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Short-course androgen deprivation therapy and the risk of death from high-risk prostate cancer in men undergoing external beam radiation therapy and brachytherapy

Ann C. Raldow[1,4,*], Danjie Zhang[2], Ming-Hui Chen[2], Michelle H. Braccioforte[3], Brian J. Moran[3], Anthony V. D'Amico[4]

[1]*Harvard Radiation Oncology Program, Boston, MA*
[2]*Department of Statistics, University of Connecticut, Storrs, CT*
[3]*Prostate Cancer Foundation of Chicago, Westmont, IL*
[4]*Department of Radiation Oncology, Brigham and Women's Hospital—Dana-Farber Cancer Institute, Boston, MA*

ABSTRACT

PURPOSE: We estimated the risks of prostate cancer–specific mortality (PCSM) and all-cause mortality (ACM) in men with high-risk prostate cancer (PC) undergoing external beam radiation therapy and brachytherapy with short-course androgen deprivation therapy (ADT) (median 4 months) as compared with men with more favorable-risk PC undergoing standard of care as per the National Comprehensive Cancer Network guidelines.

METHODS AND MATERIALS: The prospective study cohort comprised 6595 consecutively treated men with T1-4 N0M0 PC whose treatment included brachytherapy between October 16, 1997, and May 28, 2013. Fine and Gray competing risk regression and Cox regression analyses were used to assess the risks of PCSM and ACM in men with high, unfavorable intermediate, and favorable intermediate risk as compared with low-risk PC.

RESULTS: After median followup of 7.76 years, 820 men died (12.43%): 72 of PC (8.78%). Men with favorable intermediate–risk PC did not have significantly increased PCSM risk as compared with men with low-risk PC (adjusted hazard ratio [AHR], 1.26; 95% confidence interval [CI] 0.56, 2.88; *p*-Value 0.58), whereas men with high-risk PC (AHR, 3.74; 95% CI 1.12, 12.53; *p*-Value 0.032) and unfavorable intermediate–risk PC (AHR, 3.10; 95% CI 1.43, 6.72; *p*-Value 0.004) did. Based on 10-year adjusted point estimates of PCSM and ACM for men with high-risk PC being 6.01% (95% CI 3.79%, 8.94%) and 21.30% (95% CI 17.45%, 25.42%), respectively, PCSM comprised 28% of ACM.

CONCLUSIONS: In the setting of external beam radiation therapy and brachytherapy, men with high-risk PC have low absolute adjusted estimates of PCSM (~6%) during the first decade after treatment despite receiving only short-course ADT. Whether long-term ADT can lower PCSM and improve survival in these men requires additional study.

Keywords: Prostate cancer; Androgen deprivation therapy; Brachytherapy; Survival

Introduction

According to the National Comprehensive Cancer Network (NCCN) guidelines, brachytherapy as monotherapy is a recommended treatment option for healthy men with low- and select men with low volume favorable intermediate–risk prostate cancer (PC) (1) because studies suggested that cancer control rates in men with high-risk disease were unacceptably low (2,3). However, recent evidence suggests that further dose escalation provides a role for brachytherapy as a boost in men presenting with high-risk PC today. In the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy trial (4), men with unfavorable risk–localized PC were randomized to receive 12-month androgen deprivation therapy (ADT) combined with pelvic external beam radiation

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* Corresponding author. Harvard Radiation Oncology Program, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. Tel.: (617) 732-6310; fax: (617) 264-5242.

E-mail address: araldow@partners.org (A.C. Raldow).

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therapy (EBRT) followed by either additional EBRT to a total dose of 78 Gy or a brachytherapy boost. The study found that the brachytherapy boost was significantly more effective than the EBRT boost in rendering unfavorable-risk PC patients biochemically disease free (hazard ratio [HR], 0.473; 95% confidence interval [CI] 0.292, 0.765; *p*-Value 0.0022).

Currently, the addition of long-course (28–36 months) ADT to brachytherapy and EBRT is an option as per the NCCN for patients with high-risk PC (5). This trimodality therapy yields excellent results, with 9-year progression-free and disease-specific survivals of 87% and 91%, respectively (6, 7). However, it is uncertain whether the addition of long- vs. short-course ADT contributes to these outcomes. In the setting of high-dose EBRT, the randomized trials of 36 vs. 6 months from the European Organisation for Research and Treatment of Cancer (EORTC) (8) and 28 vs. 4 months from Grupo de Investigación Clínica en Oncología Radioterápica (GICOR) (9) showed a survival benefit to long as compared with short-course ADT. However, it remains unknown what the contribution to survival of long as compared with short-course ADT will be in the setting of high-risk PC in the setting of treatment with EBRT and a brachytherapy boost. We therefore examined the risks of prostate cancer–specific mortality (PCSM) and all-cause mortality (ACM) in men with high-risk PC who underwent EBRT and brachytherapy with short-course ADT (median 4 months and interquartile range [IQR] 3–8 months) as compared with men with more favorable-risk PC undergoing standard of care as per the NCCN guidelines.

Methods and Materials

Patient population and treatment

This was a prospective cohort study of 6595 consecutively treated men (median age 67.96 years; IQR 61.80, 73.15) with localized or locally advanced adenocarcinoma of the prostate who were treated with brachytherapy at the Prostate Cancer Foundation of Chicago between October 16, 1997, and May 28, 2013, either as primary treatment or as a boost after EBRT. Staging with pelvic CT or MRI and bone scan was performed routinely as per NCCN guidelines (5) only in men with high-risk PC; studies negative for metastatic disease in these men were required for study inclusion. These studies were not required in men with low-, favorable intermediate– or unfavorable intermediate–risk disease for inclusion. Baseline and outcome data were prospectively collected, and men were divided into low-, intermediate-, and high-risk PC based on the NCCN guidelines. Men in the intermediate-risk category were further divided into favorable- and unfavorable intermediate–risk groups based on the definition by Zumsteg *et al.* (1). They defined men with favorable intermediate–risk PC as those with Gleason 3 + 4 or less, a percentage of positive biopsy cores less than 50%, and at most one NCCN determinant of intermediate-risk PC. Men with favorable intermediate–risk PC and percent positive biopsies of 50% or less were included in the favorable intermediate–risk category.

Men with low- and favorable intermediate–risk PC were treated with prostate brachytherapy as monotherapy. Men with unfavorable intermediate–risk PC were treated with prostate brachytherapy and neoadjuvant ADT (median 4 months and IQR 3–4 months) with ($N = 176$) or without ($N = 437$) supplemental neoadjuvant EBRT. Men with high-risk disease were treated with neoadjuvant ADT (median 4 months and IQR 3–8 months) plus both prostate brachytherapy and supplemental neoadjuvant EBRT. To be included in the study, men in each risk group had to be treated as specified above.

Low-dose-rate brachytherapy was carried out using preloaded ^{125}I, ^{103}Pd, or ^{131}Cs sources with a peripheral loading technique and preplanned dosimetry. The prescribed peripheral doses for monotherapy were 144 Gy, 108 Gy, and 115 Gy for ^{125}I, ^{103}Pd, and ^{131}Cs, respectively. EBRT was delivered to the prostate and seminal vesicles to a total dose of 45 Gy in 25 fractions using three-dimensional conformal or intensity-modulated radiotherapy. Pelvic lymph nodes were also included in the radiation treatment volumes for high-risk patients only. When used in conjunction with supplemental EBRT, the prescribed peripheral doses for brachytherapy were 108 Gy, 90 Gy, and 100 Gy for ^{125}I, ^{103}Pd, and ^{131}Cs, respectively. Brachytherapy was delivered 2–4 weeks after the completion of EBRT. Neoadjuvant ADT consisted of total androgen blockage with a luteinizing hormone-releasing hormone agonist and a nonsteroidal antiandrogen.

The study was performed with the approval of IntegReview, an independent institutional review board that is fully accredited by the Association for the Accreditation of Human Research Protection Programs. All participants signed an informed consent at the time of the initial consultation permitting his deidentified clinical and PC-related information to be collected and recorded into a secure, password-protected database for outcomes research.

Followup and determination of cause of death

The primary end point of the study was PCSM risk. The risk of ACM was a secondary end point. Followup started on the date of prostate brachytherapy after the completion of all treatment and continued to the date of death or the date of last data set update (June 1, 2013), whichever came first. Followup consisted of serial prostate-specific antigen (PSA) measurements followed by a digital rectal examination every 3 months for 2 years, every 6 months for an additional 3 years, and then yearly thereafter. Men were classified as having died of PC if they, at the time of death, had radiographic documentation of metastatic PC and a rising PSA despite salvage ADT, as well as a history of undergoing cytotoxic chemotherapy.

Statistical methods

Distributions of patient clinical characteristics at the time of presentation stratified by risk group

Descriptive statistics were used to characterize clinical factors at the time of diagnosis stratified by risk group.