HHS Public Access

Author manuscript

Scand J Urol. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

Scand J Urol. 2016 August ; 50(4): 246–254. doi:10.3109/21681805.2016.1166153.

Immediate versus Delayed Prostatectomy: Nationwide population-based study

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Abstract

Objective—To compare the outcome of immediate versus delayed radical prostatectomy (RP) in men with low-grade prostate cancer (PCa).

Materials and Methods—Nationwide population-based cohort in the National Prostate Cancer Register (NPCR) of Sweden, of 7608 men with clinically localized, biopsy Gleason score 6 PCa who underwent immediate or delayed RP in 1997-2007. Multivariable models compared RP pathology, use of salvage radiotherapy and prostate cancer mortality based on timing of RP (<1, 1-2, >2 years after diagnosis). Median follow-up was 8.1 years.

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Prior presentations: Abstract presented at the 2014 American Urological Association meeting

COI: PS reports honoraria from Ferring and Astra Zeneca.

Results—Men undergoing RP more than 2 years after diagnosis had a higher risk of Gleason upgrading (OR 2.93, 95% CI 2.34-3.68) and an increased risk of salvage radiotherapy (HR 1.90, 95%CI 1.41-2.55), but no significant increase in PCa-specific mortality (HR 1.85, 95%CI 0.57-5.99). In competing risk analysis, 7-year PCa-specific cumulative mortality was similar at <1% for immediate RP and AS regardless of later intervention. Limitations of our study include lack of data on follow-up biopsies and a limited follow-up time.

Conclusion—Men undergoing RP more than 2 years after diagnosis had more adverse pathology features and second-line therapy, highlighting the trade-off by deferring immediate curative therapy. However, men with delayed RP constitute a minority with higher-risk cancer among the much larger group of low-risk men initially surveilled and the overall risk of prostate cancer mortality at 7 years was similarly low with immediate RP or AS.

Keywords

prostate cancer; active surveillance; radical prostatectomy; surgical delay; prognosis; outcomes

Introduction

Treatment of favorable-risk prostate cancer is curative in the vast majority of men,[1] but can have a significant negative impact on quality of life.[2] Active surveillance is an important alternative to delay or avoid curative treatment. Historically, only 10% of low risk prostate cancers in the United States were managed conservatively[3], although by 2010-2013 this had increased to approximately 40% among a large group of US practices.[4] In other countries such as Sweden, the adoption of active surveillance has also increased with 59% of very low risk and 41% of low risk prostate cancers diagnosed from 2007 to 2011 managed with active surveillance.[5]

Although many studies have shown favorable short-term outcomes with active surveillance, there is very little long-term data to confirm that this strategy does not miss the window for cure in men who might have been treated upon diagnosis. In a recent review, the median follow-up across active surveillance programs was only 3 years, and the longest median follow-up of any individual cohort was 7 years.[6] More recently, Klotz et al. reported updated follow-up of the Sunnybrook cohort (median follow-up of 6 years from first biopsy) in which 1.5% had died from prostate cancer and an additional 1.3% developed metastatic disease.[7] Updated data from the Johns Hopkins active surveillance program (median follow-up of 5 years) reported 2 prostate cancer deaths (0.15%) and 0.4% with metastatic disease.[8]

Overall, there remains limited data in the literature on the cancer specific outcomes of men with low-grade tumors undergoing surgery 1 or more years after diagnosis. The objective of our study was to examine the impact of longer treatment delays on outcomes in the National Prostate Cancer Register (NPCR) of Sweden.

Materials and Methods

The NPCR of Sweden includes 98% of all prostate cancer cases compared to the Swedish Cancer Register to which reporting is mandated by law. As previously described, data on tumor characteristics and primary treatment are recorded, and in the Prostate Cancer Data Base (PCBaSe), the NPCR has been cross-linked to other health care registries and demographic databases [9].

In this study, data in PCBaSe for men diagnosed with prostate cancer from 1997 to 2007 were analysed (**Figure 1**). The inclusion criteria were age ≤70 at diagnosis, clinical stage T1/T2, PSA <20 ng/ml, biopsy Gleason score ≤6 and receipt of an immediate or delayed radical prostatectomy, resulting in a final study population of 7608 men. Subset analysis was also performed in the 5987 men with PSA <10 ng/ml (D'Amico low risk), including 5347 treated at <1 year, 335 treated at 1-2 years, and 305 treated at >2 years after diagnosis.

The exposure in our analysis was time from date of prostate cancer diagnosis to date of surgery. We calculated this both as a continuous variable and as a categorical variable (<1, 1-2, and >2 years). We examined the following endpoints: adverse prostatectomy pathology (upgrading to a Gleason >6, extraprostatic extension or positive surgical margins), the receipt of salvage radiation therapy, and prostate cancer mortality.

The following covariates were included in the analysis: age (continuous), PSA (continuous, in 1 ng/ml increments), clinical local stage (≤T1c versus T2), comorbidity, educational level (low, middle or high), marital status (married, divorced/separated/widow, or single), and type of hospital (non-university versus university hospital). Comorbidity was assessed by use of the Charlson Comorbidity Index (CCI) which is a score based on International Classification of Diseases (ICD) codes that we applied to the discharge diagnoses in the In-Patient Register during ten years prior to the date of diagnosis of the index case, as previously described.[10, 11] The term “healthy men” is used for men with no registered comorbidity *i.e.* CCI 0. Information on the level of education was obtained from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA), a socioeconomic database, and was categorized as low (< 10 years, mandatory school), intermediate (10-12 years, high school) or high (> 12 years, university or equivalent).

Statistical Analysis

All statistical analysis was performed using R, version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and statistical significance was set at $\alpha=0.05$. Logistic regression was used to examine predictors of upgrading from diagnosis to RP (prostatectomy Gleason ≥7), extraprostatic extension and positive surgical margins. Cumulative incidence of salvage radiation therapy and prostate cancer specific mortality in the presence of competing risks were estimated, treating other-cause mortality as a competing risk. This was also used to assess the need to adjust for such competing risks in the multivariable models by employing more sophisticated methods. Cox proportional hazards models were ultimately used to examine the endpoints of salvage radiation therapy and prostate cancer specific mortality after delayed and immediate prostatectomy.

Finally, to compare PCa-specific mortality between immediate prostatectomy and active surveillance in an unselected setting, 7-year cumulative incidences were estimated in a competing risk analysis of 6981 men who underwent a primary RP within 6 months from diagnosis versus 1729 men who were prospectively registered as choosing active surveillance (**Supplemental Figure 1**),[12] regardless of later treatment (i.e. date of diagnosis was used as t=0 and time to treatment was disregarded). The Research Ethics Board at Umeå University Hospital approved of the study.

Results

The median age at diagnosis was 62 years (IQR 58.3-65.5), median PSA level was 6.5 ng/ml (IQR 4.8-9.2), and the majority of men (67%) had clinical stage T1c disease (**Table 1**). Radical prostatectomy was performed within 1 year after diagnosis in 6864 men, 1-2 years in 397 men, and >2 years in 347 men. Gleason scores ≥7 were present in 27%, 37%, and 49% of the prostatectomy specimens, extraprostatic extension was present in 13%, 13% and 21%, and positive surgical margins were present in 23%, 17%, and 24% of men with delays <1, 1-2 and >2 years, respectively.

Multivariable models to predict adverse prostatectomy pathology are shown in **Figure 2**. Compared to men who had radical prostatectomy within the first year, delays of 1-2 years and 2-7 years were associated increased risk of Gleason upgrading, OR 1.64 (95% CI 1.32-2.03) and OR 2.93 (95% CI 2.34-3.68), respectively. A separate model showed that for each additional year of delay, the odds ratio for upgrading was 1.45 (95% CI, 1.35-1.55) (**Supplemental Table 1**). However, there was no significant difference in risk of extraprostatic extension or positive surgical margins between immediate and delayed prostatectomy.

During a median follow-up of 8.1 years (IQR 6.6-10.1), 1179 (15%) men received salvage radiation therapy, and there were 76 prostate cancer deaths among a total of 608 deaths in the study population during the follow-up period (**Figures 3 and 4**). **Figure 5** and **Supplemental Table 2** show the results of multivariable analyses to predict salvage radiation therapy and prostate cancer death. Although there was no difference in use of secondary radiation therapy between men treated immediately and within the first two years after date of diagnosis, longer delays of 2-7 years were associated with a significantly higher risk of radiation therapy (OR 1.90, 95% CI 1.41-2.55). The hazard ratio for prostate cancer death among men who received deferred radical prostatectomy after 2-7 years of surveillance was 1.85 (95% CI, 0.57-5.99). Clinical stage T2 (HR 2.71, 95% CI 1.69-4.35) and low education (HR 2.03, 95% CI 1.06-3.86) were also significantly associated with prostate cancer death.

Subset analysis of men with PSA <10 ng/ml is shown in **Supplemental figures 2** and **3**. In this subgroup of 5987 men, 1610 men (27%) had prostatectomy Gleason scores of 7-10, 733 (12%) had extraprostatic extension, and 1224 (20%) had positive margins at prostatectomy. Similar to the overall results, the risk of upgrading was significantly higher with delays of 1-2 years (OR 1.82, 95% CI 1.43-2.30) and >2 years (OR 2.96, 95% CI 2.32-3.78). There was also a significantly higher risk of salvage therapy with delays >2 years (HR 1.91, 95%

CI 1.37-2.68) but the difference in prostate cancer death did not reach statistical significance (HR 2.29, 95% CI 0.70-7.56).

Finally, in competing risk analysis, the 7-year PCa-specific cumulative mortality from date of diagnosis to last follow-up, i.e within six months after date of diagnosis, was similar at <1% for 6981 men with primary RP and 1729 men managed with active surveillance regardless of later intervention (**Figure 6)**.

Discussion

In this large population based study, we compared outcome in men with biopsy Gleason ≤6 prostate cancer undergoing immediate versus delayed prostatectomy after a period of surveillance. Delays in surgery longer than 2 years were associated with a higher risk of adverse pathology features, salvage radiation therapy, and non-significant increase in the risk of prostate-cancer death at 8 years of median follow-up. Importantly, men undergoing delayed prostatectomy represent a selected subset of men with higher risk features out of all men on active surveillance. Overall, we observed a <1% prostate cancer mortality at 7 years, with no difference between men undergoing primary prostatectomy compared to men on active surveillance irrespective of later treatment.

This is the first population-based study to examine the impact of treatment delays of >2 years on prostate cancer death, and such data are important as the use of active surveillance is rapidly increasing for Gleason 6 prostate cancer worldwide. Several previous studies have reported the outcomes of immediate prostatectomy for men who would have met criteria for active surveillance[13, 14], or have examined the impact of very short treatment delays. At a European referral center, Graefen et al reported that short delays (median of 54 days) did not increase the risk of biochemical progression, but only 12 and 4 patients in this study had delays longer than 6 and 12 months, respectively.[15] In the US SEARCH database, Abern et al. compared pathology results and biochemical progression rates at a median follow-up of 53 months between men having surgery at <3, 3-6, 6-9, and >9 months.[16] In the low-risk group, there were no differences in adverse pathology or biochemical recurrence based on timing of surgery; whereas, for intermediate risk patients, delays >9 months were associated with significantly higher rates of positive surgical margins and biochemical progression.

Using a similar study design, Andrews et al. examined time to radiation therapy (<3, 3-6, 6-9 and >9 months) and treatment outcomes in 1322 patients from a single institution.[17] During a median follow-up of approximately 5 years, there were no differences in biochemical progression-free, metastasis-free or cancer-specific survival between the groups. By contrast, O'Brien et al. reported significantly higher rates of biochemical progression on multivariable analysis for low-risk patients with surgical delays ≥6 months. [18] Salvage therapy and cancer-specific survival were not evaluated in that study.

Other groups have performed matched comparisons between men undergoing immediate versus delayed prostatectomy. For example, van den Bergh compared 158 immediate versus 69 delayed prostatectomy for men with low risk disease (T1/T2, PSA <10, PSAD <0.2,

Gleason 6 and 1-2 positive cores) from the Swedish section of the ERSPC.[19] They found no significant differences in tumor volume, upgrading, capsular penetration, positive surgical margins or biochemical recurrence between the groups. The median follow-up in this study was 6 years after diagnosis.

An important limitation of the study design in all observational studies on immediate versus deferred RP is the selection process that occurs at several steps. First, men on surveillance in this study have lower risk features at the time of diagnosis compared to men who undergo immediate prostatectomy, eg. in our study significantly lower PSA ($p<0.001$), less clinical stage T2 disease ($p<0.001$), and a lower ratio of positive biopsy cores ($p<0.001$). Second, men who ultimately undergo radical prostatectomy after a period of surveillance constitute a subgroup with higher-risk cancer within the group of low-risk cancer of whom the majority remain on surveillance without any trigger for conversion.

One explanation for a higher rate of upgrading in the delayed RP group is that increases in grade during surveillance are a common reason for conversion to active treatment. Indeed, biopsy progression was the reason for discontinuing surveillance in 24% of men in our cohort, with the remainder discontinuing due to PSA progression (52%), patient preference (20%) or other reasons (3%).[12] Thus, men on surveillance who receive delayed prostatectomy represent a selection of men with higher risk features within the group of men with low-risk prostate cancer on AS. Notably, Tosoian et al. recently compared 3788 men undergoing immediate prostatectomy at Johns Hopkins versus 89 men who had delayed prostatectomy after active surveillance (at a median of 2 years, IQR 1-4).[20] The delayed surgery group was selected to represent the entire cohort, including 36% with disease reclassification leading to treatment and the remaining 64% without a protocol-based trigger for intervention. The risk of adverse pathology was not significantly different between the groups (multivariable OR 1.33, 0.82-2.79, $p=0.13$), although the sample size was small.

Another potential source of selection bias in studies of delayed radical prostatectomy is that men who progress to incurable disease during surveillance in the absence of definitive treatment are not included. However, the 7-year PCa-specific cumulative mortality in our study was similarly low for men who received immediate prostatectomy or active surveillance regardless of later intervention, suggesting that this was not the case.

It is important to note that data on biochemical recurrence were not available and the use of secondary radiation therapy in our study was not per protocol, but was performed at the discretion of the individual provider and the patient. Due to the inherent subjectivity, we recommend caution when evaluating this endpoint. In addition, since this was a nationwide registry with data from all health care providers in Sweden, uniform criteria were not used to initiate active surveillance or curative treatment, nor was there a standardized follow-up protocol. Data on follow-up biopsies are not available in this dataset, precluding an analysis of the impact of more stringent followup on the outcomes of delayed treatment. Finally, in order to examine long-term treatment outcomes we included men treated between 1997-2007, and there has been a significant stage migration over time also within the low-risk group. Thus, our results for deferred prostatectomy are a worst-case scenario compared to per- protocol selection and follow-up of surveillance, as is currently implemented in trials

such as the Study on Active Monitoring in Sweden (SAMS) and PRIAS.[21, 22] Finally, we did not compare quality of life between the early and delayed groups, since our dataset did not include information on this topic.

Strengths of the study include our nationwide population-based dataset, resulting in a large group of men who underwent delayed RP and greater generalizability than many previous studies reporting on single institutions. Also, we examined treatment delays of >2 years, which is longer than any of the previous papers on this topic and the median overall follow-up was 8 years. Although this is substantially longer than previous studies on surgical delay and on active surveillance,[23] at least 15 years of follow-up are needed for an optimal assessment of prostate cancer mortality in men with low risk disease so these results should be interpreted with caution. In addition, PCBaSe contains extensive and complete data on important confounders such as comorbidity and educational level which were not considered in most other studies.[23] Indeed, we did find a significant association between low education with adverse pathology and prostate cancer death after radical prostatectomy. Since the majority of men on active surveillance remain free from intervention at 5 years, [12, 24, 25] the impact of longer delays on prostatectomy outcomes is an important but understudied issue. Our study also offers methodological advantages over previous studies from our group and others comparing immediate versus delayed treatment between men matched on a limited number of features.[26, 27] Finally, we examined multiple endpoints ranging from pathology features to cancer-specific survival which was not included in previous studies, and performed an “intent-to-treat” comparison of men who received primary prostatectomy versus active surveillance to place these data into a larger context. Given the very low rate of disease-specific mortality among men with favorable-risk prostate cancer, very large datasets will be necessary to compare prostate cancer mortality based upon initial management strategy.

In conclusion, delayed RP after more than two years was associated with a significantly higher risk of adverse pathology and salvage radiation, and a non-significant increase in risk of death from prostate cancer highlighting the trade-offs by deferring initial curative therapy. However, men who receive delayed RP are a selection of higher-risk cancer among men with low-risk cancer on surveillance and since our population-based study was based on real-life data, these men represent a worst case scenario compared to men who are selected and followed per protocol. Importantly, there was no difference in 7-year prostate cancer mortality between men with localized Gleason 6 disease on surveillance compared to men who underwent immediate prostatectomy indicating that active surveillance is a viable management strategy for men with low-risk prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This project was made possible by the continuous work of the National Prostate Cancer Register of Sweden (NPCR) steering group: Pär Stattin (chairman), Anders Widmark, Camilla Thellenberg, Ove Andrén, Anna Bill Axelson, Ann-Sofi Fransson, Magnus Törnblom, Stefan Carlsson, Marie Hjälm-Eriksson, Bill Pettersson, David

Robinson, Mats Andén, Jan-Erik Damber, Jonas Hugosson, Ingela Franck Lissbrant, Maria Nyberg, Göran Ahlgren, Ola Bratt, René Blom, Lars Egevad, Calle Wallér, Olof Akre, Per Fransson, Eva Johansson, Fredrik Sandin, Hans Garmo, Mats Lambe, Karin Hellström.

Funding: This work was supported by The Swedish Research Council 825-2012-5047 and The Swedish Cancer Foundation 11 0471, Västerbotten County Council, the Lion's Cancer Research Foundation at Umeå University, the Swedish Cancer Foundation (2012/475) to OB, the Louis Feil Charitable Lead Trust to SL, the Laura and Isaac Perlmutter Cancer Center at NYU Langone Medical Center to SL, and the National Institutes of Health (Award Number K07CA178258) to SL. The content is solely the responsibility of the authors and does not represent the official views of the NIH.

Abbreviations

AS	active surveillance
PCa	Prostate cancer
RP	Radical prostatectomy
NPCR	National Prostate Cancer Register

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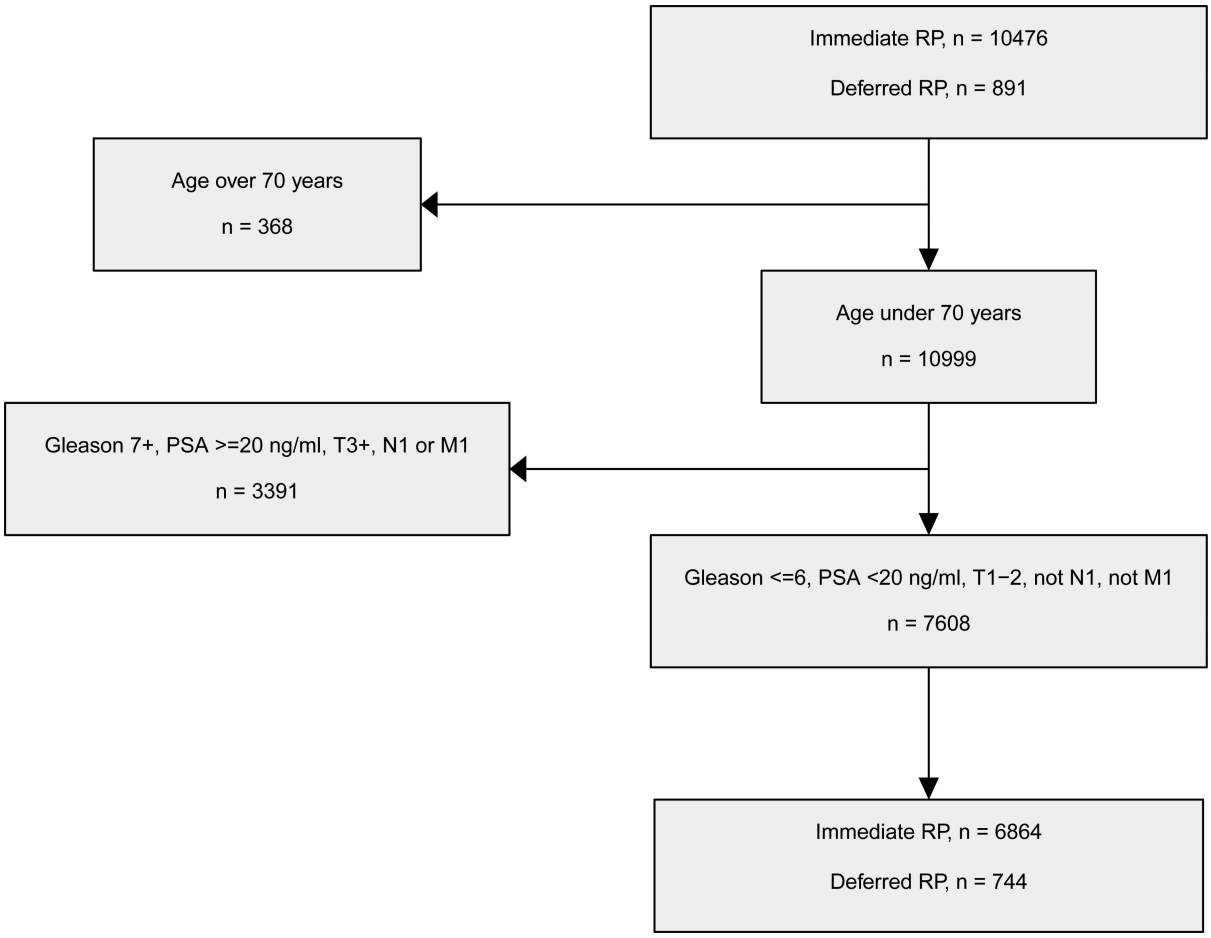

Figure 1.
Selection of the main study population comparing immediate versus deferred prostatectomy

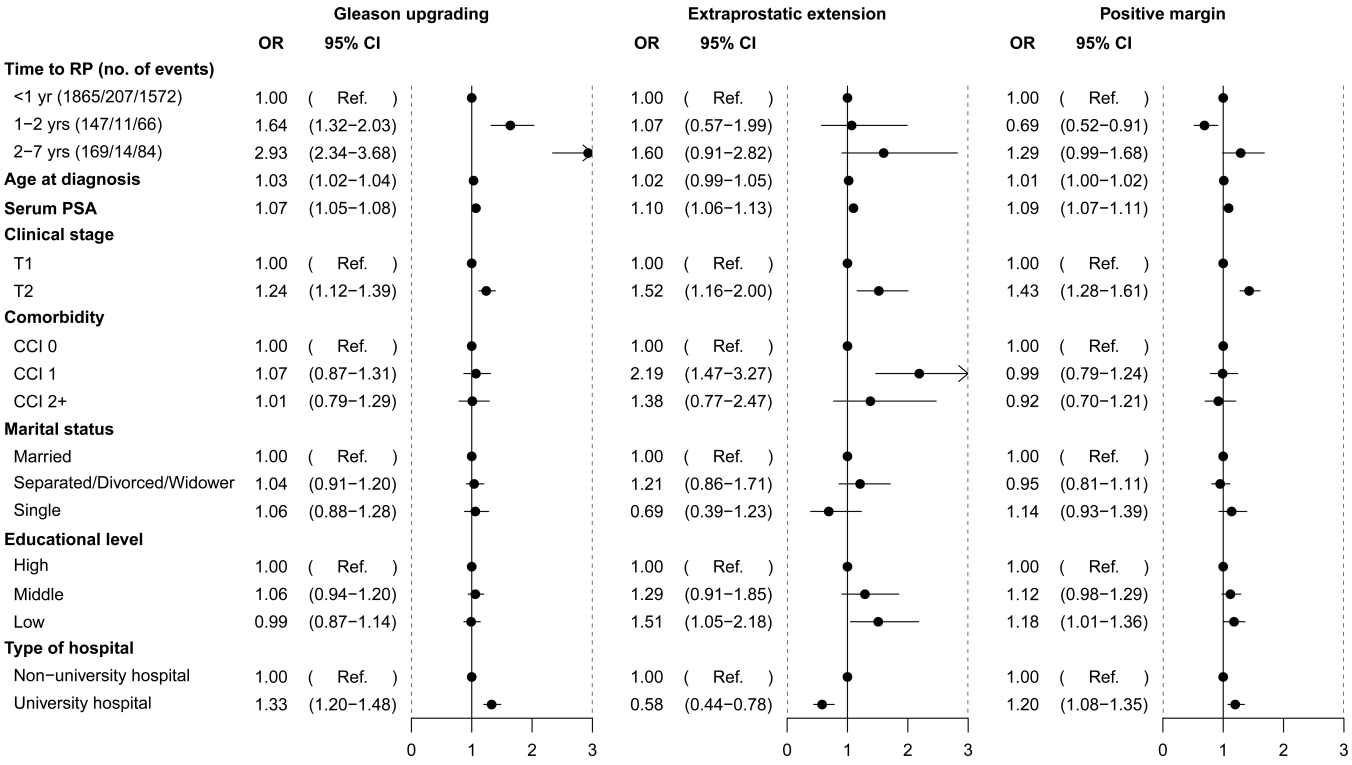

Figure 2.
Multivariable logistic regression for adverse surgical pathology

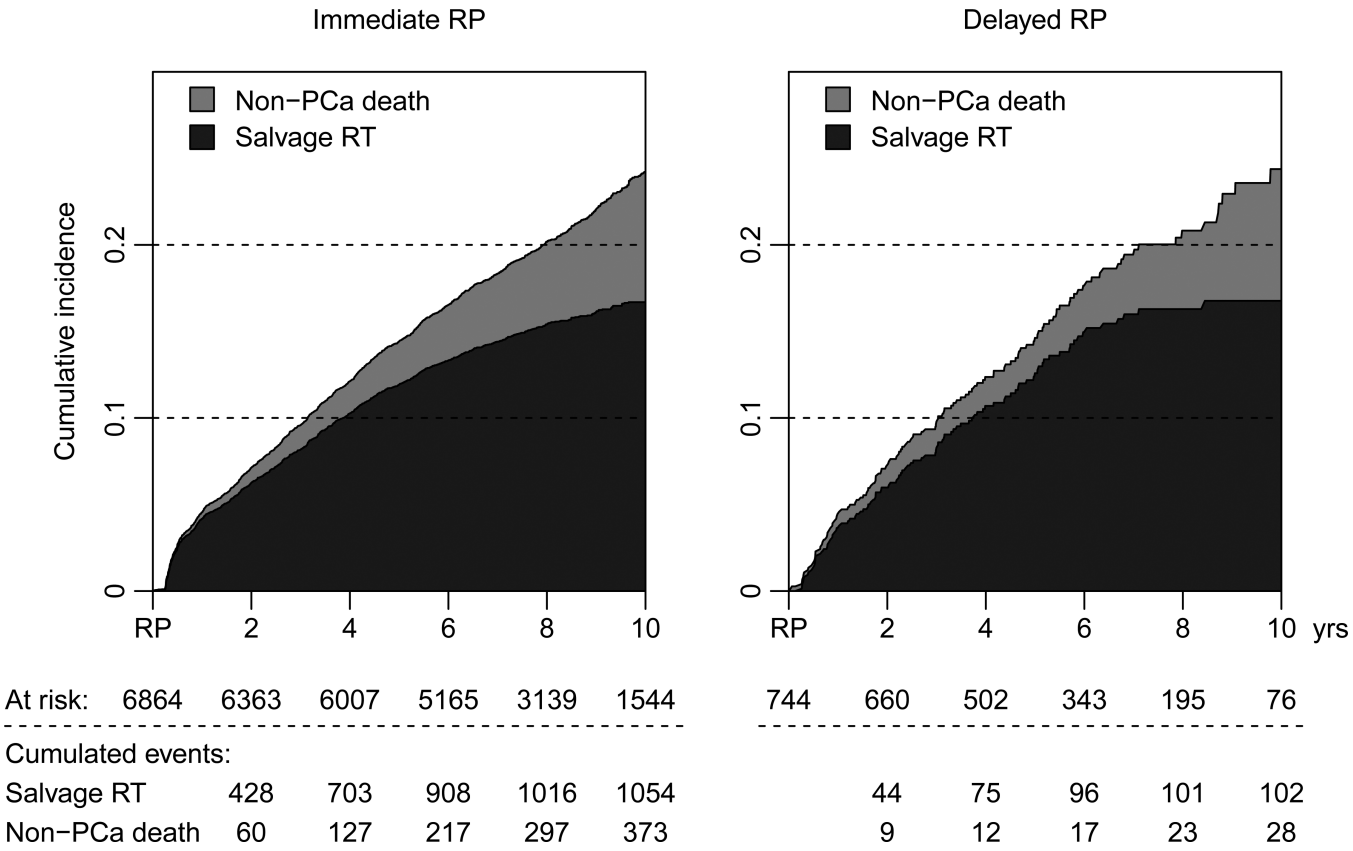

Figure 3.

Cumulative incidence of salvage radiation therapy after immediate versus delayed radical prostatectomy (RP), treating non-PCa death as a competing risk

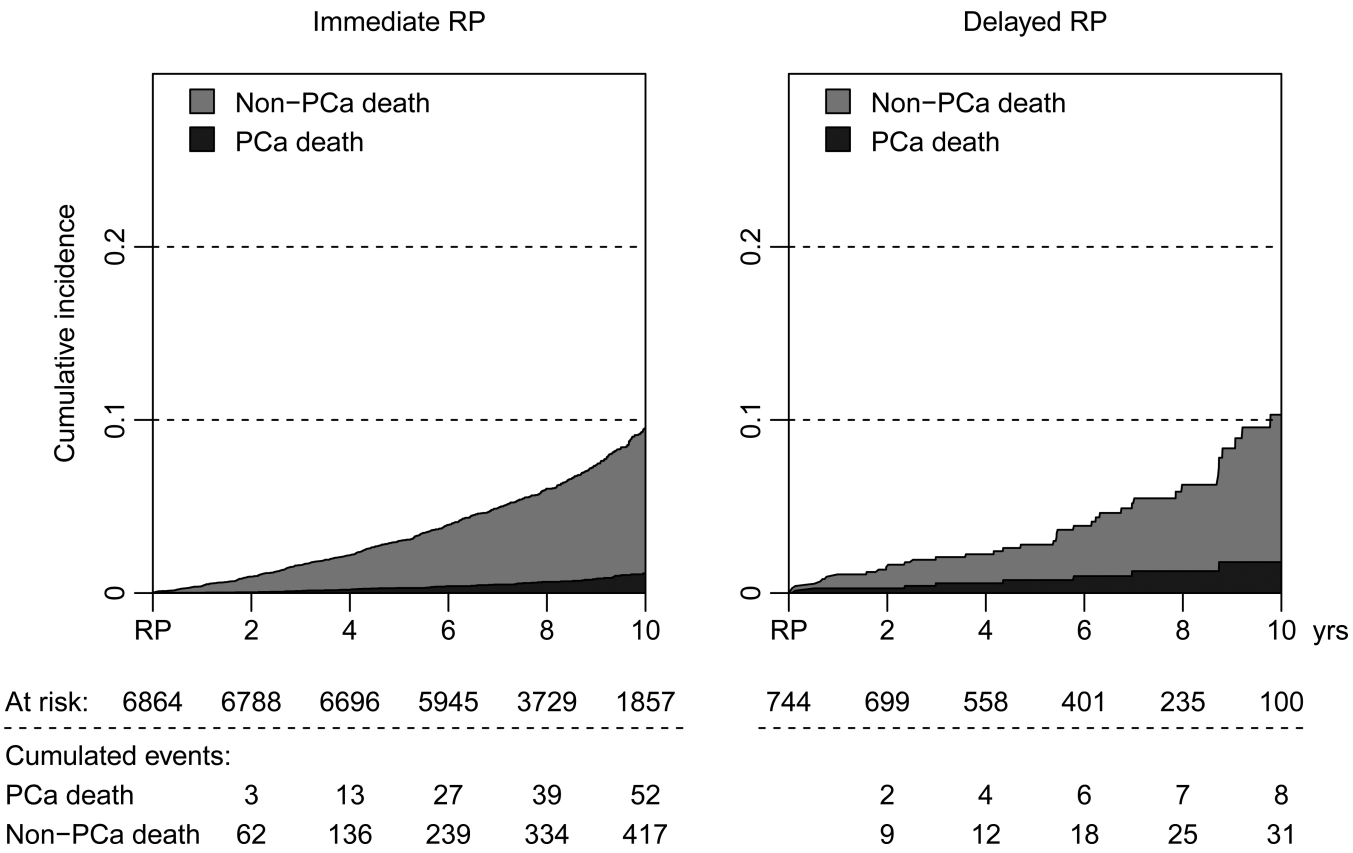

Figure 4.

Cumulative incidence of prostate cancer death after immediate versus delayed radical prostatectomy (RP), treating non-PCa death as a competing risk

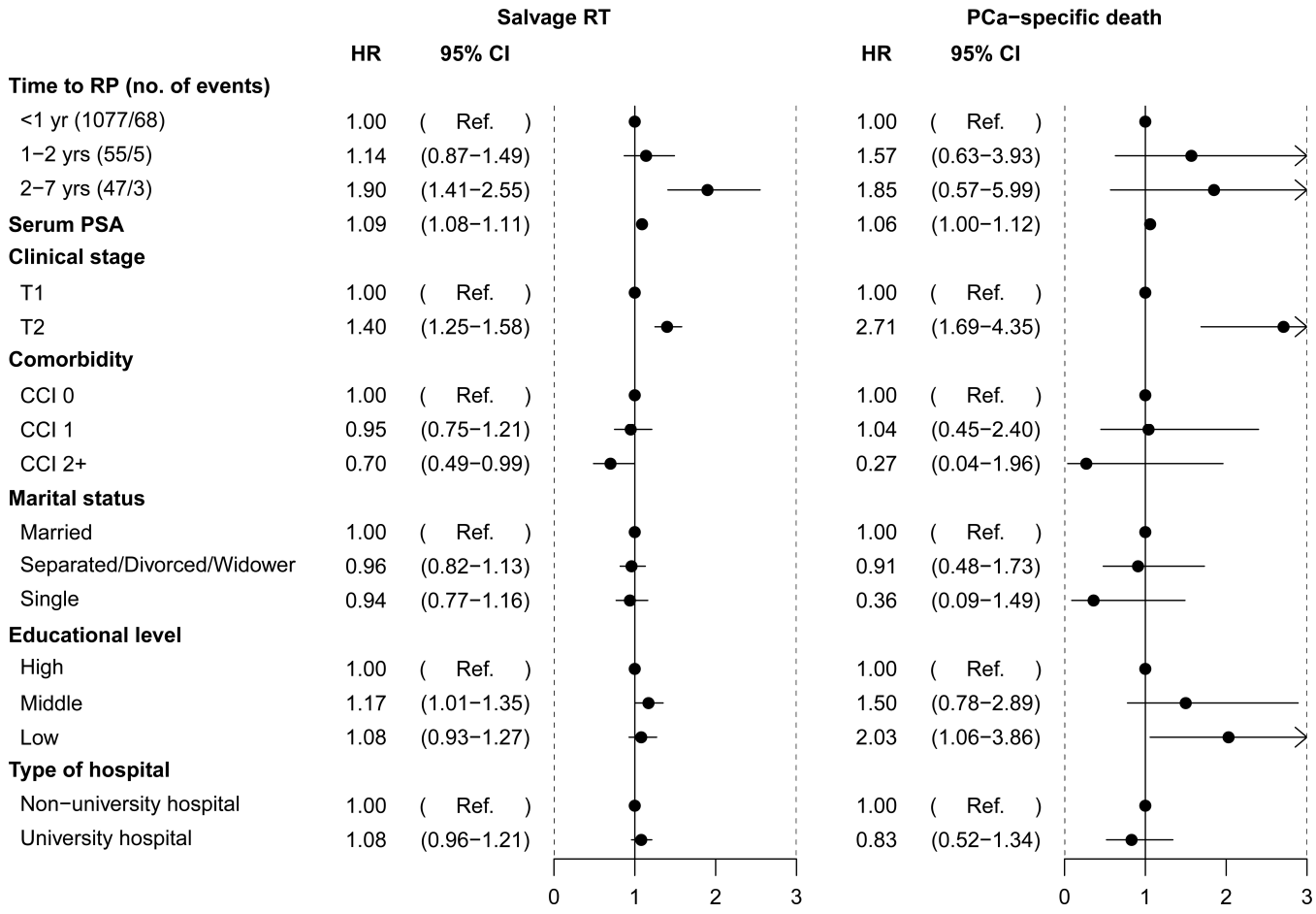

Figure 5.

Multivariable Cox regression for salvage radiotherapy and prostate cancer-specific death after radical prostatectomy

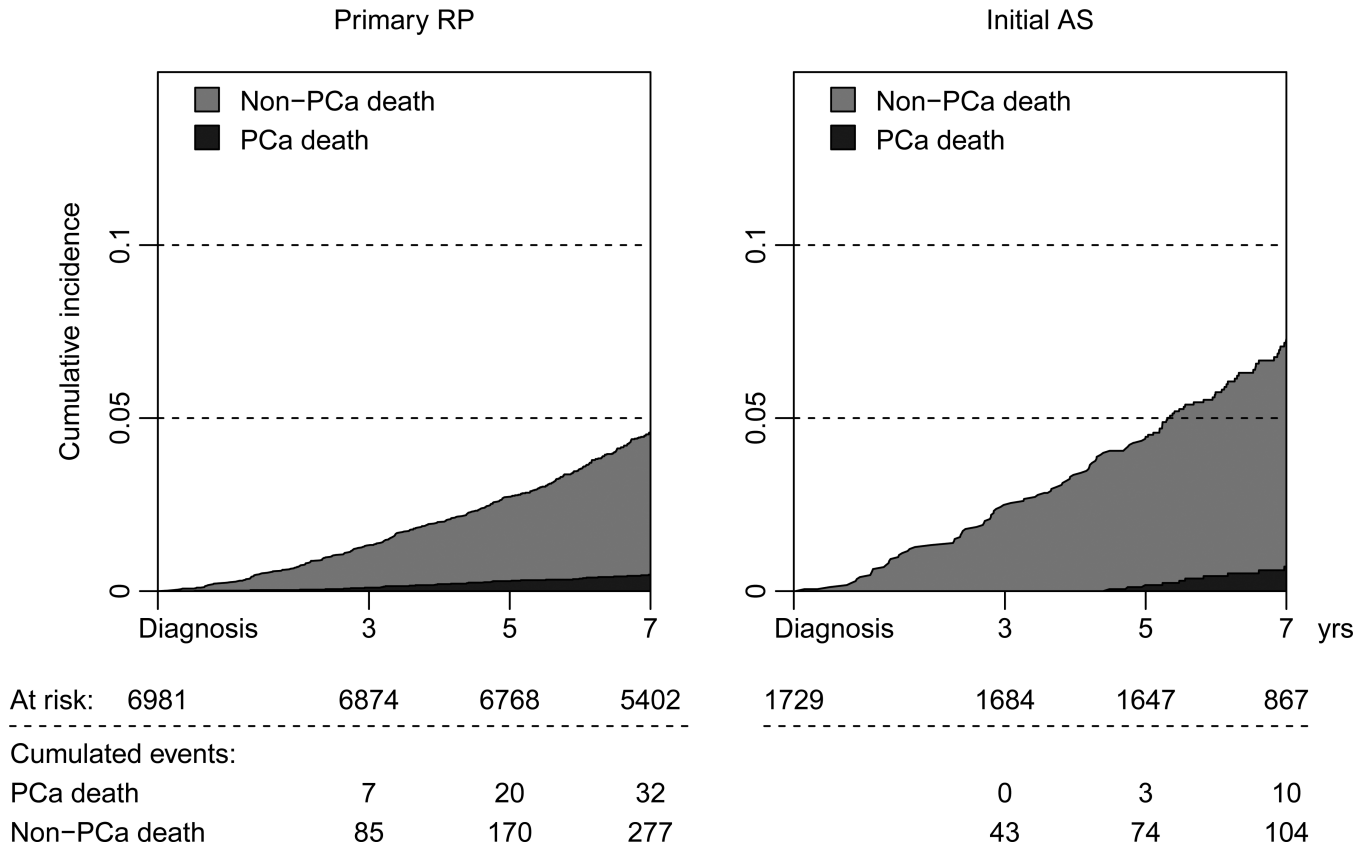

Figure 6.

Competing risk analysis comparing all men undergoing primary prostatectomy versus active surveillance irrespective of subsequent treatment.

Table 1

Demographics and tumor characteristics for men in the Prostate Cancer Database of Sweden (PCBaSe) 3.0 who underwent immediate or delayed radical prostatectomy with follow-up data

Time to RP	<1 yr	1-2 yrs	2-7 yrs	Total
Men	6864	397	347	7608
Year of diagnosis				
1997-1998	243 (4%)	15 (4%)	10 (3%)	268 (4%)
1999	328 (5%)	22 (6%)	11 (3%)	361 (5%)
2000	460 (7%)	27 (7%)	22 (6%)	509 (7%)
2001	512 (8%)	33 (9%)	21 (6%)	566 (8%)
2002	623 (9%)	32 (8%)	20 (6%)	675 (9%)
2003	956 (14%)	60 (16%)	42 (12%)	1058 (14%)
2004	1204 (18%)	62 (16%)	41 (12%)	1307 (18%)
2005	1125 (17%)	48 (12%)	52 (15%)	1225 (16%)
2006-2007	1261 (19%)	88 (23%)	121 (36%)	1470 (20%)
Age at diagnosis (yrs)				
Median (IQR)	62.0 (58.1-65.5)	62.7 (59.7-65.3)	62.4 (59.1-65.7)	62.0 (58.3-65.5)
Charlson Comorbidity Index				
CCI 0	6098 (89%)	361 (91%	301 (87%)	6760 (89%)
CCI 1	466 (7%)	21 (5%)	25 (7%)	512 (7%)
CCI 2+	300 (4%)	15 (4%)	21 (6%)	336 (4%)
Marital status				
Married	5211 (76%)	288 (73%)	266 (77%)	5765 (76%)
Separated/Divorced/Widower	1086 (16%)	75 (19%)	53 (15%)	1214 (16%)
Single	565 (8%)	34 (9%)	28 (8%)	627 (8%)
Missing data	2 (0%)	0 (0%)	0 (0%)	2 (0%)
Educational level				
High	1933 (28%)	112 (28%)	99 (29%)	2144 (28%)
Middle	2849 (42%)	179 (45%)	148 (43%)	3176 (42%)
Low	2061 (30%)	106 (27%)	98 (28%)	2265 (30%)
Type of hospital				
Non-university hospital	3936 (57%)	197 (50%)	183 (53%)	4316 (57%)
University hospital	2928 (43%)	200 (50%)	164 (47%)	3292 (43%)
Serum PSA (ng/mL)				
Median (IQR)	6.7 (4.8-9.3)	6.1 (4.5-8.6)	5.4 (4.2-7.6)	6.5 (4.8-9.2)
<4	860 (13%)	64 (16%)	61 (18%)	985 (13%)
4-10	4487 (65%)	271 (68%)	244 (70%)	5002 (66%)
10-20	1517 (22%)	62 (16%)	42 (12%)	1621 (21%)
Clinical stage				
T1a	51 (1%)	10 (3%)	8 (2%)	69 (1%)

Time to RP	<1 yr	1-2 yrs	2-7 yrs	Total
T1b	34 (0%)	3 (1%)	3 (1%)	40 (1%)
T1c	4528 (66%)	301 (76%)	285 (82%)	5114 (67%)
T2	2251 (33%)	83 (21%)	51 (15%)	2385 (31%)
Number of biopsy cores				
Median (IQR)	6 (6-8)	6 (6-8)	8 (6-10)	6 (6-8)
<10	3313 (48)	189 (48)	167 (48)	3669 (48)
10+	740 (11)	52 (13)	61 (18)	853 (11)
Ratio of positive cores				
<33%	1926 (28)	178 (45)	168 (48)	2272 (30)
33-66%	1696 (25)	54 (14)	51 (15)	1801 (24)
>66%	424 (6)	7 (2)	9 (3)	440 (6)
Missing data	2818 (41%)	158 (40%)	119 (34%)	3095 (41%)
Prostatectomy Gleason score				
<=6	4805 (70%)	236 (59%)	163 (47%)	5204 (68%)
7	1757 (26%)	136 (34%)	150 (43%)	2043 (27%)
8-10	108 (2%)	11 (3%)	19 (5%)	138 (2%)
Missing data	194 (3%)	14 (4%)	15 (4%)	223 (3%)
Pathological features				
OC	4940 (72%)	289 (73%)	237 (68%)	5466 (72%)
EPE	875 (13%)	51 (13%)	73 (21%)	999 (13%)
Missing data	1049 (15%)	57 (14%)	37 (11%)	1143 (15%)
Positive margin				
No	4514 (66%)	290 (73%)	221 (64%)	5025 (66%)
Yes	1572 (23%)	66 (17%)	84 (24%)	1722 (23%)
Missing data	778 (11%)	41 (10%)	42 (12%)	861 (11%)
Follow-up after RP (yrs)				
Median (IQR)	8.3 (6.8-10.2)	7.6 (5.7-9.7)	4.7 (3.0-7.3)	8.1 (6-6-10.1)