



Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

Active Surveillance Versus Radical Prostatectomy in Favorable-risk Localized Prostate Cancer

Thomsen, Frederik B; Røder, M Andreas; Jakobsen, Henrik; Langkilde, Niels Christian; Borre, Michael; Jakobsen, Erik B; Frey, Anders; Lund, Lars; Lunden, Dagmar; Dahl, Claus; Brasso, Klaus

Published in:
Clinical genitourinary cancer

DOI (link to publication from Publisher):
[10.1016/j.clgc.2019.05.005](https://doi.org/10.1016/j.clgc.2019.05.005)

Creative Commons License
CC BY-NC-ND 4.0

Publication date:
2019

Document Version
Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):
Thomsen, F. B., Røder, M. A., Jakobsen, H., Langkilde, N. C., Borre, M., Jakobsen, E. B., Frey, A., Lund, L., Lunden, D., Dahl, C., & Brasso, K. (2019). Active Surveillance Versus Radical Prostatectomy in Favorable-risk Localized Prostate Cancer. *Clinical genitourinary cancer*, 17(4), e814-e821.
<https://doi.org/10.1016/j.clgc.2019.05.005>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- ? Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- ? You may not further distribute the material or use it for any profit-making activity or commercial gain
- ? You may freely distribute the URL identifying the publication in the public portal ?

Accepted Manuscript

Active surveillance vs. radical prostatectomy in favourable-risk localised prostate cancer

Frederik B. Thomsen, M. Andreas Røder, Henrik Jakobsen, Niels Christian Langkilde, Michael Borre, Erik B. Jakobsen, Anders Frey, Lars Lund, Dagmar Lunden, Claus Dahl, Klaus Brasso

PII: S1558-7673(19)30144-2

DOI: <https://doi.org/10.1016/j.clgc.2019.05.005>

Reference: CLGC 1267

To appear in: *Clinical Genitourinary Cancer*

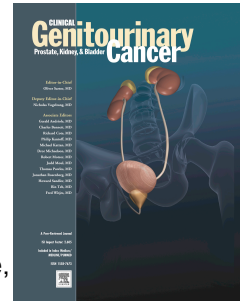
Received Date: 26 February 2019

Revised Date: 1 May 2019

Accepted Date: 12 May 2019

Please cite this article as: Thomsen FB, Røder MA, Jakobsen H, Langkilde NC, Borre M, Jakobsen EB, Frey A, Lund L, Lunden D, Dahl C, Brasso K, Active surveillance vs. radical prostatectomy in favourable-risk localised prostate cancer, *Clinical Genitourinary Cancer* (2019), doi: <https://doi.org/10.1016/j.clgc.2019.05.005>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Active surveillance vs. radical prostatectomy in favourable-risk localised prostate cancer

Frederik B. Thomsen¹, M. Andreas Røder^{1,2}, Henrik Jakobsen³, Niels Christian Langkilde⁴, Michael Borre⁵, Erik B. Jakobsen⁶, Anders Frey⁷, Lars Lund^{8,9}, Dagmar Lunden¹⁰, Claus Dahl⁶, and Klaus Brasso^{1,2}

¹ Copenhagen Prostate Cancer Center, Rigshospitalet, Copenhagen, Denmark

² Dept of Urology, Rigshospitalet, Copenhagen, Denmark

³ Dept of Urology, Herlev and Gentofte Hospital, Herlev, Denmark

⁴ Dept of Urology, Aalborg University Hospital, Aalborg, Denmark

⁵ Dept of Urology, Aarhus University Hospital, Skejby, Denmark

⁶ Dept of Urology, Zealand University Hospital, Roskilde, Denmark

⁷ Dept of Urology, Sydvestjysk Sygehus, Esbjerg, Denmark

⁸ Dept of Clinical Research Urology, University of Southern Denmark, Denmark

⁹ Dept of Urology, Odense University Hospital, Odense, Denmark

¹⁰ Dept of Urology, Hospitalsenhed Midt, Viborg, Denmark

Corresponding author: Frederik B. Thomsen, MD, PhD, Copenhagen Prostate Cancer Center, Rigshospitalet, Ole Maaløes Vej 24, afsnit 7521, 2200 Copenhagen, Denmark

Tel: +45 35457125

Fax: +45 35452726

e-mail: thomsen.frederik@gmail.com

Word count: 2.164

Keywords: prostate cancer; localised; active surveillance; radical prostatectomy; survival

Author Contributions: All authors contributed to the study design, data collection, data interpretation and approved the final version. FBT performed the statistical analyses. FBT, AR and KB drafted the manuscript. HJ, NCL, MB, EBJ, AF, LL, DL and CD provided critical review of the manuscript. There were no other contributors to the manuscript except those on the author list.

Conflict of interest: The authors report no conflict of interest.

Funding: FBT is supported by research grant from IMK Almene fond.

Role of Funding Source: The sponsor had no involvement with the planning, execution or completion of the study.

Microabstract

We found no difference in prostate cancer death between men with favourable-risk localised prostate cancer managed with immediate radical prostatectomy or on active surveillance following 10 years. Additionally, we found difference in use of salvage radiotherapy and hormonal therapy between the strategies.

Short summary

Localised prostate cancer with favourable-risk characteristics often progresses slowly with a subsequent low risk of dying from prostate cancer and a high risk of dying from other causes.

Although curative options are available the management of men with favourable-risk characteristics remains controversial. Active surveillance has been introduced as a tailored management for these men in order to reduce curative overtreatment without compromising cancer-specific survival.

In the current study we included 647 men who were managed on active surveillance and 647 men who underwent primary radical prostatectomy identified following propensity score matching and who were followed for a median of 8.6 years. The 10-year prostate cancer mortality was similar and very low for men managed on active surveillance (0.4%) and who underwent primary radical prostatectomy (0.5%). In addition only few men required subsequent prostate cancer therapies or developed castration resistant prostate cancer with no significant difference between the treatment strategies. 10-year cumulative estimates for use of salvage radiotherapy were 2.7% for men on active surveillance and 5.4% for men who underwent radical prostatectomy. Corresponding numbers for definitive hormonal therapy was 6.9% (active surveillance) and 4.1% (radical prostatectomy), and for developing castration-resistant prostate cancer 1.7% (active surveillance) and 2.0% (radical prostatectomy).

Our study supports active surveillance as a treatment strategy for men with favourable-risk localised prostate cancer; however, longer follow-up is needed to determine the long-term safety of an initial observational approach.

Abstract

Background: Active surveillance (AS) and radical prostatectomy (RP) are both accepted treatments for men with favourable-risk localised prostate cancer (PCa) – i.e. clinical tumour category 1-2b, Gleason Grade Group 1-2 and prostate-specific antigen <20 ng/mL. However, head-to-head studies comparing oncological outcomes and survival between these two treatment strategies are warranted.

Objective: To compare use of prostate cancer treatments and PCa death in men managed on AS and men who underwent immediate RP.

Design, setting, and participants: Observational study including 647 men on AS and 647 men treated with RP propensity score matched.

Outcome measurements and statistical analysis: 10-year cumulative incidence of salvage radiotherapy, hormonal therapy, castration-resistant PCa (CRPC) and PCa death.

Results and limitations: The 10-year curative treatment-free survival for men on AS was 61% (95% CI 57-65%). No differences in use of salvage radiotherapy (AS 2.7% [95% CI 1.4-4.1%] vs. RP 5.4% [95% CI 3.4-7.3%]), hormonal therapy (AS 6.9% [95% CI 4.4-9.4%] vs. RP 4.1% [95% CI 2.5-5.6%]), developing CRPC (AS 1.7% [95% CI 0.5-2.9%] vs. RP 2.0% [95% CI 0.7-3.4%]) or cumulative PCa mortality (AS 0.4% [95% CI 0-1.0%] vs. RP 0.5% [95% CI 0-1.5%]) were observed between the treatment strategies. The main limitation was the non-random allocation to treatment strategy.

Conclusion: In this observational study on men with favourable-risk localised PCa we found similar PCa mortality at 10-years between men on AS and men who underwent immediate RP. Moreover, there were no differences in the use of PCa therapies between the groups. Our study supports active surveillance as a treatment strategy for men with favourable-risk localised PCa.

Patient summary: The risk of dying from PCa was similar between men with favourable-risk localised prostate cancer who were managed on active surveillance (close observational strategy with the possibility of curative treatment) or radical prostatectomy (surgical removal of the prostate).

INTRODUCTION

As a consequence of increased focus on early detection of prostate cancer the incidence of prostate cancer has increased drastically in the last decades¹. This has led to more men that are diagnosed with localised, low-volume disease². Although curative options for men with localised prostate cancer are available the management of these men remains controversial. Prostate cancer often progresses slowly and men with localised prostate cancer have a high risk of dying from causes other than prostate cancer³. This is especially the case in men with favourable-risk characteristics, i.e. clinical tumour category (cT) 1-2b, prostate-specific antigen (PSA) less than 20 ng/mL and Gleason score less than or equal to 7 (3+4). Still, some men with favourable-risk localised prostate cancer will die from the disease³.

Active surveillance has been introduced as a tailored management for selected men with localised prostate cancer in order to reduce curative overtreatment by identifying men who will likely benefit from definitive therapy, while men with true favourable-risk prostate cancer are spared curative interventions and its adverse effects^{4,5}. The first randomized controlled trial comparing an initially observational strategy to immediate curative interventions (either radical prostatectomy or radiotherapy) in men with localised prostate cancer, found no survival difference between the treatment strategies following 10 years of observation⁶.

Well conducted observational studies are important additions to clinical trials to evaluate the outcome of managements in a real-world setting⁷. The objective of this study was to compare oncological outcomes in two Danish cohorts of men diagnosed with localised prostate cancer managed either on active surveillance or having radical prostatectomy as their primary treatment.

MATERIAL AND METHODS

This study is based on two cohorts of Danish men with prostate cancer managed on either active surveillance in 2002-2012 or radical prostatectomy in 1995-2011, both cohorts have been described previously^{8,9}. Available diagnostic characteristics in all men included age, type, date and region of primary treatment, cT, PSA and Gleason score, which in this study is reported according to the five-tier Gleason Grade Group (GGG)¹⁰. No uniform surveillance strategy was adhered to as men were managed at 10 different urological departments⁸. However, all centers assessed men with a combination of surveillance biopsies, regular PSA measurement and digital rectal examinations. MRi was not part of the diagnostic work-up and for the vast majority not used for surveillance. Following radical prostatectomy men were usually assessed in the out-patient clinic with PSA measurements after 3, 6, 12, 18 and 24 months and annually henceforth either in the out-patient clinic or at their General Practitioner⁹. PSA recurrence was defined as a confirmed PSA of 0.2 or higher.

In order to identify two comparable cohorts we performed a propensity score matching for treatment strategy. We excluded men treated prior to 2002, men with cT2c-4 and/or GGG 3-5 and/or PSA above 20 ng/mL, **Figure 1**. In total, 908 men on active surveillance and 3.772 men treated with radical prostatectomy were included for matching. Patient chart review was performed during March-May 2018 in men who following propensity score matching were included in this study. The following was recorded: date and type of all subsequent prostate cancer treatments, date of fulfilling the EAU's definition of castration-resistant prostate cancer¹¹ and survival status. Cause of death was defined as prostate cancer or other. Follow-up was calculated from the date of treatment to event of interest or censored at last known date alive.

We risk stratified men into low-risk prostate cancer (cT1-2a and GGG 1 and PSA less than 10 ng/mL) or intermediate-risk prostate cancer (cT2b and/or GGG 2 and/or PSA 10-20 ng/mL).

The study was approved by the Danish Data Protection Agency (file#2011-41-6926), the Capital Region of Denmark (file#2012-58-0004) and the Danish Patient Safety Authority (file#3-3013-1887 and file#6-8011-916).

Statistics

Propensity score matching was performed with the MatchIt package for R using a caliper of 0.05 and included the following variables: age (continuous), diagnostic region (Capital and Zealand, Central, North, South), year of treatment (2002-2005, 2006-2009, 2010-2012), cT (1 vs. 2a/b), GGG (1 vs. 2) and PSA (continuous). Baseline characteristics between the matched cohorts were compared with Chi-squared test and Kruskal-Wallis test. Follow-up was calculated with the reverse Kaplan-Meier method. Kaplan-Meier analyses were used to estimate curative treatment-free survival for men on active surveillance presented with 95% confidence interval (CI). Cumulative incidence of commencing salvage radiotherapy, definitive hormonal therapy (either antiandrogen monotherapy or castration therapy), castration-resistant prostate cancer and prostate cancer death was assessed with non-prostate cancer death treated as competing event. Gray's test was used to assess differences between the treatment strategies. Cause specific multivariable Cox proportional hazards regression analyses were performed adjusting for: age (<60, 60-64, 65-69, 70+), diagnostic region (Capital and Zealand, Central, North, South), year of treatment (2002-2005, 2006-2009, 2010-2012), cT (1 vs. 2a/b), GGG (1 vs. 2) and PSA (<5, 5-<10, 10-<20). Results are presented as hazard ratios (HR) with 95% CI. All tests were two-sided and the significance level was set to $p < 0.05$. Statistical analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In total, 647 men from each treatment strategy were identified in the propensity score matching with a median follow-up of 8.6 years (95% CI 8.4-8.8 years). The cohorts were well balanced on baseline characteristics with no significant differences, **Table 1**. The largest differences were that 13% of men on active surveillance had GGG 2 compared to 16% of men treated with radical prostatectomy and that 15% of men on active surveillance were younger than 60 years of age compared to 18% of men treated with radical prostatectomy. According to risk stratification 376 (58%) men on active surveillance and 371 (57%) men who underwent radical prostatectomy had low-risk prostate cancer. Thus, 271 (42%) men on active surveillance and 276 (43%) of men who underwent radical prostatectomy had intermediate-risk prostate cancer.

The 5-year curative treatment-free survival for men on active surveillance was 68% (95% CI 64-71%) and at 10 years it was 61% (95% CI 57-65%). The median time on active surveillance before changing to curative treatment was 1.8 years, **Figure 2**. Overall, there were no differences in use of either salvage radiotherapy or hormonal therapy or in developing castration-resistant prostate cancer between the treatment strategies, **Figure 3**. At 10 years the cumulative incidence of salvage radiotherapy was 2.7% (95% CI 1.4-4.1%) for men primary on active surveillance compared to 5.4% (95% CI 3.4-7.3%) of men treated with radical prostatectomy, $p = 0.46$. Corresponding numbers for commencing definitive hormonal therapy were 6.9% (95% CI 4.4-9.4%) and 4.1% (95% CI 2.5-5.6%), $p = 0.81$, and for developing castration-resistant were 1.7% (95% CI 0.5-2.9%) and 2.0% (95% CI 0.7-3.4%), $p = 0.92$. Comparable results were attained when stratified on risk category, **Table 2**. For men on active surveillance the median time to salvage radiotherapy was 3.3 years, while the median time to definitive hormonal therapy was 4.8 years, **Figure 2**. Corresponding numbers for men who underwent radical prostatectomy was 3.0 years and 2.1 years, respectively.

In cause specific multivariable COX regression analyses compared to men treated with radical prostatectomy men on active surveillance had similar risk of commencing hormonal therapy, HR 1.56

(95% CI 0.92-2.65), as well as similar risk of developing castration-resistant prostate cancer, HR 1.21 (95% CI 0.49-3.03), **Table 3**.

In total, 129 men died during follow-up – including 9 prostate cancer deaths. The 10-year prostate cancer mortality was 0.4% (95% CI 0-1.0%) for men on active surveillance compared to 0.5% (95% CI 0-1.5%) for men treated with radical prostatectomy, $p = 0.15$. The 10-year cumulative non-prostate cancer mortality was 9.4% (95% CI 7.2-11.7%) for men on active surveillance and 9.0% (95% CI 6.8-11.7%) for men who underwent radical prostatectomy, $p = 0.61$.

DISCUSSION

In this observational study we observed very low prostate cancer mortality in men with favourable-risk localised prostate cancer managed on either active surveillance or immediate radical prostatectomy in Denmark. Following 10 years there was no difference between the two treatment strategies in use of salvage radiotherapy, hormone therapy or development of castration-resistant prostate cancer.

The main limitation is the non-random allocation to treatment strategy where residual confounding cannot be ruled out. We were unable to account for comorbidities that could have influenced treatment decisions; however, the overall mortality was almost identical at 10 years between the strategies indicating that any major differences in comorbidity were unlikely. Also, we lack diagnostic information on number of positive biopsy cores and maximum tumour involvement. It is therefore possible that the tumour burden on biopsy is larger in one cohort compared to the other – most likely the radical prostatectomy cohort. This is the probable reason for why men with intermediate-risk prostate cancer who underwent radical prostatectomy had a non-significant higher cumulative prostate cancer death compared to men on active surveillance. On the other hand we were able to perform complete follow-up including all cancer therapies utilized as well as survival status.

In contrast to many other countries, Danish guidelines recommend antiandrogen monotherapy (i.e. Bicalutamide 150 mg/day) as primary hormonal therapy in men with locally advanced, non-metastatic prostate cancer, where curative therapy is not an option (i.e. typically men with life expectancy < 10 years and/or significant comorbidity), and for men with biochemical recurrence after curative therapy without distant metastases on imaging but where distant failure is suspected (i.e. short PSA doubling time and/or high PSA level) or in men with rising PSA following salvage radiotherapy. Castration therapy is normally first initiated in men who presents or develops metastatic prostate cancer visible on imaging. Thus, some men on active surveillance who did not undergo curative treatment but had clinical progression to locally advanced stage and/or high PSA and some men with biochemical

recurrence following radical prostatectomy initiated antiandrogen monotherapy before reaching metastatic prostate cancer. Therefore we were unable to assess metastases-free survival.

Although 10-years follow-up is too short a timeframe to conclude on the long-term safety of an active surveillance strategy compared to an immediate curative strategy, the prostate cancer mortality was less than 1% in the current study – which is in accordance with results from randomized trials in the PSA era^{6,12} and cohort studies on radical prostatectomy^{13,14} and active surveillance^{15,16}. Moreover, a Swedish observational study including 7.608 men with localised prostate cancer who underwent radical prostatectomy did not find a higher risk of prostate cancer death among men who underwent surgery more than two years after their diagnosis¹⁷. In addition, in the current study we observed no differences in subsequent prostate cancer therapies administered and less than 7% required hormonal therapy. Still, concerns about the long-term safety of active surveillance persist. Two Scandinavian studies have demonstrated that the cause-specific mortality in men with localised prostate cancer managed on watchful waiting (i.e. curative treatment not an option) is not insignificant in men surviving more than 10 years^{18,19}.

Propensity matched studies try to resemble a randomized controlled trial using observational data; however, without the capacity to control for residual confounding. The results from the current study indicate that the active surveillance strategy can achieve similar outcomes as compared to immediate radical prostatectomy in men with low- and intermediate-risk PCa with 10-years follow-up.

Prospective randomized studies with follow-up beyond 10 or may be even 20 years will be required to evaluate long-term results. And even in such studies results may be difficult to interpret as grading systems, diagnostic strategies i.e. introduction of MR guided biopsies will gradually develop and be integrated in management of the patients. This is clearly illustrated in a recent mortality comparison between men included in the active arm of SPCG-4 (the only randomized trial to show a survival benefit in favour of curative treatment in men with localised prostate cancer²⁰), which found that men diagnosed and treated 10-20 years later than men enrolled in SPCG-4 had half the prostate cancer mortality compared to men in SPCG-4²¹.

Active surveillance is an accepted treatment strategy in men very low- or low-risk prostate cancer, whereas, men with intermediate-risk prostate cancer are generally considered for curative interventions^{4,5}. A report from the Sunnybrook active surveillance cohort, which until 2000 included men with intermediate-risk prostate cancer found a 84% 15-year metastases-free survival in men with PSA less than 20 ng/mL and GGG²². The current study, where the majority of men were diagnosed after 2005, found no significant differences in use of hormone therapy and similar risks of developing castration-resistant prostate cancer. It is plausible that the changes made to the Gleason reporting in 2005²³, with the subsequent improved prognosis in men with GGG^{22,25}, is one of the reasons for the similar oncological outcomes in the current study among men with intermediate-risk prostate cancer managed on active surveillance and radical prostatectomy.

CONCLUSION

The prostate cancer mortality was very low in men with favourable-risk localised prostate cancer managed on either active surveillance or radical prostatectomy in Denmark and we found no difference between the two treatment strategies at 10-years. In addition only few men required subsequent prostate cancer therapies and again no difference was observed between the strategies. Our study supports active surveillance as a treatment strategy for men with favourable-risk localised prostate cancer; however, longer follow-up is needed to determine the long-term safety of an initial observational approach.

Figure legends

Figure 1 CONSORT diagram

Figure 2 Number of men commencing prostate cancer treatments during following for each treatment strategy. The median time (t) from initiation of primary treatment (i.e. active surveillance or radical

prostatectomy) to commencing a given treatment is presented in years (yrs).

Figure 3 Cumulative incidence of salvage radiotherapy, hormonal therapy, castration-resistant prostate cancer, prostate cancer death and non-prostate cancer death for men managed on active surveillance and men treated with radical prostatectomy.

References

1. Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. *Eur Urol.* 2012;61(6):1079-1092. doi:10.1016/j.eururo.2012.02.054
2. Boevee SJ, Venderbos LDF, Tammela TLJ, et al. Change of tumour characteristics and treatment over time in both arms of the European Randomized study of Screening for Prostate Cancer. *Eur J Cancer.* 2010;46(17):3082-3089. doi:10.1016/j.ejca.2010.09.033
3. Rider JR, Sandin F, Andrén O, Wiklund P, Hugosson J, Stattin P. Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. *Eur Urol.* 2013;63(1):88-96. doi:10.1016/j.eururo.2012.08.001
4. Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate Cancer, Version 1.2016. *J Natl Compr Canc Netw.* 2016;14(1):19-30. <http://www.ncbi.nlm.nih.gov/pubmed/26733552>. Accessed January 19, 2016.
5. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol.* 2016;71(4):1-12. doi:10.1016/j.eururo.2016.08.003
6. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med.* 2017;375(15):1415-1424. doi:10.1056/NEJMoa1606220
7. Observational data TSD – NICE Decision Support Unit. <http://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/observational-data-tds/>. Accessed September 26, 2017.
8. Thomsen FB, Jakobsen H, Langkilde NC, et al. Active surveillance for localized prostate cancer. Nationwide, observational study. *J Urol.* 2018;In press. doi:10.1016/j.juro.2018.09.045
9. Heering M, Berg KD, Brasso K, Iversen P, Røder MA. Radical prostatectomy in Denmark: Survival analysis and temporal trends in clinicopathological parameters with up to 20 years of follow-up. *Surg Oncol.* 2017;26(1):21-27. doi:10.1016/j.suronc.2016.12.002

10. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. *Eur Urol.* 2015;69(3):doi:10.1016/j.eururo.2015.06.046. doi:10.1016/j.eururo.2015.06.046
11. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. *Eur Urol.* 2016;71(4):1-13. doi:10.1016/j.eururo.2016.08.002
12. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. *N Engl J Med.* 2017;377(2):132-142. doi:10.1056/NEJMoa1615869
13. Eggener SE, Scardino PT, Walsh PC, et al. Predicting 15-year prostate cancer specific mortality after radical prostatectomy. *J Urol.* 2011;185(3):869-875. doi:10.1016/j.juro.2010.10.057
14. Røder MA, Brasso K, Christensen IJ, et al. Survival after radical prostatectomy for clinically localised prostate cancer: a population-based study. *BJU Int.* 2014;113(4):541-547. doi:10.1111/bju.12065
15. Klotz L, Vesprini D, Sethukavalan P, et al. Long-Term Follow-Up of a Large Active Surveillance Cohort of Patients With Prostate Cancer. *J Clin Oncol.* 2014;33(3):272-277. doi:10.1200/JCO.2014.55.1192
16. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. *J Clin Oncol.* 2015;33(30):3379-3385. doi:10.1200/JCO.2015.62.5764
17. Loeb S, Folkvaljon Y, Robinson D, et al. Immediate versus delayed prostatectomy: Nationwide population-based study *. *Scand J Urol.* 2016;50(4):246-254. doi:10.3109/21681805.2016.1166153
18. Popiolek M, Rider JR, Andrén O, et al. Natural history of early, localized prostate cancer: a final report from three decades of follow-up. *Eur Urol.* 2013;63(3):428-435. doi:10.1016/j.eururo.2012.10.002
19. Brasso K, Friis S, Juel K, Jørgensen T, Iversen P. Mortality of patients with clinically localized

- prostate cancer treated with observation for 10 years or longer: a population based registry study. *J Urol*. 1999;161(2):524-528. <http://www.ncbi.nlm.nih.gov/pubmed/9915440>.
20. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical Prostatectomy or Watchful Waiting in Prostate Cancer — 29-Year Follow-up. *N Engl J Med*. 2018;379(24):2319-2329. doi:10.1056/NEJMoa1807801
21. Cazzaniga W, Garmo H, Robinson D, Holmberg L, Bill-Axelson A, Stattin P. Mortality after radical prostatectomy in a matched contemporary cohort in Sweden compared to the Scandinavian Prostate Cancer Group 4 (SPCG-4) study. *BJU Int*. September 2018. doi:10.1111/bju.14563
22. Musunuru HB, Yamamoto T, Klotz L, et al. Active Surveillance for Intermediate Risk Prostate Cancer: Survival Outcomes in the Sunnybrook Experience. *J Urol*. 2016;196(6):1651-1658. doi:10.1016/j.juro.2016.06.102
23. Epstein JI, Allsbrook WC, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol*. 2005;29(9):1228-1242. <http://www.ncbi.nlm.nih.gov/pubmed/16096414>. Accessed March 8, 2014.
24. Thomsen FB, Folkvaljon Y, Brasso K, et al. Prognostic implications of 2005 Gleason grade modification. Population-based study of biochemical recurrence following radical prostatectomy. *J Surg Oncol*. 2016;(April):1-7. doi:10.1002/jso.24408
25. Berg KD, Thomsen FB, Nerstrøm C, et al. The impact of the 2005 International Society of Urological Pathology consensus guidelines on Gleason grading - a matched pair analysis. *BJU Int*. 2016;117(6):883-889. doi:10.1111/bju.13439

Table 1 Diagnostic characteristics of men with localized prostate cancer managed on active surveillance or radical prostatectomy.

| | Active surveillance <i>n</i> = 647 | | Radical prostatectomy <i>n</i> = 647 | | <i>p</i> |
|----------------------------------|---------------------------------------|------|---|------|----------|
| | <i>n</i> | % | <i>n</i> | % | |
| Year of treatment | | | | | 0.97* |
| 2002-2005 | 58 | (9) | 59 | (9) | |
| 2006-2009 | 310 | (48) | 313 | (48) | |
| 2010-2012 | 279 | (43) | 275 | (43) | |
| Region of Denmark | | | | | 0.59* |
| Capital and Zealand | 402 | (62) | 379 | (59) | |
| Central | 67 | (10) | 77 | (12) | |
| North | 117 | (18) | 128 | (20) | |
| Southern | 61 | (9) | 65 | (10) | |
| Age, year | | | | | 0.26* |
| Median (IQR) | 65 (61-67) | | 64 (61-67) | | |
| <60 | 96 | (15) | 116 | (18) | |
| 60-64 | 216 | (33) | 228 | (35) | |
| 65-69 | 260 | (40) | 240 | (37) | |
| ≥70 | 75 | (12) | 63 | (10) | |
| Clinical tumor category | | | | | 0.45* |
| 1 | 547 | (85) | 536 | (83) | |
| 2a/b | 100 | (15) | 111 | (17) | |
| Gleason Grade Groups | | | | | 0.11* |
| 1 | 565 | (87) | 544 | (84) | |
| 2 | 82 | (13) | 103 | (16) | |
| Prostate-specific antigen, ng/mL | | | | | 0.78** |
| Median (IQR) | 6.8 (5.2-9.5) | | 6.8 (5.3-9.4) | | |
| <5 | 136 | (21) | 130 | (20) | |
| 5-<10 | 378 | (58) | 375 | (58) | |
| 10-20 | 133 | (21) | 142 | (22) | |

* Chi-squared test **Kruskal-Wallis test

Table 2 Cumulative incidence estimated with competing risk analyses for 647 managed on active surveillance and 647 men managed with radical prostatectomy and stratified on risk category*

| | All men | | | | Low-risk | | | | Intermediate-risk | | | |
|--------------------------------------|---------------------------------------|----------|---|----------|---------------------------------------|----------|---|---------|---------------------------------------|----------|---|----------|
| | Active surveillance <i>n</i> = 647 | | Radical prostatectomy <i>n</i> = 647 | | Active surveillance <i>n</i> = 376 | | Radical prostatectomy <i>n</i> = 371 | | Active surveillance <i>n</i> = 271 | | Radical prostatectomy <i>n</i> = 276 | |
| | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI |
| Salvage radiotherapy | | | | | | | | | | | | |
| 10-year estimate | 2.7 | 1.4-4.1 | 5.4 | 3.4-7.3 | 2.2 | 0.7-3.7 | 4.7 | 2.1-7.3 | 1.4 | 0.9-6.3 | 6.4 | 3.4-9.3 |
| Hormonal therapy | | | | | | | | | | | | |
| 10-year estimate | 6.9 | 4.4-9.4 | 4.1 | 2.5-5.6 | 5.6 | 2.7-8.5 | 2.9 | 1.1-4.5 | 9.0 | 4.2-13.8 | 5.8 | 3.1-8.6 |
| Castration-resistant prostate cancer | | | | | | | | | | | | |
| 10-year estimate | 1.7 | 0.5-2.9 | 2.0 | 0.7-3.4 | 1.1 | 0.3-2.1 | 1.5 | 0-3.2 | 3.0 | 0-5.9 | 2.7 | 0.7-4.8 |
| Prostate cancer death | | | | | | | | | | | | |
| 10-year estimate | 0.4 | 0-1.0 | 0.8 | 0.01-1.4 | 0.5 | 0-1.3 | 0.3 | 0-0.8 | 0.4 | 0-1.1 | 1.5 | 0.04-2.9 |
| Non-prostate cancer death | | | | | | | | | | | | |
| 10-year estimate | 9.4 | 7.2-11.7 | 9.0 | 6.8-11.2 | 8.5 | 5.7-11.3 | 6.7 | 4.2-9.3 | 10.7 | 7.0-14.4 | 12.0 | 8.1-15.8 |

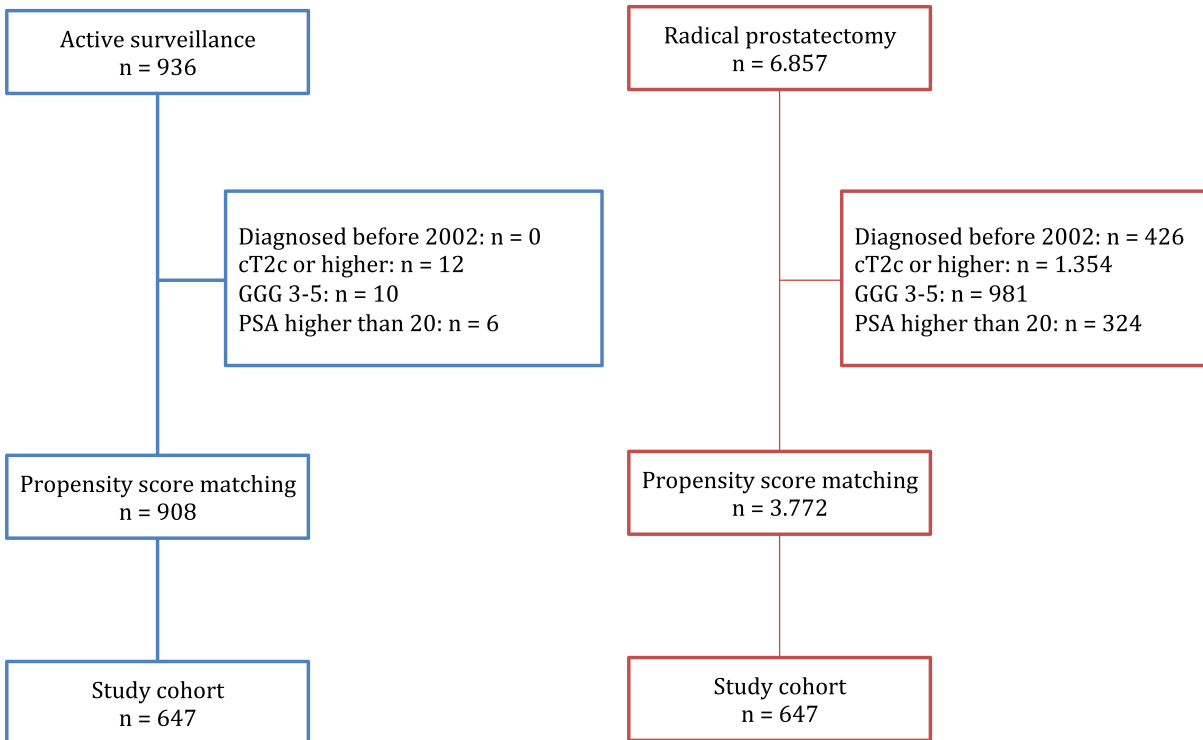
Abbreviations CI confidence interval

*Risk category definition: Low-risk: cT1-2a and GGG 1 and PSA less than 10 ng/mL; Intermediate-risk: cT2b-c and/or GGG 2-3 and/or PSA 10-20 ng/mL;

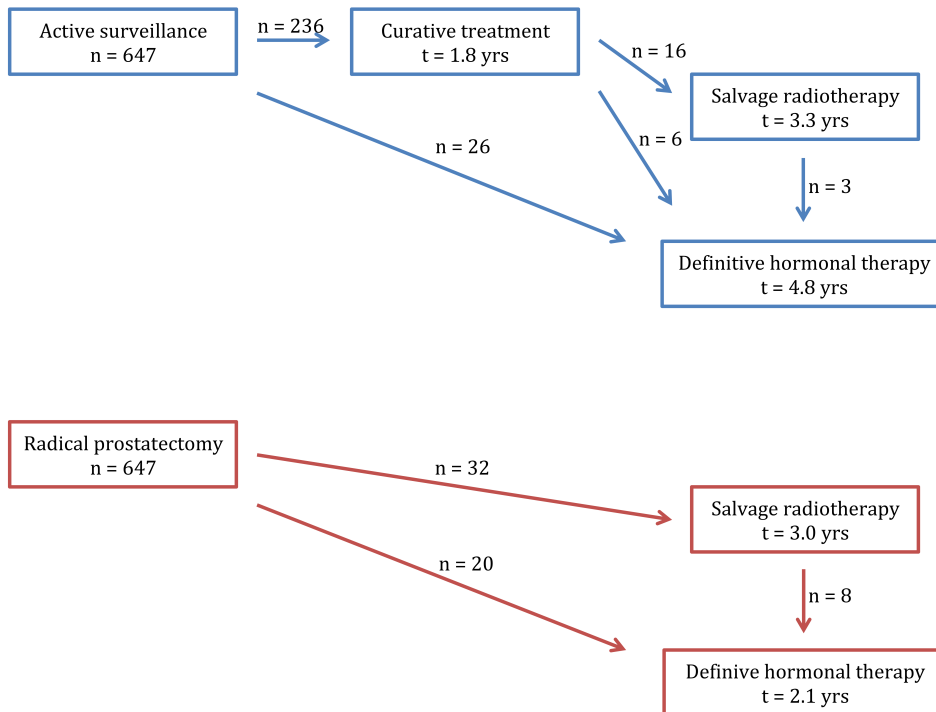
Table 3 Cause specific multivariable Cox regression analyses for commencing hormonal therapy or developing castration-resistant prostate cancer. Non-prostate cancer deaths were treated as competing events.

| | Hormonal therapy | | | Castration-resistant prostate cancer | | |
|--|------------------|-----------|-------|--------------------------------------|------------|-------|
| | HR | 95% CI | p | HR | 95% CI | p |
| Treatment strategy | | | | | | |
| Radical prostatectomy | 1 | ref | | 1 | ref | |
| Active surveillance | 1.56 | 0.92-2.65 | 0.10 | 1.21 | 0.49-3.03 | 0.68 |
| Year of commencing active surveillance | | | | | | |
| 2002-2005 | 1 | ref | | 1 | ref | |
| 2006-2009 | 0.39 | 0.20-0.76 | 0.005 | 0.20 | 0.06-0.64 | 0.007 |
| 2010-2012 | 0.40 | 0.19-0.83 | 0.01 | 0.37 | 0.12-1.21 | 0.10 |
| Region | | | | | | |
| Capital and Zealand | 1 | ref | | 1 | ref | |
| Central | 1.97 | 1.03-3.76 | 0.04 | 0.81 | 0.18-3.56 | 0.78 |
| North | 0.71 | 0.31-1.41 | 0.28 | 0.67 | 0.18-2.48 | 0.55 |
| Southern | 0.66 | 0.25-2.04 | 0.52 | 1.44 | 0.39-5.28 | 0.58 |
| Age, years | | | | | | |
| <60 | 1 | ref | | 1 | ref | |
| 60-64 | 0.92 | 0.41-2.10 | 0.85 | 5.18 | 0.64-41.59 | 0.12 |
| 65-69 | 1.28 | 0.58-2.83 | 0.54 | 5.83 | 0.73-46.94 | 0.10 |
| ≥70 | 1.78 | 0.73-4.36 | 0.21 | 1.99 | 0.11-33.06 | 0.63 |
| Clinical tumor category | | | | | | |
| 1 | 1 | ref | | 1 | ref | |
| 2a/b | 1.87 | 1.06-3.31 | 0.03 | 2.63 | 1.02-6.74 | 0.04 |
| Gleason Grade Group | | | | | | |
| 1 | 1 | ref | | 1 | ref | |
| 2 | 1.68 | 0.91-3.10 | 0.10 | 1.49 | 0.46-4.79 | 0.50 |
| Prostate-specific antigen, ng/mL | | | | | | |
| <5 | 1 | ref | | 1 | ref | |
| 5-<10 | 1.85 | 0.77-4.46 | 0.12 | 0.86 | 0.26-2.79 | 0.79 |
| 10-20 | 3.21 | 1.28-8.02 | 0.01 | 1.22 | 0.33-4.48 | 0.76 |

Abbreviations HR hazard ratio; CI confidence interval



ACCEPTED



ACCEPTED

