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Original Article

Population-based study of disease trajectory after radical treatment for high-risk prostate cancer

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Objectives

To investigate long-term disease trajectories among men with high-risk localized or locally advanced prostate cancer (HRLPC) treated with radical radiotherapy (RT) or radical prostatectomy (RP).

Material and Methods

Men diagnosed with HRLPC in 2006–2020, who received primary RT or RP, were identified from the Prostate Cancer data Base Sweden (PCBaSe) 5.0. Follow-up ended on 30 June 2021. Treatment trajectories and risk of death from prostate cancer (PCa) or other causes were assessed by competing risk analyses using cumulative incidence for each event.

Results

In total, 8317 men received RT and 4923 men underwent RP. The median (interquartile range) follow-up was 6.2 (3.6–9.5) years. After RT, the 10-year risk of PCa-related death was 0.13 (95% confidence interval [CI] 0.12–0.14) and the risk of death from all causes was 0.32 (95% CI 0.31–0.34). After RP, the 10-year risk of PCa-related death was 0.09 (95% CI 0.08–0.10) and the risk of death from all causes was 0.19 (95% CI 0.18–0.21). The 10-year risks of androgen deprivation therapy (ADT) as secondary treatment were 0.42 (95% CI 0.41–0.44) and 0.21 (95% CI 0.20–0.23) after RT and RP, respectively. Among men who received ADT as secondary treatment, the risk of PCa-related death at 10 years after initiation of ADT was 0.33 (95% CI 030–0.36) after RT and 0.27 (95% CI 0.24–0.30) after RP.

Conclusion

Approximately one in 10 men with HRLPC who received primary RT or RP had died from PCa 10 years after diagnosis. Approximately one in three men who received secondary ADT, an indication of PCa progression, died from PCa 10 years after the start of ADT. Early identification and aggressive treatment of men with high risk of progression after radical treatment are warranted.

Keywords

prostate cancer, radiotherapy, prostatectomy, androgen deprivation therapy, disease trajectories, disease progression, mortality

Introduction

In 2020, prostate cancer (PCa) was the most common cancer among men in 112 countries and the leading cause of cancer mortality among men in 48 countries [1]. For men with high-risk localized or locally advanced PC Pca (HRLPC), radical treatment with external beam radiotherapy (RT) in combination with neoadjuvant and adjuvant androgen deprivation therapy (ADT) or with radical prostatectomy (RP) is used [2–5]. However, men with HRLPC who undergo primary RT or RP remain at risk of relapse. If relapse occurs, current treatments include salvage RT or ADT after RP, and salvage RP or ADT after RT [2]. Novel strategies to prevent PCa relapse and progression in men with HRLPC are currently under investigation to assess whether they may improve outcomes [6,7].

The aim of this study was to investigate disease trajectories for men with HRLPC who underwent primary RT or RP.

Materials and Methods

Data Sources

A retrospective observational study, ODYSSEY (**O**bservational stu**D**y to assess the disease trajector**Y** among men who undergo intervention with radiotherapy or radical pro**S**tatecomy in the localized and locall**Y** for HRLPC), using data from the Prostate Cancer data Base Sweden (PCBaSe) 5.0 was conducted. PCBaSe 5.0 is a research database that consists of men in the National Prostate Cancer Register (NPCR) of Sweden, a clinical cancer register [8–11] with data on evaluation, clinical cancer characteristics, and primary cancer treatment, and captures 98% of diagnosed PCa cases in Sweden, versus the Cancer Register, to which reporting is mandated by law. The primary aim of the NPCR is to ensure high quality of care for men with PCa and to assess adherence to national guidelines [12–14]. In PCBaSe, the NPCR has been enriched with links to other national healthcare registers using the unique Swedish personal identity number and includes data on inpatient and outpatient medical encounters, filled prescriptions, and date and cause of death. Table S1 provides additional information on PCBaSe.

Identification of Men with HRLPC

Study participants were selected from the population of men diagnosed with PCa between 1 January 2006 and 31 December 2020 who are registered in the NPCR. The start of the study period in 2006 was selected because the Gleason grading system, which was used to identify high-risk men, was modified in 2005. Inclusion criteria were no metastasis on imaging, receipt of radical treatment with primary RT within 12 months of PCa diagnosis or primary RP within 6 months of PCa diagnosis, and Charlson Comorbidity Index (CCI) 0–2 at date of radical treatment and one of the following: (1) Gleason score (GS) 7 (4 + 3)/GS 8 (4 + 4)/GS 8 (3 + 5) and >33% of biopsy cores containing PCa; (2) GS 8 (5 + 3)/GS 9/GS 10; (3) GS ≥7 and local stage T3; (4) GS 7 (4 + 3) and PSA ≥20 ng/mL; and (5) local stage T4.

These criteria mimicked the inclusion criteria of the ATLAS study (ClinicalTrials.gov identifier: NCT02531516), a randomized clinical trial on primary RT and ADT with and without apalutamide (Table S2), and the PROTEUS study (ClinicalTrials.gov identifier: NCT03767244), a randomized clinical trial on primary RP and ADT with or without apalutamide (Table S3) [6,7].

Disease Trajectories after Primary Treatment

After RT, men could receive ADT, die from PCa or another cause, be censored, or experience several of these events. Salvage RP is extremely uncommon in Sweden and was not included. After RP, men could receive RT, receive ADT, die from PCa or another cause, be censored, or experience several of these events. The ADT start date was defined as the earliest date when prescriptions for at least 180 defined daily doses had been filled for an antiandrogen or a gonadotropin-releasing hormone agonist. Because the start of treatment with ADT was considered a sign of progression, ADT registered in the NPCR as neoadjuvant, and adjuvant ADT in combination with RT, were not included in this analysis.

Follow-Up

Events of interest included subsequent treatments as an indication of PCa progression, and death. The index date was the date of start for RT or date for RP. Time to event for PCa was defined as the interval between the index date and start of secondary treatment or death, whichever came first. Men who emigrated were censored at date of emigration and those alive at the end of follow-up were censored. The follow-up period ended on 30 June 2021 for all men except those living in regions in which ADT was delivered through the urology departments, who, hence, were not registered in the Prescribed Drug Register (approximately 5% of total study group) and for whom follow-up ended earlier.

Statistical Analyses

Plots of cumulative incidences were used to display the risk of each cause of death as well as time to first event; in all analyses the events were analysed as competing risks. Events that could occur after RT were ADT, death from PCa, or death from other causes. After RP, events that could occur were RT, ADT, and death. For analyses of cause of death, follow-up started at date of primary treatment (index date). For analyses of start of ADT, follow-up began at the date of primary treatment and ended at the start date of ADT, date of death, or last date of follow-up, whichever came first. For PCa-related death for men who started ADT, follow-up began at date of first ADT and ended at date of death or last date of follow-up.

Risk of initiation of ADT and risk of PCa-related death were investigated using a Cox regression model including the variables GS, T stage, PSA level, N status, proportion of cancer in diagnostic biopsies, age, and comorbidities at the start of primary treatment.

Results

A total of 8317 men met the RT inclusion criteria and 4923 met the RP inclusion criteria (Figs S1 and S2). The median (interquartile range) follow-up was 6.2 (3.6–9.5) years.

For men who received RT, the median age at RT was 70 years, median PSA was 13 ng/mL, 79% had clinical T stage of T2 or higher, 55% had a GS ≥8, and 36% had a CCI score >0 (Table 1). RT was delivered as external beam RT 74–82 Gy in 53% of the men, as external beam RT + brachytherapy in 23%, and as hypofractionated RT with doses >2.4 Gy in 24%. Neoadjuvant ADT was used in 57% of the men and adjuvant ADT was used in 75%.

Men who underwent RP were younger and had fewer adverse cancer characteristics and fewer comorbidities than men treated with RT. Among men who underwent RP, the median age at RP was 66 years, the median PSA was 8 ng/mL, 59% had clinical T stage of T2 or greater, 44% had GS ≥8, and 25% had a CCI score >0. Robot-assisted laparoscopic RP was performed in 60% of men with RP. The percentages of men who received medication for cardiovascular disease or diabetes, or lipid-lowering agents, were slightly lower among those who received RP than those who received RT (Table S4).

Death from PCa and Other Causes

After primary RP, the cumulative incidence of death from PCa was 0.09 (95% CI 0.08–0.10) and the cumulative incidence of death from all causes was 0.19 (95% CI 0.18–0.21). Among men who received primary RT, the risk of PCa-related death at 10 years was 0.13 (95% CI 0.12–0.14) and the risk of death from all causes at 10 years was 0.32 (95% CI 0.31–0.34; Fig. 1).

Disease Trajectories, Including Further Treatments and Subsequent Death

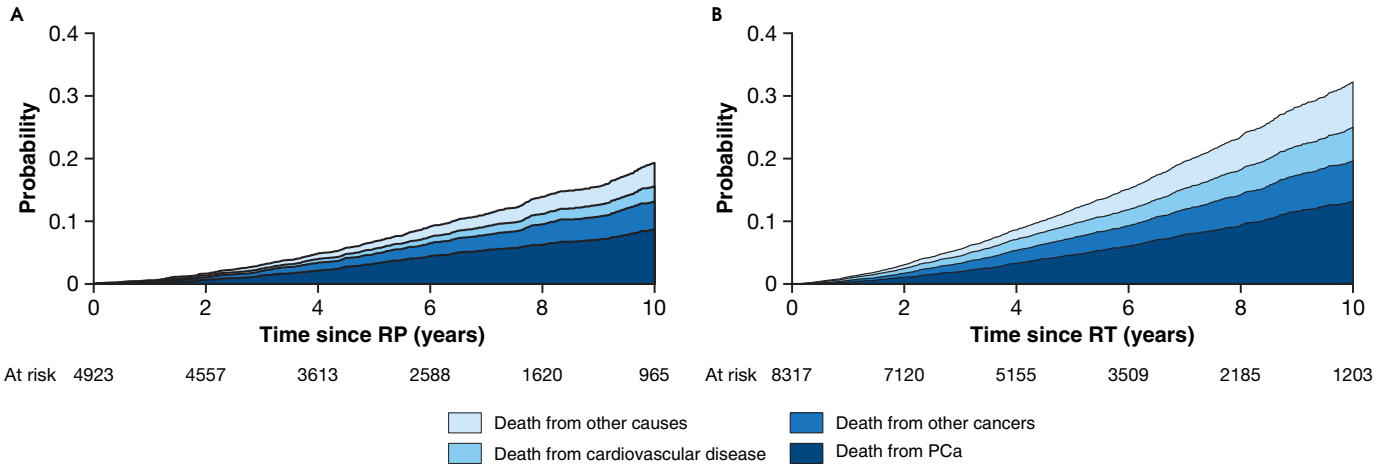
The risk of secondary treatment with ADT 10 years after primary RT was 0.42 (95% CI 0.41–0.44; Fig. 2 and Table 2). Among men who underwent primary RP, the risk of ADT as secondary treatment was 0.21 (95% CI 0.20–0.23) and the risk of RT as secondary treatment was 0.35 (95% CI 0.34–0.37). For men with primary RP followed by RT, the risk of ADT as third treatment was 0.68 (0.65–0.72).

Table 1 Baseline characteristics of men with HRLPC in the ODYSSEY study who underwent primary radical radiotherapy or radical prostatectomy selected within the PCBaSe 5.0 between 2006 and 2020.

	Radical radiotherapy (*n* = 8317)		Radical prostatectomy (*n* = 4923)	
Median age, years (IQR)	70	(65–74)	66	(61–70)
Median PSA, ng/mL (IQR)	13.0	(7.5–26)	8.2	(5.4–14.1)
Clinical local T stage, *n* (%)				
T1c	1800	(22)	2014	(41)
T2	3307	(40)	2204	(45)
T3	3122	(38)	696	(14)
T4	88	(1)	9	(0)
Gleason score, *n* (%)				
≤6	3	(0)	0	(0)
7 (3 + 4)	746	(9)	264	(5)
7 (4 + 3)	3094	(37)	2515	(51)
8 (3 + 5)	391	(5)	272	(6)
8 (4 + 4)	1396	(17)	840	(17)
8 (5 + 3)	46	(1)	30	(1)
9	2490	(30)	958	(19)
10	151	(2)	44	(1)
Charlson Comorbidity Index, *n* (%)				
0	5353	(64)	3669	(75)
1–2	2553	(31)	1131	(23)
3	411	(5)	123	(2)
Type of radical RT, *n* (%)				
EBRT 74–82 Gy	4409	(53)		
EBRT + brachytherapy	1889	(23)		
Hypofractionated >2.4 Gy	2019	(24)		
ADT with RT, *n* (%)				
Neoadjuvant	4774	(57)		
Adjuvant	6245	(75)		
Type of RP, *n* (%)				
Robot-assisted laparoscopic RP			2933	(60)
Retropubic RP			1900	(39)
Laparoscopic RP			90	(2)

Charlson Comorbidity Index based on International Classification of Diseases codes for discharge diagnoses in the National Patient Registry up to 10 years before PCa diagnosis. ADT, androgen deprivation therapy; EBRT, external beam radiation therapy; IQR, interquartile range; PCa, prostate cancer; PCBaSe, Prostate Cancer data Base Sweden; RT, radiotherapy; RP, radical prostatectomy.

Fig. 1 Death from prostate cancer and other causes after (**A**) primary radical prostatectomy (RP) or (**B**) radiotherapy (RT).



Among men who received ADT after RT, the 10-year risk of PCa-related death after start of ADT was 0.33 (95% CI 0.30–0.36) and the 10-year risk of death from other causes was 0.20 (95% CI 0.18–0.24). Among those who received ADT as secondary treatment after RP, the risk of PCa-related death was 0.27 (95% CI 0.24–0.30) and the risk of death from other causes was 0.14 (95% CI 0.12–0.17). Among men with primary RP followed by RT who received ADT as third treatment, the risk of PC-related death was 0.19 (95% CI 0.15–0.24) and the risk of death from other causes was 0.13 (95% CI 0.10–0.18).

Factors Associated with Progression to ADT and PCa-related Death

Gleason score, T stage, PSA level, and proportion of cancer in biopsies at baseline were all factors strongly associated with risk of starting ADT, but the association of these factors with the risk of PCa-related death after ADT in men treated with RP or RT differed substantially (Table 3). Higher GS was associated with increased risk of PCa-related death, but higher PSA levels were not. Higher T stage and proportion of cancer in biopsies were associated with increased risk of PCa-related death in men treated with RT but not in those treated with RP.

Discussion

This population-based cohort study indicated that approximately 10% of men with HRLPC treated with primary RT or primary RP died from PCa after 10 years of follow-up. Men who received ADT as secondary treatment after RT or RP, approximately a third of the study population, were considered to have progressed. Of these, around one third died from PCa within 10 years of starting ADT therapy.

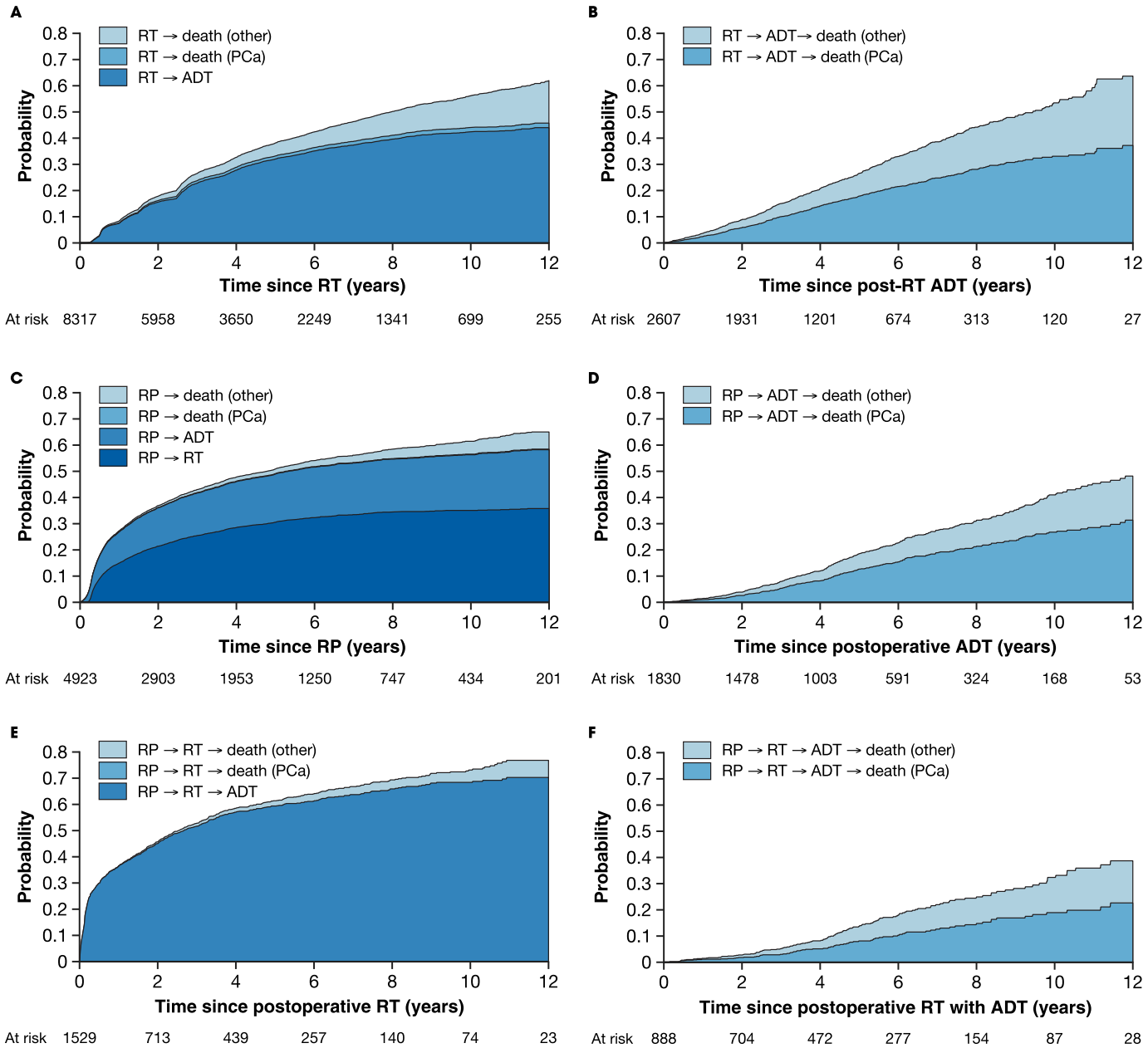
ODYSSEY has several notable strengths. PCBaSe contains detailed information and extensive follow-up on approximately 98% of all PCa cases in Sweden, with data from healthcare registers with high capture rates, high data validity, high rates of completeness [10,11,15], and follow-up times of up to 12 years. Some limitations of this study should be noted. There were no data on PSA during follow-up, so the start of ADT was used as a proxy for progression. The sensitivity of this proxy was probably quite low; we do not know how many men had a PSA relapse without receiving ADT, but we can argue that the specificity was high as few men would receive ADT without a sign of progression. The homogeneity of the Swedish study population could limit external validity, as could differences between Sweden and other countries in policies and healthcare practices for PCa screening, diagnosis and treatment [16].

Historically, outcomes have been poor for men with HRLPC in Sweden. In a previous study in PCBaSe, men with locally advanced PCa, GS ≥8, or PSA 20–50 ng/mL diagnosed in the period 1991–2009 who were treated conservatively had a 10-year risk of PCa-related death of 29% [17]. The outcome for men in our study who received primary radical therapy was better, although among the one third of men who received secondary ADT as an indication of progression, one in three had died within 10 years of starting ADT.

Our data indicate that more aggressive treatment strategies are warranted for men with HRLPC who are at high risk of progression. The only factor among the clinical characteristics at baseline that was associated with PCa-related death after RT or RP was GS, whereas T stage and proportion of cancer in biopsies were significantly associated with risk of PCa-related death after RT only.

One way to reduce the risk of death from PCa is to identify men with HRLPC who are at high risk of PCa progression

Fig. 2 Risk of subsequent treatment or death after primary radiotherapy (RT) or radical prostatectomy (RP). (**A**) Time from RT to androgen deprivation therapy (ADT) or death; (**B**) time from ADT after RT to death; (**C**) time from RP to RT, ADT, or death; (**D**) time from ADT after RP to death; (**E**) time from RT after RP to ADT or death; (**F**) time from RT after RP plus ADT to death.



and death following primary treatment, ideally at time of primary treatment or early during follow-up, in order to provide aggressive treatment at an early stage. Another approach is to treat all men with HRLPC with additional treatment immediately after primary radical therapy. In the randomized ATLAS and PROTEUS trials, treatment with the androgen receptor pathway inhibitor apalutamide is used immediately after RP or RT [6,7]. Our study, ODYSSEY, was designed to mimic the inclusion criteria of these trials in order to provide an estimate of outcome for men with HRLPC who were treated according to current clinical practice.

In conclusion, one in 10 men with HRLPC who received primary radical treatment died from PCa after 10 years of follow-up. For the one third of men who received secondary ADT as an indication of progression, approximately one in three had died from PCa 10 years after the start of ADT. Men with HRLPC who receive secondary ADT as a sign of

Table 2 Cumulative incidence of events during disease trajectories among men with high-risk localized or locally advanced prostate cancer.

	10-year cumulative incidence	(95% CI)
First event after RT*		
RT → death (other)	0.12	(0.11–0.13)
RT → death (PCa)	0.02	(0.01–0.02)
RT → ADT	0.42	(0.41–0.44)
First event after RT → ADT†		
RT → ADT → death (other)	0.20	(0.18–0.24)
RT → ADT → death (PCa)	0.33	(0.30–0.36)
First event after RP*		
RP → death (other)	0.05	(0.04–0.06)
RP → death (PCa)	0.00	(0.00–0.00)
RP → ADT	0.21	(0.20–0.23)
RP → RT	0.35	(0.34–0.37)
First event after RP → ADT†		
RP → ADT → death (other)	0.14	(0.12–0.17)
RP → ADT → death (PCa)	0.27	(0.24–0.30)
First event after RP → RT		
RP → RT → death (other)	0.05	(0.03–0.07)
RP → RT → death (PCa)	0.00	(0.00–0.00)
RP → RT → ADT	0.68	(0.65–0.72)
First event after RP → RT → ADT		
RP → RT → ADT → death (other)	0.13	(0.10–0.18)
RP → RT → ADT → death (PCa)	0.19	(0.15–0.24)

*These proportions are derived from Fig. 1. *Follow-up after first event after primary treatment started at date of treatment (index date). †Follow-up after start of ADT started at date of ADT. ADT, androgen deprivation therapy; PCa, prostate cancer; RT, radiotherapy; RP, radical prostatectomy.*

progression after radical treatment are at high risk of PCa-related death and, for these men, new treatment strategies are warranted.

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Disclosure of Interests

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Table 3 Risk of androgen deprivation therapy or death from prostate cancer according to cancer characteristics at diagnosis among men with high-risk localized or locally advanced prostate cancer.

	Risk of ADT*		Risk of PCa-related death following ADT in men treated with RP†		Risk of PCa-related death following ADT in men treated with RT†	
Gleason score						
6 or 7 (4 + 3)	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
7 (4 + 3)	1.31	(1.14–1.50)	0.93	(0.44–1.97)	1.58	(1.05–2.38)
8	1.73	(1.51–1.99)	1.37	(0.64–2.93)	1.58	(1.04–2.41)
9	2.13	(1.86–2.44)	2.17	(1.03–4.55)	1.84	(1.22–2.75)
10	2.65	(2.09–3.37)	3.12	(1.00–9.70)	2.17	(1.18–4.00)
T stage						
T1c	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
T2	1.32	(1.22–1.43)	1.25	(0.94–1.67)	1.29	(0.94–1.78)
T3	1.57	(1.43–1.72)	1.02	(0.69–1.52)	1.63	(1.20–2.23)
T4	1.76	(1.33–2.35)	1.41	(0.19–10.33)	2.43	(1.31–4.51)
PSA, ng/mL						
0–19.9	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
20–49.9	1.51	(1.40–1.62)	0.84	(0.60–1.18)	0.77	(0.62–0.95)
50+	1.74	(1.57–1.93)	0.94	(0.56–1.57)	0.66	(0.49–0.88)
N stage						
N0/Nx	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
N1	1.54	(1.38–1.72)	0.65	(0.39–1.09)	1.14	(0.78–1.66)
Proportion of cancer in biopsies						
1–33%	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
34–66%	1.22	(1.10–1.35)	1.11	(0.73–1.69)	1.21	(0.80–1.83)
67–83%	1.48	(1.31–1.67)	1.24	(0.75–2.06)	1.34	(0.84–2.11)
84–100%	1.92	(1.72–2.14)	1.51	(0.97–2.35)	1.79	(1.19–2.68)

*Cox regression analysis of risk of initiation of ADT; androgen deprivation therapy or PC death. ADT, androgen deprivation therapy; PCa, prostate cancer; RP, radical prostatectomy; RT, radiotherapy. *Stratified for radical prostatectomy or radical radiotherapy. †Adjusted for age, Charlson comorbidity index, and Drug comorbidity index at start of radical treatment.*

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Data Availability Statement

The aggregated data used in this study may be made available at a remote server upon application to the Prostate Cancer data Base Sweden reference group and the Research Ethics Authority.

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Abbreviations: ADT, androgen deprivation therapy; CCI, Charlson Comorbidity Index; GS, Gleason score; HRLPC, high-risk localized or locally advanced prostate cancer; NPCR, National Prostate Cancer Register of Sweden; PCa, prostate cancer; PCBaSe, Prostate Cancer data Base Sweden; RP, radical prostatectomy; RT, radiotherapy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Identification of men who received primary radical radiotherapy (RT) for high-risk localized or locally advanced prostate cancer (HRLPC). CCI, Charlson Comorbidity Index; GS, Gleason score; PC, prostate cancer; PSA, prostate-specific antigen.

Fig. S2 Identification of men who received primary radical prostatectomy (RP) for high-risk localized or locally advanced prostate cancer (HRLPC). CCI, Charlson Comorbidity Index; GS, Gleason score; PC, prostate cancer; PSA, prostate-specific antigen.

Table S1 Healthcare register data in the Prostate Cancer data Base Sweden (PCBaSe).

Table S2 ATLAS inclusion criteria comparison to variables in the Prostate Cancer data Base Sweden (PCBaSe).

Table S3 PROTEUS inclusion criteria comparison to variables in the Prostate Cancer data Base Sweden (PCBaSe).

Table S4 Clinical characteristics: the ODYSSEY study.