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Combination therapy improves prostate cancer survival for patients with potentially lethal prostate cancer: The impact of Gleason pattern 5

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ABSTRACT

PURPOSE: To investigate the impact of Gleason pattern 5 (GP5) prostate cancer after either external beam radiotherapy (EBRT) or the combination of EBRT with low-dose rate brachytherapy boost (combo).

METHODS AND MATERIALS: Between 1998 and 2008, 467 patients with National Comprehensive Cancer Network high-risk prostate cancer were treated with EBRT ($n = 326$) or combo (low-dose rate to 90–108 Gy using I-125 followed by EBRT) ($n = 141$). Freedom from biochemical failure, freedom from metastasis (FFM), cancer-specific survival (CSS), and overall survival were evaluated.

RESULTS: Combo patients were younger (66 vs. 72 years, $p < 0.001$) and had fewer comorbidities (Charlson comorbidity index 3.7 vs. 4.4, $p < 0.001$). EBRT patients had higher tumor stages (T3–4: 30% vs. 21%, $p = 0.03$) and lower Gleason scores (8–10: 61% vs. 75%, $p = 0.01$). Androgen deprivation therapy use was similar between cohorts (85% vs. 87%, $p = 0.5$), but EBRT patients had longer androgen deprivation therapy use (median 14 vs. 12 months, $p = 0.05$). GP5 predicted worse FFM ($p < 0.001$, hazard ratio [HR] 3.3, 95% confidence interval [CI]1.8–6.2]) and CSS ($p < 0.001$, HR 5.9, 95% CI 2.7–12.9) for the EBRT group, but not for the combo group ($p = 0.86$, HR 0.48, 95% CI 0.1–2.4 for metastasis and $p = 0.5$, HR 1.6, 95% CI 0.33–8.0 for CSS). In those with GP5 ($n = 143$), combo was associated with improved outcomes in all endpoints. On univariate analysis, 5-year outcomes for combo vs. EBRT were as follows: freedom from biochemical failure 89% vs. 65%, FFM 89% vs. 67%, CSS 93% vs. 78%, and overall survival 88% vs. 67% ($p < 0.05$ for all).

CONCLUSION: Combo was associated with improved outcomes for men with GP5 prostate cancer. This highlights the importance of local therapy, especially in patients with the highest pathologic grade disease.

Keywords: Gleason pattern 5; Combination therapy; High-risk prostate cancer

Introduction

Prostate cancer remains the most common cancer diagnosis in men, with an estimated 220,800 new diagnoses in 2015, and is the second most common cause of cancer death in men with 27,540 estimated cancer deaths (1). Although risk stratification can help define the high-risk subgroup that is most likely to have recurrence after initial therapy, improving outcomes and decreasing mortality among the high-risk patients remains an unsolved challenge. For many men with high-risk prostate cancer, radiation, surgery, or androgen deprivation therapy (ADT) alone are insufficient treatment (2–4). Combining treatment modalities has been shown to yield improved results (4, 5). It

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is well established that the addition of ADT to conventional-dose (<72 Gy) external beam radiation therapy (EBRT) improves overall survival (OS) in randomized studies (2, 6, 7). Nevertheless, despite combined EBRT and ADT, clinical disease-free survival for men with high-risk disease remains less than optimal (6).

Further stratifying patients with high-risk prostate cancer can identify groups of men with an even worse prognosis. Patients with higher Gleason scores (GS) have been shown to have an increased risk of recurrence and decreased prostate cancer–specific survival after treatment (8–10). The presence of Gleason pattern 5 (GP5) prostate cancer has been correlated with an increased risk of recurrence and metastasis after prostatectomy and salvage RT, definitive external beam radiation, and brachytherapy (11–13). Studies of high-risk prostate cancer have identified the presence of GP5 as the strongest prognostic factor of all clinical endpoints (11, 12). The significance of GP5 for patients treated with EBRT and low-dose rate (LDR) brachytherapy boost (combo) has not been fully examined. It was our hypothesis that the enhancement in local radiation dose associated with combo treatment might offer superior local control over EBRT alone. Therefore, we sought to investigate if GP5 would predict for improved clinical outcomes for patients treated with combo as compared with dose-escalated EBRT.

Methods and materials

Patient selection

Through an institutional review board–approved retrospective analysis, we identified 467 patients who received definitive radiation with or without ADT for high-risk prostate cancer (defined by the National Comprehensive Cancer Network [NCCN] as T3–T4, GS 8–10, or prostate-specific antigen [PSA] >20 ng/mL). Patients were considered in the GP5 subgroup if GP5 was present as either the primary or secondary Gleason pattern in at least one core. Tertiary pattern 5 was not routinely collected during this period and was not included. All patients studied received treatment from 1998 to 2008 at the University of Michigan or at regional practices affiliated with the University of Michigan and staffed by University of Michigan physicians and physics faculty. Treatment consisted of either EBRT ($n = 326$) or combo ($n = 141$), with most patients also receiving ADT.

Treatment

EBRT treatment consisted of minimum planning target volume coverage of 75 Gy (range, 75.0–79.2 Gy) using three-dimensional conformal or intensity modulated radiotherapy with CT-based planning and conventional fractions of 1.8 to 2.0 Gy daily. Targets for patients treated with EBRT consisted of the prostate, seminal vesicles, and pelvic lymph nodes. Combo therapy consisted of an LDR permanent interstitial brachytherapy implant, using ^{125}I for all implants (90–108 Gy), followed by EBRT using three-dimensional conformal or intensity modulated radiotherapy with MRI and CT planning. The EBRT dose was calculated with consideration of the implant dosimetry to achieve a total external beam equivalent dose to the prostate plus 0.5-cm margin of 90 Gy (prostate >105 Gy) and 45 Gy to the pelvic lymph nodes. The median postimplant day 21 D90 was 113% of the prescription dose and the median postimplant V100 was 94.8%. The prostate, seminal vesicles, and pelvic lymph nodes were treated using EBRT in the combo patients as well, after LDR implant. ADT was prescribed based on the discretion of the treating physician.

Endpoints

Outcomes measured consisted of freedom from biochemical failure (FFBF), freedom from metastasis (FFM), cancer-specific survival (CSS), and OS. Time to biochemical failure (BF), distant metastasis (DM), and CSS were calculated from the initiation of therapy (either start of ADT if given neoadjuvantly or start of RT). BF was defined per the Phoenix definition as a serum PSA level at least 2 ng/mL greater than the posttreatment PSA nadir (14). DM was defined as the presence of clinical, radiographic, or pathologic evidence of metastatic disease. Cancer-specific mortality was defined as a death attributed to prostate cancer, or any death in a patient after metastasis or the development of castrate-resistant prostate cancer.

Statistical analysis

Differences between categorical variable frequencies were tested by χ^2 or Fisher exact test, whereas differences between continuous variables were determined via one-way analysis of variance. Univariate survival analyses were performed using the log-rank test and Cox proportional hazards models were used for multivariate analyses.

Results

Patient characteristics

The median age of all patients was 69 years, with combo patients younger as compared with those treated with EBRT (median 66 vs. 72 years; $p < 0.001$, Table 1). Those treated with LDR brachytherapy also had less comorbid illness (mean age-adjusted Charlson comorbidity index of 3.7) as compared those treated with EBRT (mean Charlson comorbidity index 4.4, $p < 0.001$). PSA levels were similar in both cohorts of patients with a mean PSA of 25.9 ng/mL (median 20.4 ng/mL) in the combo group and 27.4 ng/mL (median 13.5 ng/mL) in the EBRT group ($p = 0.64$). Patients in the EBRT cohort were more likely to have T3 or T4 prostate cancer as compared with patients treated with combo therapy (30% vs. 21%, $p = 0.03$). Patients treated