Received: 10 March 2023 | Revised: 10 May 2023 | Accepted: 18 May 2023

DOI: 10.1002/cncr.34916

ORIGINAL ARTICLE

Outcomes after definitive radiation therapy for localized prostate cancer in a national health care delivery system

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Funding information

National Cancer Institute, Grant/Award Number: R01 CA242559; NIH

Abstract

Purpose: Accurate information regarding real-world outcomes after contemporary radiation therapy for localized prostate cancer is important for shared decision-making. Clinically relevant end points at 10 years among men treated within a national health care delivery system were examined.

Methods: National administrative, cancer registry, and electronic health record data were used for patients undergoing definitive radiation therapy with or without concurrent androgen deprivation therapy within the Veterans Health Administration from 2005 to 2015. National Death Index data were used through 2019 for overall and prostate cancer–specific survival and identified date of incident metastatic prostate cancer using a validated natural language processing algorithm. Metastasis-free, prostate cancer–specific, and overall survival using Kaplan–Meier methods were estimated.

Results: Among 41,735 men treated with definitive radiation therapy, the median age at diagnosis was 65 years and median follow-up was 8.7 years. Most had intermediate (42%) and high-risk (33%) disease, with 40% receiving androgen deprivation therapy as part of initial therapy. Unadjusted 10-year metastasis-free survival was 96%, 92%, and 80% for low-, intermediate-, and high-risk disease. Similarly, unadjusted 10-year prostate cancer–specific survival was 98%, 97%, and 90% for low-, intermediate-, and high-risk disease. The unadjusted overall survival was lower across increasing disease risk categories at 77%, 71%, and 62% for low-, intermediate-, and high-risk disease ($p < .001$).

Conclusions: These data provide population-based 10-year benchmarks for clinically relevant end points, including metastasis-free survival, among patients with localized prostate cancer undergoing radiation therapy using contemporary techniques. The survival rates for high-risk disease in particular suggest that outcomes have recently improved.

KEYWORDS

neoplasm metastasis, population, prostatic neoplasms, radiotherapy, survival

INTRODUCTION

Over the past 2 decades, radiation therapy for treatment of localized prostate cancer has evolved with respect to dose,[1,2] fractionation,[3,4] and technique (e.g., intensity-modulated radiation therapy).[5–7] In addition, the use,[8–10] duration,[11–13] and sequencing[14,15] of androgen deprivation therapy (ADT) have been refined along with improved staging and risk group stratification.[16–18] For these reasons, clinical trial outcomes of radiation and hormone therapy for prostate cancer have improved over time.

Although radiation therapy outcomes (i.e., metastasis, death) for prostate cancer are often derived from meta-analyses of prospective clinical trials, our contemporary understanding may be compromised because of the follow-up duration needed for longer term outcomes and resulting in outdated trial data. For example, a recent meta-analysis of 12 randomized controlled trials examining ADT use and timing provided insights into metastasis-free and overall survival, but the trials spanned 1987 through 2010, with most patients treated in the 1990s when techniques were actively evolving.[14] Population-based data (e.g., National Cancer Database, Surveillance, Epidemiology, and End Results) lack key granular details that impact treatment recommendations such as development of metastatic disease, further limiting understanding of contemporary outcomes. Identification of incident metastatic disease is a longstanding, critical barrier to population-based cancer outcomes assessment. Clarifying the impact of contemporary radiation techniques and hormone therapy schedules on population-based outcomes would support better shared decision-making for both clinicians and patients.

In this context, we conducted a large population-based study of contemporary outcomes in a national cohort of patients with localized prostate cancer who received definitive radiation therapy with or without ADT over the past 15 years. We used an innovative, validated, natural language processing algorithm to identify incident metastatic prostate cancer within the electronic medical records to determine important clinically relevant outcomes, including metastasis-free survival, prostate cancer–specific survival, and overall survival.[19]

METHODS

We used national electronic health record data for patients undergoing definitive radiation therapy with or without concurrent androgen deprivation therapy within the Veterans Health Administration system from 2005 to 2015, with follow-up through 2019. We queried the Veterans Health Administration Corporate Data Warehouse and Central Cancer Registry to identify patients with incident prostate cancer, obtaining their demographics, biopsy, and treatment details. Patients who underwent definitive surgery for prostate cancer or received radiation therapy in the salvage setting for disease recurrence after primary prostatectomy were excluded from this analysis.

We stratified patients by risk group at diagnosis using National Comprehensive Cancer Network (NCCN) definitions for low-, intermediate-, and high-risk groups, as well as Grade Group based on clinical staging data. Data regarding ADT use as part of the initial treatment course were derived from the Veterans Administration Central Cancer Registry and using national pharmacy data similar to our prior work.[20] Because ADT is used in combination with radiotherapy in short- and long-term regimens, we defined a cutoff to differentiate "short-term" from "long-term" ADT of 9 months. For example, any patients receiving <9 months of ADT as part of their initial treatment course were considered to have received short-term ADT, whereas any patients receiving ≥9 months ADT as part of their initial treatment were considered to have received long-term ADT. The Cochran-Mantel-Haenszel method was used to evaluate associations between clinical stratifications and ADT use.

Our primary outcomes were overall survival, prostate cancer–specific, and metastasis-free survival. We used National Death Index data to determine cause of death and considered this as a binary variable (prostate cancer vs. any other cause). We obtained the date of incident metastatic disease using a highly sensitive and specific natural language processing algorithm applied to the national electronic health records.[19] Our time-to-event for all survival end points were measured from date of diagnosis. We assessed survival end points using the Kaplan–Meier method, with censoring at death or the end of the study period December 31, 2019. The Hall-Wellner method was used to generate 95% confidence bands. Log-rank testing was used for between-group comparisons, with $p < .05$ considered significant. All analyses were conducted in SAS, version 8.3. This study was approved by our institutional review board.

RESULTS

Patient demographics and tumor characteristics

We included a total of 41,735 patients in this analysis, with a median follow-up of 8.7 years. The median age at diagnosis was 65 years. Most men had cT1 (68.0%) or cT2 (28.7%) disease, and nearly all (96.8%) were clinically node-negative according to the registry. Almost two-thirds (62%) of men had a prostate-specific antigen (PSA) between 4 and 10 ng/mL at diagnosis. We found similar distributions of Grade Group 1 (32.0%) and 2 (31.9%) disease, with 14.1% Grade Group 3, 12.2% Grade Group 4, and 8.8% Grade Group 5 disease. In terms of NCCN risk status, 24.8% had low-risk, 42.2% intermediate-risk, and 32.9% had high-risk disease at diagnosis (Table 1). We found ADT was used in conjunction with definitive-intent radiation therapy in 40.3% of patients further explicated in the following section.

TABLE 1 Disease characteristics and use of androgen deprivation therapy in 41,735 patients undergoing definitive radiation therapy for localized prostate cancer.

Variable	All patients undergoing radiation therapy ± ADT (*N* = 41,735)
Age (median, years)	65
Clinical T-stage	
cT1	28,361 (68.0%)
cT2	11,967 (28.7%)
cT3	924 (2.2%)
cT4	133 (0.3%)
Missing	350 (0.8%)
Clinical N-stage	
N0	40,383 (96.8%)
N1	345 (0.8%)
Missing	1007 (2.4%)
PSA at diagnosis	
≤4	4665 (11.2%)
4–10	25,887 (62.0%)
10–20	6778 (16.3%)
≥20	3844 (9.2%)
Unknown	561 (1.3%)
Biopsy Grade Group	
1	13,343 (32.0%)
2	13,327 (31.9%)
3	5868 (14.1%)
4	5108 (12.2%)
5	3654 (8.8%)
Unknown	435 (1.0%)
NCCN Risk Group	
Low	10,332 (24.8%)
Intermediate	17,634 (42.2%)
High	13,715 (32.9%)
Missing	54 (0.1%)
ADT use: initial treatment	
Yes	16,833 (40.3%)
No	24,902 (59.7%)

Abbreviations: ADT, androgen deprivation therapy; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen.

Patterns of ADT use by Grade Group and NCCN risk groups

Radiation therapy alone was used in 59.7% of patients, and radiation with concurrent ADT in the remaining 40.3% (22.6% and 17.7% short- and long-term ADT, respectively). The use of any ADT in conjunction with definitive radiation therapy increased with increasing Grade Group, with 51.2% of patients with Grade Group 3 disease, 73.8% with Grade Group 4 disease, and 81.4% of patients with Grade Group 5 receiving ADT compared with 37.2% of patients with Grade Group 2 and 14.2% of patients with Grade Group 1 disease ($p < .001$). Similarly, when examined by NCCN risk status, more than two thirds (68.4%) of men with high-risk disease received ADT as part of their initial treatment course, compared with 36.1% and 10.2% of men with intermediate and low risk, respectively ($p < .001$). Most patients receiving long-term ADT had Gleason Grade 4 or 5 disease (61.4%), and 77.7% had high-risk disease per NCCN. We observed higher median PSA levels to be associated with increasing treatment intensity: PSA 6.0 ng/mL for patients who received radiation therapy alone, 7.6 ng/mL for those who received radiation plus short-term ADT, and 9.7 ng/mL for patients who received radiation plus long-term ADT ($p < .001$) (Table 2).

Survival

Overall survival worsened as disease risk classification increased following definitive radiation therapy for localized prostate cancer. For example, 10-year overall survival was 77% for patients with low-risk, 70% for those with intermediate-risk, and 62% for those with high-risk disease at diagnosis ($p < .001$). Corresponding 10-year prostate cancer–specific survival was 98% for patients with low-risk, 97% for those with intermediate-risk, and 90% for patients with high-risk disease at diagnosis ($p < .001$). Similarly, 10-year metastasis-free survival for patients was 96% for low-, 92% for intermediate-, and 80% for high-risk disease ($p < .001$) (Figure 1).

Moreover, 10-year metastasis-free, prostate cancer–specific, and overall survival also correlated with Grade Group. Ten-year metastasis-free survival was 96% for patients with Grade Group 1, 92% for patients with Grade Group 2, 87% for those with Grade Group 3, 83% for those with Grade Group 4, and 67% for patients with Grade Group 5 disease ($p < .001$). Similarly, 10-year prostate cancer–specific survival for Grade 1, 2, 3, 4, and 5 disease was 98%, 97%, 94%, 93%, and 82%, respectively ($p < .001$), and 10-year overall survival for Grade 1, 2, 3, 4, and 5 disease was 76%, 70%, 66%, 63%, and 53%, respectively ($p < .001$) (Figure 2).

DISCUSSION

In this retrospective, population-based analysis of patients undergoing definitive radiation therapy with or without ADT for localized prostate cancer, we observed improved 10-year survival outcomes compared with those found in historical trials. Our use of an innovative natural language processing tool to identify incident metastatic disease using population-based data opens a new realm of understanding time-to-event clinically relevant outcomes for radiation therapy, extending beyond traditional use of clinical trials to

TABLE 2 Frequency of radiation therapy alone, as well as short- and long-term ADT use analyzed by disease characteristics.

Variable	Radiation therapy alone (*N* = 24,902)	Radiation therapy + short-term ADT (*N* = 9436)	Radiation therapy + long-term ADT (*N* = 7387)	*p*
Age (median, years)	65.0	65.9	66.5	<.001
T-stage (*n*, %)				<.001
cT1-2	24,493 (98.4%)	9127 (96.7%)	6698 (90.7%)	
cT3-4	208 (0.8%)	257 (2.7%)	592 (8.0%)	
Missing	201 (0.8%)	52 (0.6%)	97 (1.3%)	
Grade Group (*n*, %)				<.001
1	11,428 (45.9%)	1460 (15.5%)	453 (6.1%)	
2	8363 (33.6%)	3620 (38.4%)	1340 (18.1%)	
3	2862 (11.5%)	2069 (21.9%)	935 (12.7%)	
4	1336 (5.4%)	1360 (14.4%)	2412 (32.7%)	
5	680 (2.7%)	853 (9.0%)	2121 (28.7%)	
Unknown	233 (0.9%)	74 (0.8%)	126 (1.7%)	
Median PSA (ng/mL)	6.0	7.6	9.7	<.001
NCCN Risk Group (*n*, %)				<.001
Low	9278 (37.3%)	870 (9.2%)	184 (2.5%)	
Intermediate	11,266 (45.2%)	4916 (52.1%)	1444 (19.6%)	
High	4334 (17.4%)	3642 (38.6%)	5737 (77.7%)	
Missing	24 (0.1%)	8 (0.1%)	22 (0.2%)	

Abbreviations: ADT, androgen deprivation therapy; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen.

characterize important disease progression outcomes. Not surprisingly, we found disease severity at diagnosis was associated with 10-year disease-specific and overall survival outcomes. Taken together, our findings suggest favorable freedom from metastasis at 10 years following radiation therapy for 8 in 10 men with high-risk features at diagnosis.

Recently, much attention has been directed at defining clinically meaningful end points in prostate cancer research. Given the long natural history of prostate cancer and rapid advances in treatment, biochemical recurrence is often used as a primary clinical trial end point because recurrence occurs much sooner and more frequently than distant metastasis or prostate cancer–related death. However, multiple studies have demonstrated that biochemical recurrence is a poor surrogate for survival in patients with prostate cancer.[21,22] For example, in a recent meta-analysis of 75 trials involving 53,631 patients primarily undergoing radiation therapy for localized prostate cancer, biochemical failure–related end points (biochemical failure, biochemical failure–free survival, biochemical and clinical failure) all correlated poorly with overall survival. Meanwhile, metastasis-free survival correlated strongly with overall survival, with an R^2 of 0.78.[21] Similarly, a recent analysis of men treated for recurrent disease after prostatectomy on NRG/Radiation Therapy Oncology Group 9601 found a weak correlation between first or second biochemical failure after prostatectomy and overall survival ($\tau = 0.25$ and $\tau = 0.40$, respectively, as assessed by Kendall rank correlation), whereas metastasis-free survival correlated strongly with overall survival ($\tau = 0.86$).[22] These studies, among others, have identified metastasis-free survival as a clinically relevant surrogate end point for overall survival, suggesting this end point merits further exploration and consideration in contemporary clinical trial design and population-based observational data.

On the other hand, increasing use of metastasis-free survival as an end point in major studies has produced heterogenous results. For example, the Meta-analysis of Randomized Trials in Cancer of the Prostate (MARCAP) consortium recently performed a meta-analysis of 12 trials involving 10,853 patients to assess the benefit of various treatment intensification strategies using radiation and ADT.[14] The 10-year metastasis-free survival in this study was 61% for patients receiving ADT in addition to radiation therapy. Nearly one half (47%) of patients included had high-risk disease. Importantly, this 10-year metastasis-free survival is lower than recent trials enrolling a sizeable proportion of patients with high-risk disease.[2,6] The 10-year metastasis-free survival we observed for patients with high-risk disease is similar to the previously mentioned clinical trials that enrolled during this period, suggesting improvement in metastasis-free survival in contemporary cohorts persists in real-world settings outside of highly regulated clinical trial environments.

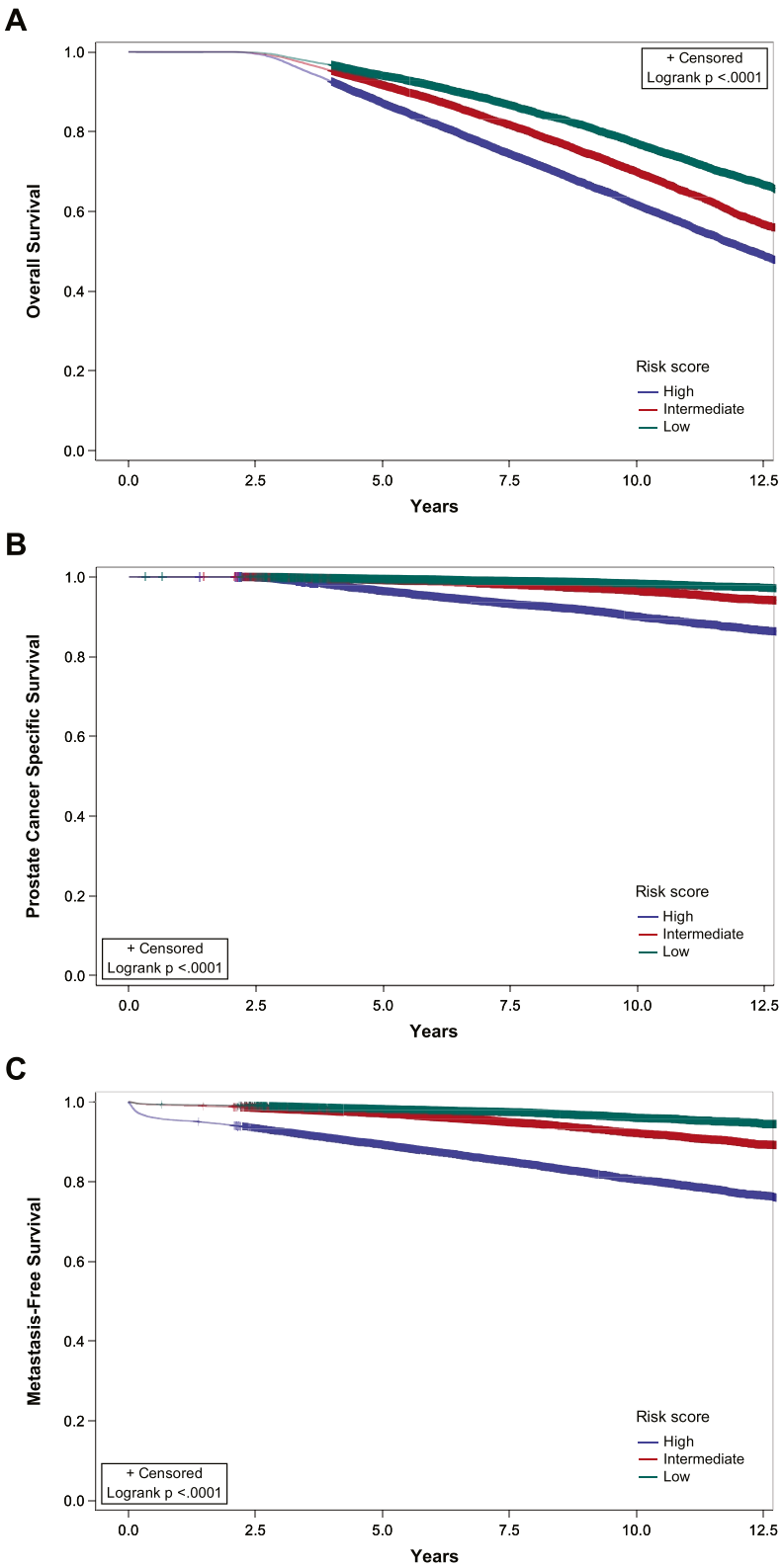

FIGURE 1 Survival estimates for overall survival (A), prostate cancer–specific survival (B), and metastasis-free survival (C) by NCCN risk group, with 95% confidence bands. NCCN indicates National Comprehensive Cancer Network.

This discrepancy between the metastasis-free survival observed in the MARCAP analysis of historical trials (i.e., six in 10 men metastasis-free at 10 years) and the metastasis-free survival observed in our study (i.e., eight in 10 men metastasis-free at 10 years) may be due to multifactorial improvements in diagnosis and treatment over time. This is especially likely because most patients

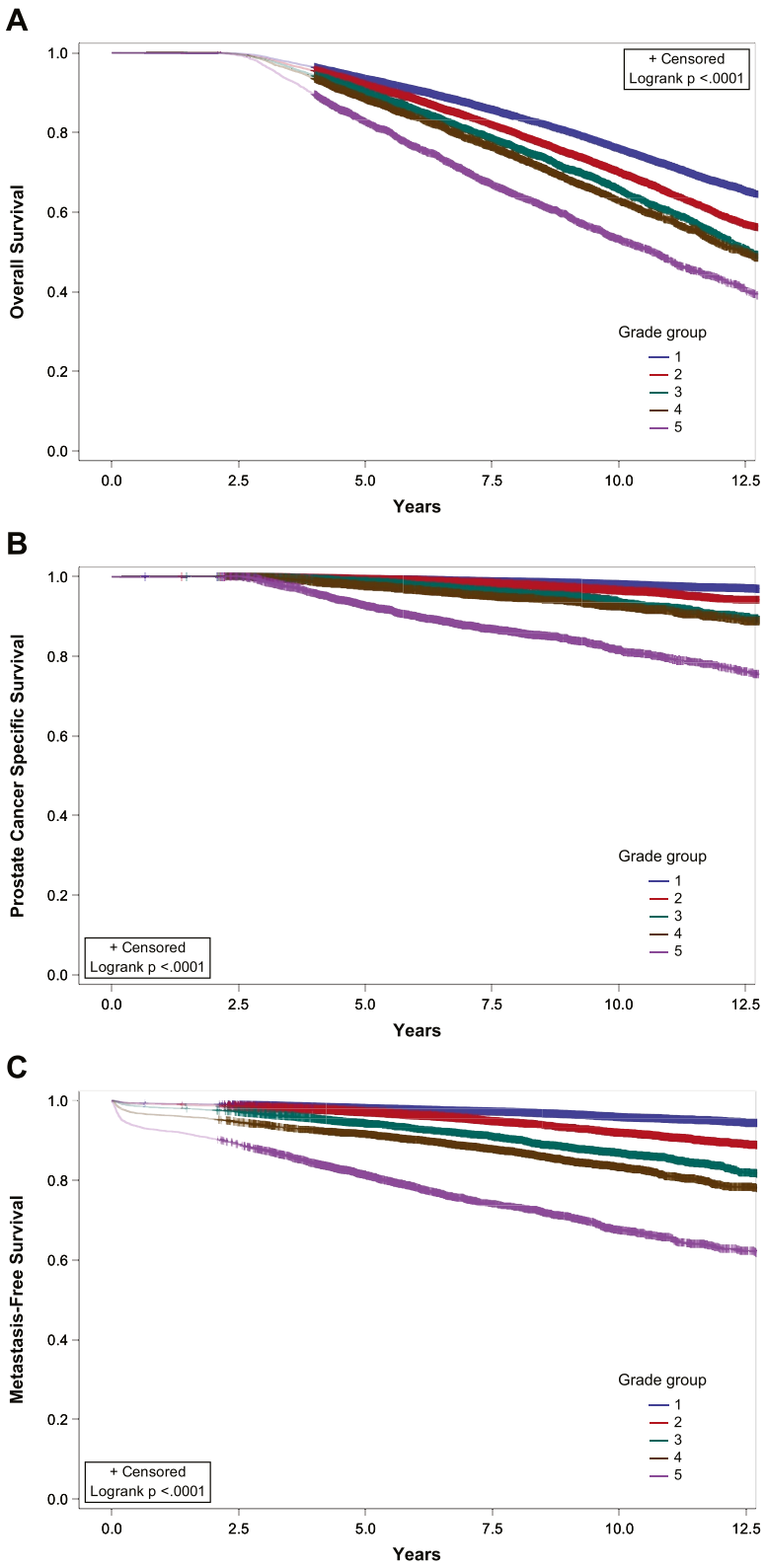

FIGURE 2 Survival estimates for overall survival (A), prostate cancer–specific survival (B), and metastasis-free survival (C) by Grade Group, with 95% confidence bands.

included in the MARCAP analysis were treated in the 1990s and early 2000s and our study examined patients treated between 2005 and 2015. Although the chronology of historical studies allows for robust follow-up, advances in the delivery of radiation therapy, refinement of ADT use and timing, and improvement of therapy in the metastatic setting over time challenge historical benchmarks. In

other words, these developments complicate the application of historical survival outcomes to patients diagnosed and treated using contemporary techniques. Clarifying our understanding of survival outcomes in contemporary real-world cohorts is important for setting patient expectations during shared decision-making, guiding treatment intensification or deescalation, and future clinical trial development.

Despite the advantage of identifying incident metastatic disease at the patient level within a large population, some limitations merit consideration. One is the use of NCCN risk groupings for classification of patient risk. Although newer methods, such as clinical-genomic risk group classification[17] and advanced clinical prognostic stage grouping,[18] provide improved patient-level prognostication of outcomes, our use of NCCN risk groupings remains common clinical practice within clinical and research communities. We also used Grade Group to better align our findings with current clinical practice. Second, we used the National Death Index to determine overall survival. Although there are some limitations to cause of death attribution, overall survival observed in this study is consistent with what would be expected. Third, this analysis exclusively used data within a national health system of veterans, which may introduce subtle differences inherent to a large integrated delivery system that could limit extrapolation to the broader US population. Nonetheless, the majority of veterans with prostate cancer are cared for outside the Veterans Administration system, and our comprehensive chart and national data abstraction add to the rigor and validity of our data and outcomes collection. In addition, our median age at diagnosis was 65 years, providing relevance to Medicare and younger non-Medicare eligible patients. Additionally, in this data set, lower risk patients appear to have a lower other-cause mortality risk compared with those with higher risk disease. Age did not differ substantially between risk groups, with a median age of 64 years for low-risk, 65 years for intermediate-risk, and 66 years for high-risk patients. The potential reasons for this discrepancy are the subject of ongoing work by our group. Finally, this work is also subject to the inherent limitations of retrospective database studies, including the potential for selection bias, data coding errors, and missing data that may have affected our findings. While keeping these limitations in mind, our findings did reveal the expected relationships between disease severity and outcomes in real-world practice.

In conclusion, our study found favorable 10-year metastasis-free survival using contemporary diagnosis and radiation therapy treatment approaches among men with localized prostate cancer higher than observed in some historical trial data. This information is valuable for setting patient expectations for treatment during shared decision-making and as benchmarks in future trial design. Furthermore, these data may serve as a basis for future studies identifying patients at high risk of metastatic disease for whom treatment escalation is indicated as well as those at lower risk of metastatic disease for whom ADT may be deescalated or omitted.

AUTHOR CONTRIBUTIONS

Daniel J. Herr: Conceptualization, methodology, and writing – original draft; **David A. Elliott:** Conceptualization, methodology, and writing – review & editing. **Gillian Duchesne:** Writing – review & editing. **Kristian D. Stensland:** Investigation and writing – review & editing. **Megan E.V. Caram:** Conceptualization and writing – review & editing. **Christina Chapman:** Investigation and writing – review & editing. **Jennifer A. Burns:** Investigation, formal analysis, and writing - review & editing. **Brent K. Hollenbeck:** Writing – review & editing. **Jordan B. Sparks:** Writing – review & editing. **Chris Shin:** Methodology, and writing – review & editing. **Alexander Zaslavsky:** Conceptualization and writing - review & editing. **Alexander Tsodikov:** Conceptualization, methodology, and writing – review & editing. **Ted A. Skolarus:** Conceptualization, methodology, and writing – review & editing.

ACKNOWLEDGMENTS

The authors thank Steven Kronenberg for his excellent technical assistance. This work is supported by NIH NCI R01 CA242559 (AT, TAS).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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How to cite this article: Herr DJ, Elliott DA, Duchesne G, et al. Outcomes after definitive radiation therapy for localized prostate cancer in a national health care delivery system. *Cancer*. 2023;1-8. doi:10.1002/cncr.34916