Active surveillance for localized prostate cancer

Nationwide, observational study

Thomsen, Frederik B; Jakobsen, Henrik; Langkilde, Niels Christian; Borre, Michael; Jakobsen, Erik B; Frey, Anders; Lund, Lars; Lunden, Dagmar; Dahl, Claus; Helgstrand, J Thomas; Brasso, Klaus

Published in:
The Journal of Urology

DOI (link to publication from Publisher):
10.1016/j.juro.2018.09.045

Publication date:
2019

Document Version
Accepted author manuscript, peer reviewed version

Author's Accepted Manuscript

Active surveillance for localized prostate cancer. Nationwide, observational study

Frederik B. Thomsen , Henrik Jakobsen , Niels Christian Langkilde , Michael Borre , Erik B. Jakobsen , Anders Frey , Lars Lund , Dagmar Lunden , Claus Dahl , J. Thomas Helgstrand , Klaus Brasso

PII: S0022-5347(18)43911-0
DOI: 10.1016/j.juro.2018.09.045
Reference: JURO 15829

To appear in: *The Journal of Urology*
Accepted Date: 7 September 2018

Please cite this article as: Thomsen FB, Jakobsen H, Langkilde NC, Borre M, Jakobsen EB, Frey A, Lund L, Lunden D, Dahl C, Helgstrand JT, Brasso K, Active surveillance for localized prostate cancer. Nationwide, observational study, *The Journal of Urology*® (2018), doi: https://doi.org/10.1016/j.juro.2018.09.045.

Active surveillance for localized prostate cancer. Nationwide, observational study

Running head: Active surveillance for localized prostate cancer

Frederik B. Thomsen[1], Henrik Jakobsen[2], Niels Christian Langkilde[3], Michael Borre[4], Erik B. Jakobsen[5], Anders Frey[6], Lars Lund[7,8], Dagmar Lunden[9], Claus Dahl[5], J. Thomas Helgstrand[1] and Klaus Brasso[1,10]

[1] Copenhagen Prostate Cancer Center, Rigshospitalet, Copenhagen, Denmark

[2] Dept of Urology, Herlev and Gentofte Hospital, Herlev, Denmark

[3] Dept of Urology, Aalborg University Hospital, Aalborg, Denmark

[4] Dept of Urology, Aarhus University Hospital, Skejby, Denmark

[5] Dept of Urology, Zealand University Hospital, Roskilde, Denmark

[6] Dept of Urology, Sydvestjysk Sygehus, Esbjerg, Denmark

[7] Dept of Clinical Research Urology, University of Southern Denmark, Denmark

[8] Dept of Urology, Odense University Hospital, Odense, Denmark

[9] Dept of Urology, Hospitalsenhed Midt, Viborg, Denmark

[10] Dept of Urology, Rigshospitalet, Copenhagen, Denmark

Corresponding author: Dr. Frederik B. Thomsen, 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: Word of ms excluding abstract: 2,497 (abstract 222)

Author Contributions: All authors contributed to the study design, data collection, data interpretation and approved the final version. FBT performed the statistical analyses. FBT, JTH 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.

Transparency declaration: FBT affirms that the manuscript is an honest, accurate, and transparent account of the study and that no important aspects of the study have been omitted.

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.

Abstract

Purpose: The objective of this study was to investigate nationwide survival outcomes in men with localized prostate cancer managed on active surveillance.

Material and methods: 936 men with localized prostate cancer initiated active surveillance in Denmark in 2002-2012. Kaplan-Meier estimated curative treatment-free-, hormonal therapy-free-, castration-resistant prostate cancer-free- and cause-specific survival were calculated.

Results: Two hundred and twenty-three men were classified with very low-risk prostate cancer, 436 men with low-risk prostate cancer, 259 men with intermediate-risk prostate cancer (87% had favorable intermediate-risk prostate cancer), and 18 men with high-risk prostate cancer. The median follow-up was 7.5 years (IQR 6.1-9.1 years). Kaplan-Meier estimated 10-year curative treatment-free survival was 62.8% (95% CI 59.1-66.3%), 10-year hormonal therapy-free survival was 92.2 (95% CI 89.2-94.4%), 10-year castration-resistant prostate cancer-free survival was 97.2% (95% CI 95.3-98.4%) and the 10-year cause-specific survival was 99.6% (95% CI 98.6-99.9%). Compared to men with low-risk prostate cancer, men with intermediate-risk prostate cancer had a higher curative treatment-free survival (69% vs. 56%, $p = 0.008$), a lower hormonal therapy-free survival (88% vs. 95%, $p = 0.005$), and similar castration-resistant prostate cancer-free survival (95% vs. 99%, $p = 0.17$).

Conclusion: In this nationwide cohort the 10-year cause-specific survival was similar to prospective active surveillance cohorts. Our study supports the use of active surveillance for men with localized prostate cancer – including men with favorable intermediate-risk characteristics.

Keywords: prostate cancer; localized; active surveillance; survival; nationwide

INTRODUCTION

Curative options for localized prostate cancer are available, however, the effect on survival in men with more favorable-risk features is very limited[1–5]. Still, some men with favorable-risk prostate cancer dye from the disease[1]. Active surveillance has been introduced as a tailored management for selected men with localized prostate cancer in order to reduce overtreatment by identifying men who will likely benefit from definitive therapy, while men with true favorable-risk prostate cancer are spared curative interventions and its adverse effects[2,3].

Large prospective active surveillance cohorts with predefined follow-up programs and criteria for recommending curative therapy have achieved excellent 10-year cause-specific survival of 98-99%[6–9]. Follow-up in these cohorts include regular prostate-specific antigen (PSA) testing, digital rectal examinations and sequential surveillance biopsies. The ProtectT study, the first randomized controlled trial comparing curative interventions (i.e. radical prostatectomy and radiotherapy) to an "active monitoring" strategy found no survival difference between the treatment strategies[10]. In that study men on active monitoring was managed with regular PSA testing and change to curative treatment primarily based on PSA. The 10-year cause-specific survival for men on active monitoring was 98.8%.

The safety of men with localized prostate cancer managed on active surveillance outside of prospective cohorts is unknown. Well conducted observational studies can elucidate on the effectiveness of managements in a real world setting and are important additions to clinical trials in clinical decision making[11,12]. The objective of this study was to investigate results for men with localized prostate cancer managed on active surveillance in Denmark. We identified men who initiated active surveillance in 2002-2012. This enabled us to define a magnetic resonance imaging (MRi) "naïve" cohort – i.e. MRi was not part of the diagnostic work-up and for the vast majority a surveillance MRi was not available for the initial years of surveillance, the period in which the majority of men on active surveillance, who undergo subsequent curative treatment, will change strategy[13].

MATRIAL AND METHODS

Patients diagnosed with prostate cancer and initially managed on active surveillance in the period between 1 Jan 2002 and 31 December 2012 were identified at ten Danish urological departments (Aalborg, Esbjerg, Frederiksberg, Herlev, Næstved, Odense, Rigshospitalet, Roskilde, Skejby, and Viborg). Patient chart review was performed at Aalborg, Esbjerg, Frederiksberg, Næstved, Roskilde, Skejby, and Viborg for men who had two or more prostate biopsies, while local registration of men on active surveillance was performed at Herlev, Odense and Rigshospitalet. The following data was retrieved at the time of initiating active surveillance: year, age, clinical tumor category (cT), diagnostic Gleason score (recorded according to the five-tier Gleason Grade Group [GGG])[14], PSA (ng/mL), transrectal ultrasound (TRUS) estimated prostate volume, number of biopsies, number of positive core biopsies, and maximum tumor involvement in any one core. Number of surveillance biopsies was also registered. Baseline PSA was defined for men diagnosed with biopsy as the last PSA before the diagnostic biopsy, while for men diagnosed following transurethral resection of the prostate, the PSA nadir after the procedure was used. In men diagnosed following a biopsy PSA density was calculated as PSA divided by TRUS estimated prostate volume (ng/mL/cc).

Prostate cancer was grouped into four risk categories according to a modified NCCN risk categorisation[2]: Very low-risk: cT1 and GGG 1 and PSA <10 and PSA density <0.15 and 1-2 positive biopsy cores and ≤50% cancer in any one core; Low-risk: cT1-2a and GGG 1 and PSA <10; Intermediate-risk: cT2b-2c and/or GGG 2-3 and/or PSA 10-20; High-risk: PSA >20 (no patients had cT3 or GGG 4-5). Intermediate-risk prostate cancer was further sub-divide into favorable (only 1 intermediate-risk criteria and GGG 1-2 and ≤50% tumor in any one core) or unfavorable (2-3 intermediate-risk criteria and/or GGG 3 and/or >50% tumor in any one core).

During March-April 2018 patient chart review was performed to record date and type of all prostate cancer treatments, date of fulfilling the EAU's definition of castration-resistant prostate cancer[15], and

survival status. Cause of death was defined as prostate cancer or other. Follow-up was calculated from start of active surveillance to event of interest or censured at last known date alive.

The study was approved by the Capital Region of Denmark (file no. 2012-58-0004) and by the Danish Patient Safety Authority (file no. 3-3013-1887).

Statistics

Descriptive statistics was used to describe baseline characteristics. Follow-up was calculated with the reverse Kaplan-Meier method. Survival probabilities were assessed with Kaplan-Meier analyses and presented with 95% confidence interval (CI). The log-rank test was used to assess differences between subgroups. The association between baseline characteristics and subsequent treatments were assessed with Cox proportional hazard regression analyses including the following categorical variables: year of commencing active surveillance, age, cT, PSA, PSA density, GGG, number of positive biopsy cores, and maximum percent tumor in any one core. Missing values were included in as an individual group. Results are presented as hazard ratios (HR) with 95% CI. Statistical analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided and the significance level was set to $p < 0.05$.

RESULTS

In total, 936 men diagnosed with prostate cancer and initially followed on active surveillance were identified, **Table 1**. The median follow-up was 7.5 years (Interquartile range [IQR] 6.1-9.1 years) and 840 men (90%) underwent at least one surveillance biopsy, the median number of surveillance biopsies were 2 (IQR 1-2). The majority was classified with very low-risk prostate cancer (24%) or low-risk prostate cancer (47%), while 28% had intermediate-risk prostate cancer (of which 33 men had unfavorable intermediate-risk prostate cancer), and 2% high-risk prostate cancer (all because of a PSA above 20).

During follow-up 320 men underwent curative treatment. Two hundred and fifty men underwent radical prostatectomy, 53 men underwent external beam radiotherapy, 15 men underwent brachytherapy and 2 men underwent a radical cystoprostatectomy because of a subsequent bladder cancer. The 5-year curative treatment-free survival was 69.1% (95% CI 66.0-71.9%) and the 10-year curative treatment-free survival was 62.8% (95% CI 59.1-66.3%), **Figure 1A**. Men diagnosed in 2010-2012 and men aged 70 years or older at diagnosis were less likely to undergo curative treatment, whereas a PSA density higher than 0.1 was associated with an increased risk of undergoing curative treatment, **Table 2**.

In sub-group analyses, with men with low-risk prostate cancer as reference, the curative treatment-free survival was higher in men with very low-risk (p = 0.005) and intermediate-risk prostate cancer (p = 0.008), but similar to men with high-risk prostate cancer (p = 0.59), **Table 3**.

Ninety-one men died during follow-up – three from prostate cancer. Corresponding to a 10-year overall survival of 87.2% (95% CI 84.0-89.9) and a 10-year cause-specific survival of 99.6% (95% CI 98.6-99.9), **Figure 1B**. There was no difference between risk groups, **Table 3**. Two of the three men who died of prostate cancer were classified with low-risk prostate cancer, while the third man had intermediate-risk prostate cancer. Two of the three men underwent radical prostatectomy within one year of initiating surveillance and both experience early biochemical recurrence and commenced

hormonal therapy. The third man with low-risk prostate cancer was diagnosed with distant metastases following 3 years of surveillance and commenced hormonal therapy. Imaging in this man was performed during work-up following a surveillance biopsy, which revealed an upgrade to GGG 4.

Fifty men (5%) commenced hormonal therapy (i.e. antiandrogen monotherapy [*n* = 27] or castration therapy [*n* =23]) during follow-up corresponding to a 10-year hormonal therapy-free survival of 92.2% (95% CI 89.2-94.4%), **Table 3**. No difference was observed between men who had undergone curative treatment and men who had not, **Figure 2A**. Men aged 70 years or older, men with a PSA higher than 5, and men with a missing PSA density (including the 64 men diagnosed following TUR-P) had a higher risk of commencing hormonal therapy, **Table 2**. Compared to men with low-risk prostate cancer, men with intermediate-risk prostate cancer ($p = 0.005$) and men with high-risk prostate cancer ($p < 0.001$) had a lower hormonal therapy-free survival, **Table 3**.

Finally, the 10-year castration-resistant prostate cancer-free survival was 97.2% (95% CI 95.3-98.4%), **Table 3**. Again no difference between men who had undergone curative treatment and men who had not, **Figure 2B**. Men with high-risk prostate cancer had a lower castration-resistant prostate cancer-free survival compared to men with low-risk prostate cancer, $p < 0.001$; whereas there was no difference between men with low-risk and intermediate risk prostate cancer, $p = 0.17$, **Table 3**.

Compared to men with favorable intermediate-risk prostate cancer men with unfavorable intermediate-risk prostate cancer were more likely to receive hormonal therapy and had a higher risk of developing castration-resistant prostate cancer, **Supplemental Table**.

DISCUSSION

In this nationwide, observational study on men with localized prostate cancer managed on active surveillance in Denmark we found 10-year cause-specific survival similar to prospective active surveillance cohorts.

The main limitation of the retrospective design is potential incomplete capture as there was no national database in the period studied with data on which men were managed on active surveillance. Moreover, 11 Danish urological departments were primary referral centers in the period studied; however, one department chose not to participate. Although this department refers men diagnosed with prostate cancer who are candidates for curative treatment to a tertiary referral center, it is possible that men diagnosed at this department were not included in the study. Another limitation of the design is that there was no uniform surveillance strategy at the different departments. However, all centers assessed men with a combination of surveillance biopsies, regular PSA measurement and digital rectal examinations. On the other hand thorough patient chart review was performed in all identified men with almost complete baseline data and complete follow-up including all cancer therapies utilized and survival status.

The short-term, 5-year curative treatment-free survival of 69.1% is higher than what is observed in the prospective cohorts (50-64%)[6–9], which could indicate that the men in the current study were managed with a less intensive surveillance i.e. fewer surveillance biopsies with a subsequent lower risk of biopsy reclassification. Another possibility is that more frequent change from active surveillance to watchful waiting – i.e. a strategy where curative treatment is no longer considered an option and men are only followed with PSA and digital rectal examination in order to initiate subsequent hormonal therapy when required. This in particular seems the case for men aged 70 year or older, who were less likely to undergo curative treatment but more likely to commence hormonal therapy. Surprisingly and somewhat counterintuitive, we observed a higher curative treatment-free survival in men with intermediate-risk prostate cancer compared to men with low-risk prostate

cancer. It is likely that men with intermediate-risk prostate cancer had reluctance towards curative treatment at diagnosis and that progression on surveillance biopsies leading to recommending curative treatment is less likely for men with GGG 2 compared to men with GGG 1.

The current study constitutes an active surveillance cohort of men where a relatively large proportion (30%) had intermediate-risk or high-risk prostate cancer compared to published prospective cohorts (0-25%)[6–9]. Still, with a 10-year cause-specific survival of 99.6% we confirm that active surveillance in a real world setting can produce survival results similar to prospective active surveillance cohorts (98-99%)[6,7] and the active monitoring arm of the ProtecT study (98.8%)[10]. However, there are still concerns about this strategy's long-term safety. The prospective Swedish, Örebro cohort study and a Danish register-based study have demonstrated that the cause-specific mortality is not insignificant in men managed on watchful waiting and surviving 10 years or more[16,17]. Importantly in these studies curative treatments were not available and the Sunnybrook active surveillance cohort demonstrated a 15-year cause-specific mortality half of the observed in the comparable subgroup in the Örebro cohort (5.7% vs. 11%)[6]. Moreover, a previous report from the Sunnybrook cohort have questioned the safety of active surveillance in men with intermediate-risk prostate cancer[18]. However, that study only included men with intermediate-risk prostate cancer diagnosed before 2000. The current study almost exclusively included men with favorable intermediate-risk prostate cancer and the vast majority was diagnosed after 2005. It is therefore likely that the changes made to the Gleason reporting in 2005[19], with the subsequent improved prognosis in men with GGG 2[20,21], is one of the reasons for the better outcomes among men with intermediate-risk prostate cancer in the current study.

The practice in Denmark is to initiate castration therapy if imaging detects metastatic disease; whereas, antiandrogen monotherapy is initiated in men on surveillance who no longer are candidates to curative treatment without presence of metastases, if extraprostatic extension is suspected on digital rectal examination, if the PSA level rises rapidly and/or reaches a level above 50 or following curative treatment if distant failure is suspected. Thus, we were not able to assess metastases-free survival. We observed no difference in these surrogate endpoints, hormonal therapy-free and

castration-resistant prostate cancer-free survival, between men who had undergone curative treatment and men who had not. This indicates that only few men who could have benefitted from curative treatment do not undergo such interventions. Although these results are promising men on active monitoring in the ProtecT study had a higher risk of clinical progression including progression to metastatic disease compared to men who underwent curative interventions[10]. Thus, more studies comparing active surveillance to curative treatment modalities are still warranted.

Even though active surveillance is an accepted treatment strategy and recommended in guidelines to men with very low- or low-risk prostate cancer[2,3] the strategy is evolving. Roughly one third of men with low-risk prostate cancer who undergo immediate radical prostatectomy harbor GGG 2 or higher and more than 10% present with extra prostatic extension in the prostatectomy specimen[22]. On the other hand up to 50% of men who progressed on active surveillance and undergo radical prostatectomy had true low-risk disease at surgery – i.e. pT2 and GGG 1[22]. Efforts are made to increase the precision in which curative treatments are recommended[23–25]. Currently multiparametric MRi is the only marker that has been recommend in the EAU guidelines and introduced in the management of men on active surveillance on a large scale[3,6,24]. This modality seems able to detect potential lethal tumors missed by TRUS guided biopsy[26]; however, this could also lead to new overtreatment issues as we still do not fully understand how to clinical interpret the pathology of an MRi targeted biopsy. Moreover, it seems unlikely that an active surveillance program including MRi can achieve better outcomes in terms of cancer-specific survival. On the other hand MRi may in the future enable us to broaden the selection criteria for active surveillance, reduce the number of surveillance biopsies, and decrease the number of men who need to undergo curative treatments.

CONCLUSION

In this nationwide, observational study on men with localized prostate cancer managed on active surveillance in Denmark, we found cause-specific survival similar to prospective active surveillance

cohorts in the intermediate timeframe. Men with intermediate-risk prostate cancer were less likely to undergo curative treatment but had similar castration-resistant treatment-free survival compared to men with low-risk prostate cancer. Our study supports active surveillance as a treatment strategy for men with localized prostate cancer – including men with intermediate-risk characteristics.

Figure legends

Figure 1 Curative treatment-free survival (A) and overall- and cause-specific survival (B) estimates with 95% confidence intervals of 936 men with localized prostate cancer managed on active surveillance in Denmark.

Figure 2 Hormonal therapy-free survival (A) and castration-resistant prostate cancer-free survival (B) estimates with 95% confidence intervals of 936 men with localized prostate cancer managed on active surveillance in Denmark stratified according to curative treatment interventions.

References

1. Rider JR, Sandin F, Andrén O, et al: Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. Eur. Urol. 2013; **63**: 88–96. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22902040, accessed March 8, 2014.
2. Mohler JL, Armstrong AJ, Bahnson RR, et al: Prostate Cancer, Version 1.2016. J. Natl. Compr. Canc. Netw. 2016; **14**: 19–30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26733552, accessed January 19, 2016.
3. 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. 2017; **71**: 618–629. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27568654, accessed May 9, 2018.
4. Bill-Axelson A, Holmberg L, Garmo H, et al: Radical prostatectomy or watchful waiting in early prostate cancer. N. Engl. J. Med. 2014; **370**: 932–42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24597866, accessed March 6, 2014.
5. Vickers A, Bennette C, Steineck G, et al: Individualized estimation of the benefit of radical prostatectomy from the Scandinavian Prostate Cancer Group randomized trial. Eur. Urol. 2012; **62**: 204–9. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3389180&tool=pmcentrez&rendertype=abstract, accessed March 8, 2014.
6. 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. 2015; **33**: 272–277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25512465, accessed July 25, 2017.
7. 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**: 3379–3385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26324359, accessed July 25, 2017.

8. Bokhorst LP, Valdagni R, Rannikko A, et al: A Decade of Active Surveillance in the PRIAS Study: An Update and Evaluation of the Criteria Used to Recommend a Switch to Active Treatment. Eur. Urol. 2016; **70**: 954–960.

9. Thostrup M, Thomsen FB, Iversen P, et al: Active surveillance for localized prostate cancer: update of a prospective single-center cohort. Scand. J. Urol. 2017.

10. Hamdy FC, Donovan JL, Lane JA, et al: 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N. Engl. J. Med. 2016; **375**: 1415–1424.

11. Anon: Observational data TSD – NICE Decision Support Unit. Available at: http://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/observational-data-tsd/, accessed September 26, 2017.

12. Egger M, Moons KGM, Fletcher C, et al: GetReal: from efficacy in clinical trials to relative effectiveness in the real world. Res. Synth. Methods 2016; **7**: 278–81. Available at: http://doi.wiley.com/10.1002/jrsm.1207, accessed September 19, 2017.

13. Thomsen FB, Brasso K, Klotz LH, et al: Active surveillance for clinically localized prostate cancer - A systematic review. J. Surg. Oncol. 2014; **109**.

14. 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**: doi: 10.1016/j.eururo.2015.06.046. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0302283815005576, accessed June 21, 2016.

15. 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: 1–13. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0302283816304699.

16. 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**: 428–35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23084329, accessed May 21, 2014.

17. Brasso K, Friis S, Juel K, et al: 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**: 524–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9915440.

18. 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**: 1651–1658. Available at: http://dx.doi.org/10.1016/j.juro.2016.06.102.

19. Epstein JI, Allsbrook WC, Amin MB, et al: The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am. J. Surg. Pathol. 2005; **29**: 1228–42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16096414, accessed March 8, 2014.

20. 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: 1–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27511833.

21. 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**: 883–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26823232, accessed June 28, 2016.

22. Thomsen FB, Berg KD, Iversen P, et al: Poor association between the progression criteria in active surveillance and subsequent histopathological findings following radical prostatectomy. Scand. J. Urol. 2015; **49**.

23. Loeb S and Tosoian JJ: Biomarkers in active surveillance. Transl. Androl. Urol. 2018; **7**: 155–159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29594029, accessed April 24, 2018.

24. Schoots IG, Nieboer D, Giganti F, et al: Is MRI-targeted biopsy a useful addition to systematic confirmatory biopsy in men on active surveillance for low-risk prostate cancer? A systematic review and meta-analysis. BJU Int. 2018. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29679430, accessed April 24, 2018.

25. Berg KD, Vainer B, Thomsen FB, et al: ERG protein expression in diagnostic specimens is associated with increased risk of progression during active surveillance for prostate cancer. Eur. Urol. 2014; **66**.

26. Kasivisvanathan V, Rannikko AS, Borghi M, et al: MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N. Engl. J. Med. 2018: NEJMoa1801993. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29552975, accessed April 24, 2018.

Table 1 Diagnostic characteristics of 936 men on active surveillance in Denmark in 2002-2012

	N	%
Year of commencing active surveillance		
2002-2005	60	(6)
2006-2009	359	(38)
2010-2012	517	(55)
Age, years		
Median (IQR)	66	(63-68)
<60	103	(11)
60-64	260	(28)
65-69	419	(45)
≥70	154	(16)
Clinical tumour category		
cT1a/b	64	(7)
cT1c	734	(78)
cT2a	106	(11)
cT2b	20	(2)
cT2c	12	(1)
Gleason Grade Groups		
1	841	(90)
2	85	(9)
3	10	(1)
Prostate-specific antigen, ng/mL		
Median (IQR)	6.7	(5.2-9.2)
<5	193	(21)
5-<10	567	(61)
10-20	158	(17)
>20	18	(2)
PSA density, ng/mL/cc		
Median (IQR)	0.15	(0.10-0.21)
<0.10	166	(18)
0.10-<0.20	413	(44)
0.20-0.50	238	(25)
>0.50	25	(3)
Missing	94	(10)
Number of biopsy cores		
Median (IQR)	10	(10-12)
Number of positive biopsy cores		
1-2	735	(79)
3-4	103	(11)
5-6	13	(1)
7-8	2	(0.2)
9-10	2	(0.2)
Missing	81	(9)
Maximum percent tumour in any one core		
Median (IQR)	0.10	(0.05-0.20)
<0.10	377	(40)
0.10-<0.25	348	(37)
0.25-0.50	131	(14)
>0.50	18	(2)
Missing	62	(7)
NCCN risk category*		
Very Low-risk	223	(24)
Low-risk	436	(47)
Intermediate-risk	259	(28)
High-risk	18	(2)

* Risk category definition:
Very low-risk: cT1 and GGG 1 and PSA less than 10 ng/mL and PSA density less than 0.15 ng/mL/cc and 1-2 positive biopsy cores and maximum 50% cancer in any one core;
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;
High-risk: PSA higher than 20 ng/mL

Table 2 Association between baseline characteristics and undergoing curative treatment or commencing hormonal therapy. Multivariable Cox regression analysis

	Curative treatment		Hormonal therapy	
	HR	95% CI	HR	95% CI
Year of commencing active surveillance				
2002-2005	1	ref	1	ref
2006-2009	0.75	0.50-1.15	0.64	0.26-1.59
2010-2012	0.65	0.42-1.00	0.51	0.20-1.33
Age, years				
<60	1	ref	1	ref
60-64	1.03	0.72-1.49	0.72	0.21-2.53
65-69	0.85	0.59-1.22	1.20	0.39-3.67
≥70	0.42	0.26-0.69	3.09	1.01-9.46
Clinical tumour category				
1	1	ref	1	ref
2	1.21	0.89-1.65	0.71	0.31-1.67
Prostate-specific antigen, ng/mL				
<5	1	ref	1	ref
5-<10	1.01	0.72-1.42	3.64	1.10-12.01
10-20	0.90	0.57-1.42	4.76	1.30-17.44
>20	1.13	0.47-2.71	13.08	2.38-71.87
PSA density, ng/mL/cc				
<0.10	1	ref	1	ref
0.10-<0.20	1.47	1.03-2.10	0.73	0.27-1.93
0.20-0.50	1.65	1.11-2.46	1.11	0.41-3.03
>0.50	2.71	1.27-5.74	2.53	0.54-11.89
Missing	1.68	0.82-3.46	5.79	1.67-20.07
Gleason Grade Group				
1	1	ref	1	ref
2	0.80	0.51-1.26	1.93	0.80-4.66
3	0.75	0.23-2.42	3.80	0.82-17.63
Number of positive biopsy cores				
1-2	1	ref	1	ref
3-4	1.78	1.28-2.48	0.92	0.34-2.48
5-10	1.44	0.67-3.11	1.34	0.18-10.24
Missing	0.67	0.31-1.47	0.42	0.10-1.76
Maximum percent tumour in any one core				
<0.10	1	ref	1	ref
0.10-<0.25	1.12	0.86-1.46	1.27	0.63-2.56
0.25-0.50	1.10	0.76-1.60	1.24	0.51-3.02
>0.50	1.09	0.49-2.49	2.68	0.55-13.11
Missing	1.45	0.95-2.23	0.60	0.13-2.76

Abbreviations HR hazard ratio; CI confidence interval

Table 3 Survival probabilities estimated with Kaplan-Meier analyses for all men managed on active surveillance and stratified on risk category*

	All		Very low-risk		Low-risk		Intermediate-risk		High-risk	
	n = 936		*n* = 223		*n* = 436		*n* = 259		*n* = 18	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Curative treatment										
3-year	75.3	72.4-78.0	79.8	73.9-84.5	71.6	67.1-75.6	78.2	72.7-82.8	66.7	40.4-83.4
5-year	69.1	66.0-71.9	73.4	67.0-78.7	64.5	59.8-68.8	73.5	67.6-78.5	61.1	35.3-79.2
10-year	62.8	59.1-66.3	70.8	64.0-76.5	55.7	49.9-61.0	69.0	61.8-75.0	-	-
Hormonal therapy										
5-year	97.1	95.8-98.0	98.2	95.3-99.3	97.9	96.0-98.9	95.7	92.4-97.6	82.4	54.7-93.9
10-year	92.2	89.2-94.4	95.1	89.6-97.7	94.6	90.0-97.1	87.7	79.1-92.6	57.0	26.5-78.8
Castration-resistant prostate cancer										
5-year	99.6	98.8-99.8	-	-	99.3	97.8-99.8	99.6	97.2-99.9	-	-
10-year	97.2	95.3-98.4	98.5	93.8-99.6	98.7	96.9-99.5	94.7	87.7-97.7	80.0	40.9-94.6
Overall survival										
5-year	95.4	93.9-96.6	95.5	91.8-97.6	95.2	92.7-96.8	95.8	92.5-97.6	94.4	66.6-97.6
10-year	87.2	84.0-89.9	88.6	81.5-93.2	87.9	83.5-91.2	83.9	75.1-89.7	-	-
Cause-specific survival										
5-year	-	-	-	-	-	-	-	-	-	-
10-year	99.6	98.6-99.9	-	-	99.3	97.3-99.8	99.5	96.6-99.9	-	-

Abbreviations CI confidence interval

*Risk category definition:

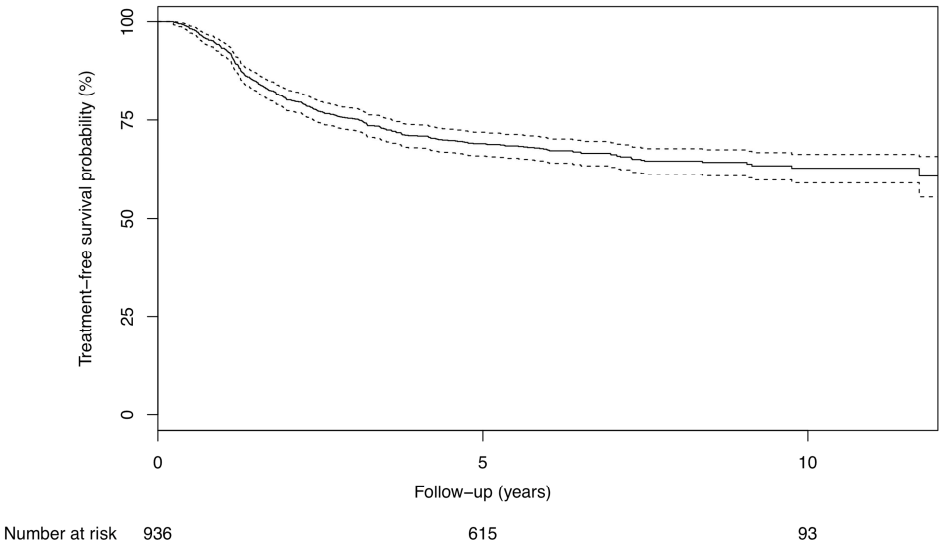
Very low-risk: cT1 and GGG 1 and PSA less than 10 ng/mL and PSA density less than 0.15 ng/mL/cc and 1-2 positive biopsy cores and maximum 50% cancer in any one core;

Low-risk: cT1-2a and GGG 1 and PSA less than 10 ng/mL;

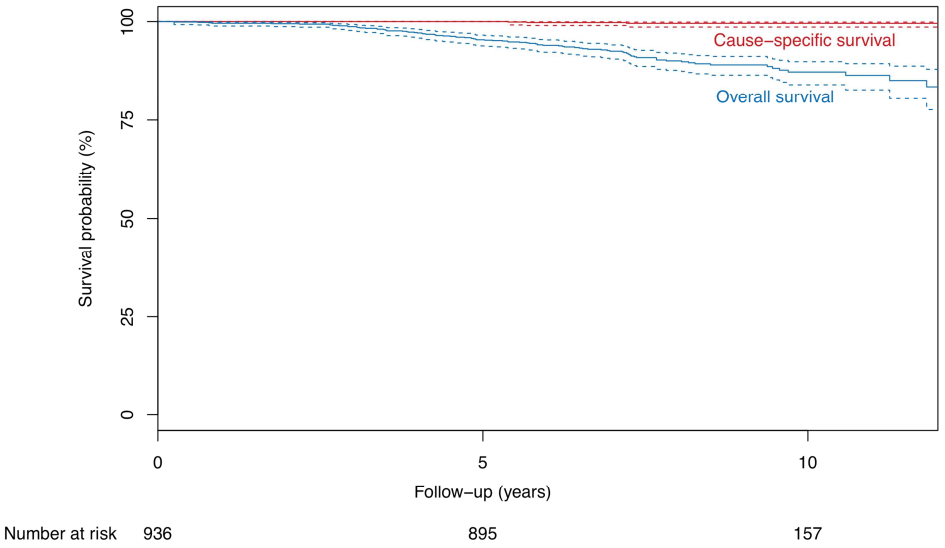
Intermediate-risk: cT2b-c and/or GGG 2-3 and/or PSA 10-20 ng/mL;

High-risk: PSA higher than 20 ng/mL

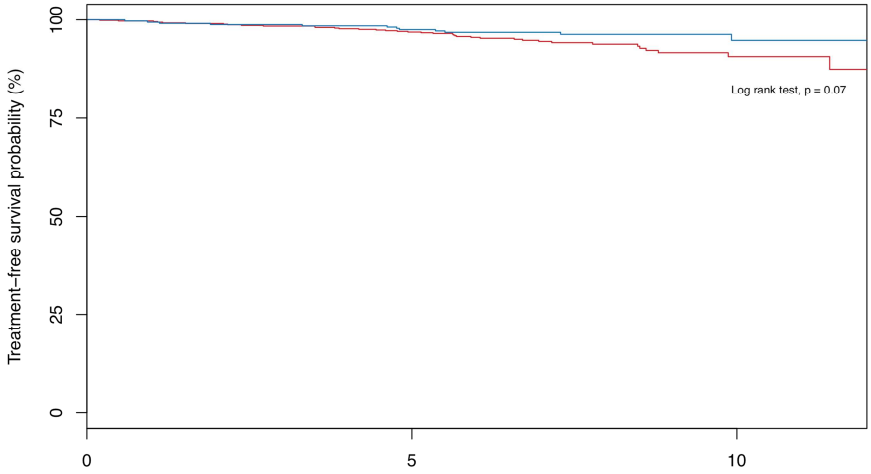
A Curative treatment



B Overall– and cause–specific survival

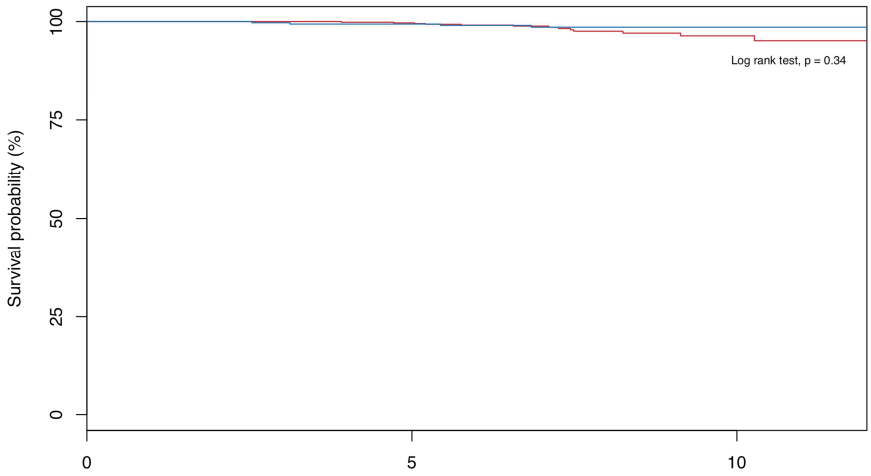


A Hormonal therapy



Number at risk			
No curative treatment	616	567	84
Undergone curative treatment	320	303	62

B Castration–resistant prostate cancer



Number at risk			
No curative treatment	616	580	93
Undergone curative treatment	320	309	65

Abbreviations

CI: confidence interval

cT: clinical tumour category

GGG: Gleason Grade Group

HR: hazard ratios

MRi: magnetic resonance imaging

TRUS: transrectal ultrasound

PSA: prostate-specific antigen

Supplemental table Survival probabilities estimated with Kaplan-Meier analyses for men with intermediate-risk prostate cancer managed on active surveillance and stratified on favourable and unfavourable intermediate-risk*

	Intermediate-risk *n* = 259		Favourable intermediate-risk *n* = 226		Unfavourable intermediate-risk *n* = 33		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	*p*
Curative treatment							0.49
3-year	78.2	72.7-82.8	79.0	73.1-83.8	72.7	54.1-84.8	
5-year	73.5	67.6-78.5	74.5	68.3-79.7	66.4	47.6-79.8	
10-year	69.0	61.8-75.0	69.1	61.1-75.8	66.4	47.6-79.8	
Hormonal therapy							0.03
5-year	95.7	92.4-97.6	97.3	94.1-98.8	84.8	67.4-93.4	
10-year	87.7	79.1-92.6	88.3	77.7-94.0	81.5	63.2-91.2	
Castration-resistant prostate cancer							0.02
5-year	99.6	97.2-99.9	99.6	96.9-99.9	-	-	
10-year	94.7	87.7-97.7	96.1	87.6-98.8	86.3	61.8-95.6	
Overall survival							0.33
5-year	95.8	92.5-97.6	95.6	91.9-97.6	97.0	80.4-99.6	
10-year	83.9	75.1-89.7	83.9	74.9-89.8	83.1	37.5-96.6	
Cause-specific survival							0.69
5-year	-	-	-	-	-	-	
10-year	99.5	96.6-99.9	99.4	96.1-99.9	-	-	

Abbreviations CI confidence interval

*Risk category definition:

Intermediate-risk: cT2b-c and/or GGG 2-3 and/or PSA 10-20 ng/mL

Favourable: Maximum of one intermediate-risk criteria and GGG 1-2 and maximum 50% cancer in any one core

Unfavourable: More than one intermediate-risk criteria and/or GGG 3 and/or more than 50% cancer in any one core