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# Clinical Outcomes for Patients with Gleason Score 9–10 Prostate Adenocarcinoma Treated With Radiotherapy or Radical Prostatectomy: A Multi-institutional Comparative Analysis

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## Abstract

***Background:*** The long natural history of prostate cancer (CaP) limits comparisons of efficacy between radical prostatectomy (RP) and external beam radiotherapy (EBRT), since patients treated years ago received treatments considered suboptimal by modern standards (particularly with regards to androgen deprivation therapy [ADT] and radiotherapy dose-escalation]. Gleason score (GS) 9–10 CaP is particularly aggressive, and clinically-relevant endpoints occur early, facilitating meaningful comparisons.
***Objective:*** To compare outcomes of patients with GS 9–10 CaP following EBRT, extremely-dose escalated radiotherapy (as exemplified by EBRT + brachytherapy [EBRT + BT]), and RP.
***Design, setting, participants:*** Retrospective analysis of 487 patients with biopsy GS 9–10 CaP treated between 2000 and 2013 (230 with EBRT, 87 with EBRT + BT, and 170 with RP). Most radiotherapy patients received ADT and dose-escalated radiotherapy.
***Outcome measurements and statistical analysis:*** Kaplan-Meier analysis and multivariate Cox regression estimated and compared 5-yr and 10-yr rates of distant metastasis-free survival, cancer-specific survival (CSS), and overall survival (OS).
***Results and limitations:*** The median follow-up was 4.6 yr. Local salvage and systemic salvage were performed more frequently in RP patients (49.0% and 30.1%) when compared with either EBRT patients (0.9% and 19.7%) or EBRT + BT patients (1.2% and 16.1%, $p < 0.0001$). Five-yr and 10-yr distant metastasis-free survival rates were significantly higher with EBRT + BT (94.6% and 89.8%) than with EBRT (78.7% and 66.7%, $p = 0.0005$) or RP (79.1% and 61.5%, $p < 0.0001$). The 5-yr and 10-yr CSS and OS rates were similar across all three cohorts.
***Conclusions:*** Radiotherapy and RP provide equivalent CSS and OS. Extremely dose-escalated radiotherapy with ADT in particular offers improved systemic control when compared with either EBRT or RP. These data suggest that extremely dose-escalated radiotherapy with ADT might be the optimal upfront treatment for patients with biopsy GS 9–10 CaP.

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***Patient summary:*** While some prostate cancers are slow-growing requiring many years, sometimes decades, of follow-up in order to compare between radiation and surgery, high-risk and very aggressive cancers follow a much shorter time course allowing such comparisons to be made and updated as treatments, especially radiation, rapidly evolve. We showed that radiation-based treatments and surgery, with contemporary standards, offer equivalent survival for patients with very aggressive cancers (defined as Gleason score 9–10). Extremely-dose escalated radiotherapy with short-course androgen deprivation therapy offered the least risk of developing metastases, and equivalent long term survival.

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## 1. Introduction

Nearly 15% of the 238 590 men diagnosed with prostate cancer (CaP) in the USA every year have high-risk disease (defined as clinical T-stage $\geq$ 3, initial prostate-specific antigen [PSA] $>$ 20 ng/ml, or Gleason score [GS] 8–10) [1,2]. The National Comprehensive Cancer Network and European Association of Urology/European Society for Radiotherapy & Oncology/International Society for Geriatric Oncology guidelines for managing high risk CaP suggest that radical prostatectomy (RP) and external beam radiotherapy (EBRT) with androgen deprivation therapy (ADT), with or without a brachytherapy boost (BT), are acceptable options [2,3]. However, recently published series comparing outcomes of RP versus RT have reached conflicting conclusions regarding efficacy [4–7]. Some suggest that RP offers superior local control and allows tailored adjuvant therapy. Others feel these comparative series are biased because of the use of anachronistic EBRT treatment strategies, an inability to properly adjust for important confounders such as age and disease burden, and an imbalance using salvage therapies [8]. Emerging data indeed suggest that dose-escalation affords increased survival for patients with high-risk CaP [9,10], and several randomized trials have demonstrated the superiority of long-term ADT [11–14].

The aforementioned studies included all high-risk CaP patients, though this group is heterogeneous. Specifically, the GS is the most important prognostic factor [15] and evidence suggests that patients with GS 9–10 disease have inferior outcomes—including more frequent biochemical recurrences (BCRs) and distant metastases (DMs) [16–20]. Indeed, the new International Society of Urological Pathology grading system separates GS 9–10 disease as a distinct entity with poorer outcomes [21,17]. The purpose of this multi-institutional study was to compare the long-term outcomes of patients with biopsy GS (bGS) 9–10 CaP treated with RP, EBRT, or extremely dose-escalated RT (as represented by EBRT + BT) in the modern era. The EBRT + BT cohort was chosen as the paradigm for extremely dose-escalated RT given the availability of long-term outcomes data. We hypothesized that the combination of extremely dose-escalated RT and ADT would lead to superior clinical outcomes in the EBRT + BT cohort.

## 2. Materials and methods

### 2.1. Patient population

The study population consisted of 487 consecutively treated men with bGS 9–10 CaP who were treated at the University of California, Los Angeles and its affiliated institutions, the California Endocurie Therapy Center, and Fox Chase Cancer Center between January 2000 and November 2013. Patients were identified using institutional registries. Institutional review board approval was obtained for all institutions. Patients diagnosed before adoption of the 2005 International Society of Urologic Pathology consensus conference guidelines [22] were included if they would have been scored as having bGS 9–10 CaP in modern times. All ADT was pharmacologic, primarily with combined androgen blockade followed by leuprolide monotherapy. One-hundred-and-seventy patients had a RP, 230 had definitive EBRT $\pm$ ADT, and 87 had EBRT + BT $\pm$ ADT. Of the EBRT + BT patients, 84 had high dose rate BT (HDR-BT) and three had low dose rate BT (LDR-BT).

### 2.2. Classification of failures and deaths

Patients undergoing RP were classified as experiencing BCRs either when their postoperative PSA became $\geq$0.2 ng/ml or at initiation of salvage RT (SRT) or salvage ADT. Patients receiving RT were classified as experiencing a BCR either when their PSA was $\geq$nadir + 2 ng/ml [23] or at initiation of local salvage or salvage ADT. Patients were classified as having DMs when they had imaging evidence of lesions that were clinically or pathologically diagnosed as metastatic. Typically, imaging to detect DMs was performed at the time of BCR or for subsequent PSA increases after an initial BCR. Prostate-cancer specific mortality (PCSM) was defined based on either clinical documentation or inclusion of CaP as a primary cause of death on a death certificate. One-hundred-and-two out of 107 patients who were deceased at last follow-up (95.3%) had either form of PCSM determination available.

### 2.3. Statistical analysis

A two-tailed Student *t* test was used to evaluate differences in age and ADT duration between the cohorts, and the Wilcoxon rank-sum test was used to evaluate differences in initial PSA. Two-tailed chi-square tests (or Fisher's exact test) were used to evaluate differences in categorical variables. Outcomes of interest included BCR-free survival (BCRFS), DM-free survival (DMFS), cancer-specific survival (CSS), and overall survival (OS), which were defined by intervals from the end of treatment to BCR, DM, PCSM, and death, respectively. Follow-up was defined from the end of local treatment (ie, date of surgery or date of completion of RT) rather than from diagnosis in order to avoid introduction of bias stemming from the different lengths of treatments between cohorts. Kaplan-Meier survival analysis was used to evaluate outcomes at 5 yr and 10 yr of follow-up. Patients were censored at the time of the defined outcome or at last follow-up. The log-rank test was used to compare survival curves at 5 yr and 10 yr. Multivariate Cox regression was used to estimate the hazard ratios of these outcomes between treatment cohorts, adjusted for patient age, bGS, clinical T-stage, initial PSA, year of treatment, local salvage (with time to salvage as a covariate), and systemic salvage (with time to salvage as a covariate). All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

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