostate cancer, there is a need for the identification of intermediate clinical endpoints (ICEs) to predict long-term overall survival (OS).

**OBJECTIVE:** To explore the role of novel potential ICEs based on clinical follow-up to predict long-term survival in patients with high-risk prostate cancer.

**DESIGN, SETTING, AND PARTICIPANTS:** Overall, 3507 patients treated at 12 tertiary referral centers between 1988 and 2016 were evaluated.

**INTERVENTION:** Radical prostatectomy (RP) with extended pelvic lymph node dissection.

**OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS:** The impact of biochemical recurrence (BCR) and clinical recurrence (CR) within 1, 3, 5, and 7yr after surgery on the risk of OS was evaluated in multivariable Cox regression analyses. In patients with BCR, the impact of progression to CR within 6mo and 1, 3, and 5yr on long-term OS was investigated. Discrimination was assessed using Harrell's c index.

**RESULTS AND LIMITATIONS:** Median follow-up for survivors was 76mo. The 5- and 10-yr OS and cancer-specific survival rates were 94% and 81% versus 98% and 95%, respectively. On a time-varying multivariable analysis, BCR (hazard ratio [HR]: 1.02; 95% confidence interval [CI]: 1.00, 1.04) and CR (HR: 1.05; 95% CI: 1.03-1.07) emerged as predictors of OS ( $p < 0.001$ ). The development of CR within 5yr after surgery was the most informative ICE for predicting OS (c index: 0.74). In patients with BCR, progression to CR within 12mo represented the most informative predictor for the subsequent risk of dying from all causes. Patients who developed BCR within 5yr after RP and progressed to CR within 12mo had a 10-yr OS rate of 47%. These results require prospective validation.

**CONCLUSIONS:** When predicting long-term survival in surgically treated high-risk patients,

progression to CR within 5yr of RP confers the highest discrimination with respect to other landmark points. In men experiencing BCR, progression to CR within the subsequent 12mo achieved the highest discrimination. Further studies are needed to validate our findings.

**PATIENT SUMMARY:** We investigated the most informative intermediate clinical endpoints for predicting overall survival (OS). Occurrence of clinical recurrence within 5yr after radical prostatectomy confers the highest discrimination to a model predicting OS.

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**KEYWORDS:** Biochemical recurrence; Clinical recurrence; Delta recurrence; Metastasis; Overall survival

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